Summary of Integrated clinical study report

Study code : KKL172014

EudraCT-No.: 2014-003470-17

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Olmesartan medoxomil/amlodipine fixed combination
Summary of integrated clinical study report

Note: This document is intended to provide the essential information on the KKL172014 clinical trial in the setting of reporting to regulatory authorities.

CONTENTS

1 Tabelaric summary

Name of the sponsor: Krka, d. d., Novo mesto	**Individual study table referring to the part of dossier** **Volume: 5.3**	*(For national authority use only)*
Name of the finished product: Olmesartan medoxomil/amlodipine 20/5 mg film-coated tablets Olmesartan medoxomil/amlodipine 40/5 mg film-coated tablets Olmesartan medoxomil/amlodipine 40/10 mg film-coated tablets		
Name of the active ingredients: olmesartan medoxomil, amlodipine besylate		

Title of Study:

The efficacy and safety of olmesartan medoxomil/amlodipine fixed combination in patients with grade 1 to grade 2 arterial hypertension. An international randomized, double-blind, 10-week multi-factorial clinical study.

Responsible investigator:
Not applicable in this clinical trial.

Operative trial sites and investigators:

Country	Number of all trial sites
Germany	10
Romania	18
Poland	18
Hungary	12

Due to a large number of trial sites (58) is detailed list of investigators and trial sites provided in Appendix 16.1.4 List of the investigators and description (CV).

Studied Period : First subject in (enrolled): 23. 2. 2015 Last subject out (completed) : 10. 10. 2015	**Phase of development:** III

Objectives:

Primary objective of this trial is to compare the treatment effect of fixed-dose combinations of olmesartan medoxomil/amlodipine (TIMP) to those of the component monotherapies (RIMPs) and placebo in subjects with grade 1 or grade 2 arterial hypertension. Within the primary objective the superiority of the treatment effect of TIMPs over each RIMP of respective strength and placebo is expected to be demonstrated.

Secondary objective is to assess the safety profile of TIMPs in comparison with each RIMP and placebo and to demonstrate similar safety profile in TIMPs and RIMPs in subjects with grade 1 or grade 2 arterial hypertension.

Methodology/Study Design:

This multicenter international phase III clinical trial was designed as eight-arm, multi-factorial, placebo-controlled, randomized, double-blind with a single-blind placebo run-in. Trial was performed on subjects with grade 1 to grade 2 arterial hypertension. Eligible screened subjects were randomly assigned to eight therapy groups. All subjects, eligible for randomization, started a 14-day washout/run-in period during which they received one unit of placebo once daily. This was followed by two 4-week active treatment periods, during which each subject orally consumed one unit of randomly assigned IMP once daily. The overall treatment duration, including the placebo run-in period, was 10 weeks. Each subject attended five visits.
All the efficacy endpoints were determined either with blood pressure measurements or 24-hour ABPM. Blood pressure measurements were performed at each trial visit. 24-hour ABPM was performed at baseline (Visit 2) and the final visit (Visit 5) in approximately the first 50% of the randomized subjects.

Number of patients:

Planned for screening: 1000
Target sample size for the per protocol analysis of primary endpoint: 717
Actually screened: 997
Actually randomised: 841
Randomization arms:
Group A: olmesartan medoxomil 20 mg / amlodipine 5 mg (OAFC 20 /5): 129
Group B: olmesartan medoxomil 40 mg / amlodipine 5 mg (OAFC 40 /5): 130
Group C: olmesartan medoxomil 40 mg / amlodipine 10 mg (OAFC 40 /10): 129
Group D: olmesartan medoxomil 20 mg (O 20): 97
Group E: olmesartan medoxomil 40 mg (O 40): 96
Group F: amlodipine 5 mg (A 5): 97
Group G: amlodipine 10 mg (A 10): 98
Group H: placebo (PLAC): 65
Altogether 388 of these subjects were randomized to receive RIMP, other 388 were randomized to receive TIMP and 65 to receive placebo.
Analyzed ITT (intention to treat): 841
Analysed PP (per protocol analysis): 725
Analysed FAS (full set analysis): 828
Analysed Safety: 841.

Diagnosis and main criteria for inclusion: Grade 1 or grade 2 arterial hypertension (mean SeDBP of 90 to 109 mm Hg). **Main inclusion criteria:** Mean SeDBP of 90 to 109 mm Hg at the screening (Visit 1) and the baseline (Visit 2).
Reference investigational medicinal product: Olmetec 20 mg film-coated tablets containing olmesartan medoxomil 20 mg **Randomisation group:** D **Dose and mode of administration:** One capsule once daily. **Batch number:** 221510R; 225905R **Reference investigational medicinal product:** Olmetec 40 mg film-coated tablets containing olmesartan medoxomil 40 mg **Randomisation group:** E **Dose and mode of administration:** One capsule once daily. **Batch number:** 223080R; 226188R **Reference investigational medicinal product:** Norvasc 5 mg tablets containing amlodipine besylate 6,94 mg **Randomisation group:** F **Dose and mode of administration:** One capsule once daily. **Batch number:** E10143630R; E10479730 POR **Reference investigational medicinal product:** Norvasc 10 mg tablets containing amlodipine besylate 13,88 mg **Randomisation group:** G **Dose and mode of administration:** One capsule once daily. **Batch number:** E10248630R; E10464034 ELR

Test investigational medicinal product: Olmesartan medoxomil/amlodipine 20/5 mg film-coated tablets containing two active pharmaceutical ingredients, olmesartan medoxomil 20 mg and amlodipine besylate 6,94 mg
Randomisation group: A
Dose and mode of administration: One capsule once daily.
Batch number: 1315 01 P002 0914; 1315 01 P003 0115

Test investigational medicinal product: Olmesartan medoxomil/amlodipine 40/5 mg film-coated tablets containing two active pharmaceutical ingredients, olmesartan medoxomil 40 mg and amlodipine besylate 6,94 mg
Randomisation group: B
Dose and mode of administration: One capsule once daily.
Batch number: 1315 02 P002 0914; 1315 02 P003 0115

Test investigational medicinal product: Olmesartan medoxomil/amlodipine 40/10 mg film-coated tablets containing two active pharmaceutical ingredients, olmesartan medoxomil 40 mg and amlodipine besylate 13,88 mg
Randomisation group: C
Dose and mode of administration: One capsule once daily.
Batch number: 1315 03 P002 0914; 1315 03 P003 0115

Placebo: Placebo tablet has the identical size and shape as Olmesartan medoxomil/amlodipine 40/10 mg. The composition of placebo includes all the excipients in the same proportions as active IMP whereby the missing active ingredient is replaced up to the identical mass of the TIMP.
Randomisation group: H
Dose and mode of administration: One capsule once daily.
Batch number: 1315 03 PL05 0914; 1315 03 PL06 0115

Duration of treatment:

The total active treatment duration is 8 weeks, while the overall study duration is 10 weeks, with maximal allowed prolongation of 3 additional days per each period due to possible unpredicted causes for delay in the follow-up visits.

Efficacy criteria for evaluation:

Primary endpoint:
The primary efficacy endpoint is determined as mean change from baseline in seated diastolic blood pressure (SeDBP) at week 8 of the active treatment.

Secondary endpoints:
The following study variables are identified as secondary efficacy endpoints:

- Mean change from baseline in SeSBP at week 8
- Mean change from baseline in SeDBP at week 2
- Mean change from baseline in SeDBP at week 4
- Mean change from baseline in SeSBP at week 2
- Mean change from baseline in SeSBP at week 4
- Proportion of subjects with SeSBP reduction from baseline ≥ 20 mm Hg at week 8
- Proportion of subjects with SeDBP reduction from baseline ≥ 10 mm Hg at week 8
- Proportion of subjects reaching BP goal of less than 140/90 mm Hg at week 2
- Proportion of subjects reaching BP goal of less than 140/90 mm Hg at week 4
- Proportion of subjects reaching BP goal of less than 140/90 mm Hg at week 8
- Mean change from baseline in average 24-hour SBP at week 8
- Mean change from baseline in average 24-hour DBP at week 8

Secondary efficacy endpoints corroborate the results of the primary efficacy endpoint, particularly in giving additional information on IMPs' blood pressure lowering efficacy at different treatment time intervals and establishing the effect on the average 24-hour blood pressure, which is determined by 24-hour ambulatory blood pressure measurement (ABPM).

Criteria for safety evaluation (planned):

- Overall incidence of adverse reactions (drug-related adverse events)
- Incidence of adverse reactions stratified by specific type of adverse reaction
- A number/percentage of subjects unable to finish both active treatment periods due to clinically significant adverse reaction
- Mean change from baseline in laboratory parameters at week 8.

Statistical methods:

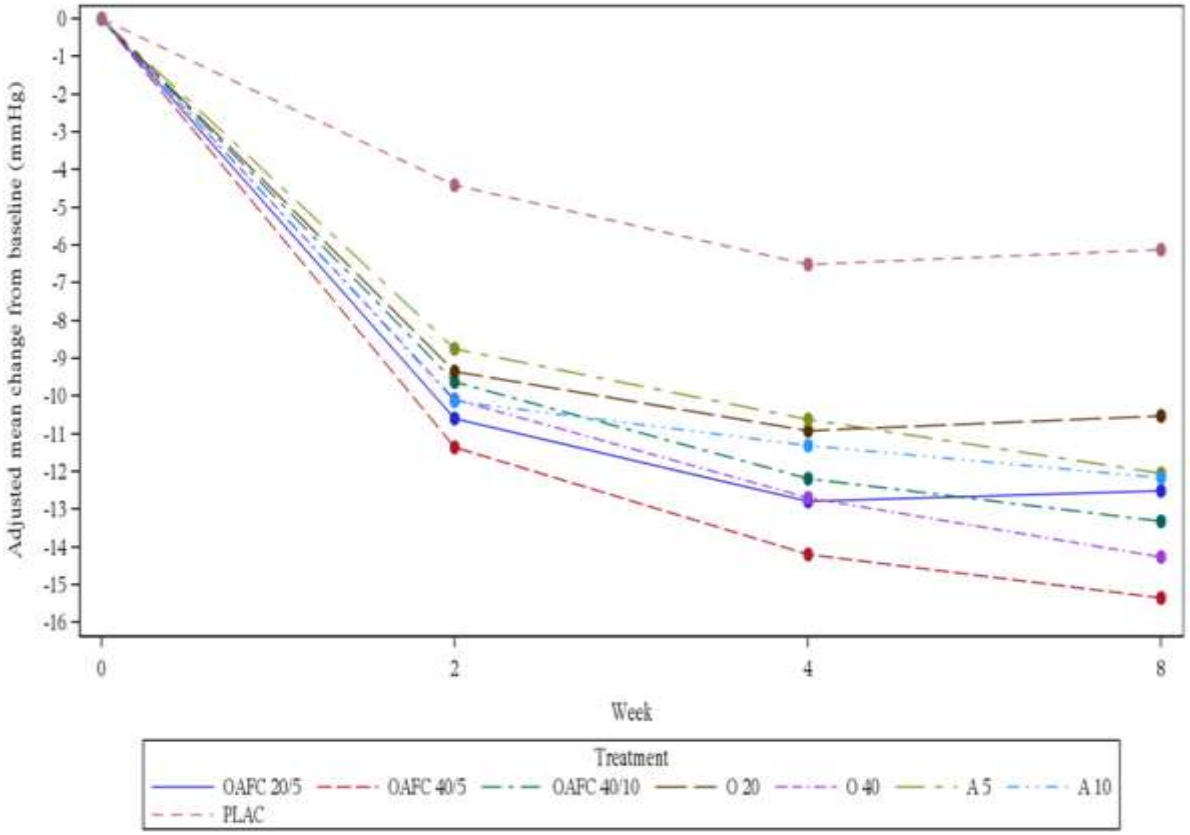
The statistical model for the primary efficacy endpoint testing was designed to test the null hypothesis of non-difference of each TIMP over monocomponents of respective strength and placebo. In case of null hypothesis rejection, the alternative hypothesis of superiority was accepted. Since this was a factorial clinical trial, multiple sets of hypotheses were constructed. Three hypotheses families were formed to reach the primary objective of the study which was to demonstrate that each of the three fixed–dose combinations of olmesartan and amlodipine was superior to placebo and the corresponding monocomponents with respect to primary efficacy endpoint. Hence the hierarchy levels were set up within each family.
The assessment of hypotheses was based on an analysis of covariance (ANCOVA) model with geographic region and treatment as factors, and baseline value of the blood pressure variable as covariate.
The same analyses as for the primary efficacy endpoint were performed for the following secondary efficacy endpoints: mean change from baseline in SeSBP at week 8, mean changes from baseline in SeDBP/SeSBP at weeks 2 and 4, mean changes from baseline in DBP/SBP assessed with 24-hour ABPM at week 8.
The proportions of subjects reaching the BP goal at weeks 2, 4, and 8 were compared using Cochran-Mantel-Haenszel test statistics.
Analysis of primary efficacy endpoint was performed on Intention-to treat set, Full Analysis set and Per Protocol set. Analyses on secondary efficacy endpoints were performed on Full Analysis set.

In case of missing information for the primary efficacy endpoint and key secondary efficacy endpoint at week 8 the missing values were to be replaced with a set of plausible values. The imputation method was based on pattern-mixture models. Sensitivity analyses were to be performed based on multiple imputations to explore the potential effect of missing data. Sensitivity analyses were also to be performed for rescue therapy, including/excluding observations after rescue therapy treatment.

Safety was assessed by statistical and/or clinical review of all safety parameters, including adverse events, laboratory values, ECG and physical examination. All subjects randomized who received at least one dose of the study medication were included in the safety analyses (Safety population).

Summary of results and conclusions:
EFFICACY RESULTS

Descriptive statistical data show clinically evident SeDBP and SeSBP reductions at all the assessment points (week 2, week 4 and week 8) against baseline values in all the treatment groups with considerable difference between placebo and all the active treatment groups. The results are consistent in all three datasets analysed. The highest reduction in mean Se DBP at week 8 was observed in OAFC 40/5 treatment group followed by O 40 and OAFC 40/10. Apart from placebo, the lowest reduction was documented in O 20 group followed by A 5. These results are presented in the figure below (Full analysis set).



Likewise, a significant decrease in both the average 24-hour DBP and SBP was observed in all active treatment groups. In the placebo group, no difference of the mean values was observed between baseline and week 8 mean value.
The descriptive statistics related to treatment goals indicated a highly effective active treatments and less so the placebo treatment. In the active treatment groups the percentage of subjects reaching therapeutic target of more than 20 mmHg SBP reduction ranged from 43.8 % in A5 group to 57, 8 % in the OA 40/5 group.

EFFICACY RESULTS continued:

Summary of the descriptive statistics related to BP reduction goals is presented in the table below.

	SeSBP reduction ≥ 20 mmHg (week 8)	**SeDBP reduction ≥ 10 mmHg (week 8)**	**BP less than 140/90 mmHg (week 2)**	**BP less than 140/90 mmHg (week 4)**	**BP less than 140/90 mmHg (week 8)**
OAFC 20/5	50.0%	66.4%	46.9%	69.5%	69.5%
OAFC 40/5	57.8%	77.3%	58.6%	72.7%	75.8%
OAFC 40/10	50.4%	65.4%	40.9%	60.6%	63.8%
0 20	50.5%	56.7%	43.3%	60.8%	60.8%
0 40	57.0%	71.0%	51.6%	63.4%	68.8%
A 5	43.8%	57.3%	42.7%	61.5%	70.8%
A 10	53.2%	62.8%	45.7%	56.4%	70.2%
Placebo	20.0%	27.7%	13.8%	32.3%	35.4%

Only 20 (2.4%) of the subjects required rescue medication during the active treatment period. The percentage of subjects with use of rescue medication per active treatment was near to zero, except for the O 40 group that has a slight increase of the percentage with respect to the other active treatment groups.

Primary efficacy endpoint

Hypotheses were tested in a hierarchical order. In order to continue with the next family of hypotheses all five null hypotheses in the previous family had to be rejected. Since not all the null hypotheses in the first family (including OAFC 40/10, O 40, A 10, and placebo) were rejected, the further hypothesis testing could not be evaluated. Therefore only the first family was tested.

The first hypothesis was rejected: the adjusted difference of the mean change from baseline in SeDBP between OAFC 40/10 and Placebo in the FAS set was - 6.99 mmHg (95% CI: (- 9.39; - 4.6) and it was statistically significant (p-value < 0.001), so the mean change from baseline in SeDBP was superior in OAFC 40/10 compared to Placebo.

Likewise, the second and the third hypothesis involving comparison of the two monotherapies against placebo were rejected, hence the mean change from baseline in SeDBP was superior in both O 40 and A 10 compared to placebo.

The fourth and fifth hypothesis were accepted: the adjusted mean change from baseline in SeDBP between OAFC 40/10 and O 40 in the FAS set was 0.73 mmHg (95% CI: -1.36; 2.81) although not statistically significant (p-value = 0.494); the mean change from baseline in SeDBP between OAFC 40/10 and A 10 in the FAS set was - 1.54 mmHg (95% CI: - 3.66; 0.58) but it was not statistically significant (p-value = 0.155).

EFFICACY RESULTS continued:

Primary efficacy endpoints (continued)

Hence, the mean change from baseline in SeDBP was not different in OAFC 40/10 compared with O 40 and A10 groups.

These results are presented in the table below.

Comparison	**Adjusted mean difference (95% CI)**	**p-value**
OAFC 40/10 – Placebo	- 6.99 (- 9.39; - 4.6)	< 0.001
O 40 – Placebo	- 7.72 (- 10.24; - 5.20)	< 0.001
A 10 – Placebo	- 5.45 (- 8.00; - 2.91)	< 0.001
OAFC 40/10 – O 40	0.73 (-1.36; 2.81)	0.494
OAFC 40/10 – A 10	- 1.54 (- 3.66; 0.58)	0.155

The sensitivity analyses were also carried out evaluating possible impact of alternative handling of the missing data, rescue medication use and GCP violations identified at a single clinical site. These sensitivity analyses turned out to have no impact on results of the primary efficacy endpoint. Likewise, subgroup analyses including age, gender and participating countries did not yield significantly different results with primary efficacy endpoint.

Secondary efficacy endpoints

For the same reason as in the primary efficacy analysis, only the hypotheses related to the highest strength of fixed combination (OAFC 40 /10) were tested.

Results obtained from the statistical analysis of secondary efficacy endpoints were comparable to the results of the primary efficacy endpoint: statistically significant difference between treatments was observed for the first three hypotheses of first family (i.e., OAFC 40/10 and Placebo, O 40 and Placebo, A 10 and Placebo) in favor of active treatments, but no statistical significant difference between treatments was detected for the fourth and fifth hypothesis of first family (i.e., OAFC 40/10 and O 40, OAFC 40/10 and A 10).

The results of the response surface model for SeDBP and SeSBP at the end of therapeutic follow-up have not shown any obvious dose response relationship for the fixed combination.

SAFETY RESULTS:

Average overall extent of exposure was 56 days per subject taking into account the ITT population set yielding 129 patient years.

In total, 255 adverse events (AE) emerged in 184 (21.9%) subjects. Among these, a total of 240 adverse reactions (AR) emerged in 177 (21.0%) subjects.

The highest incidence of adverse reactions (ARs) was reported in treatment group A10 with 30.6 % of subjects affected and the lowest incidence of ARs in group A5 with 12.4 % of subjects affected. The overall incidence of ARs was comparable between treatment groups and no particular differences in the incidence of specific types of ARs were observed.

Therapy group	OAFC 20/5 N = 129	OAFC 40/5 N = 130	OAFC 40/10 N = 129	O20 N = 97	O40 N = 96	A5 N = 97	A10 N = 98	PLAC N = 65
Number of TEARs	29	27	56	28	27	16	43	14
Number of patients with TEARs (%)	21 (16.3%)	24 (18.5%)	37 (28.7%)	21 (21.6%)	21 (21.9%)	12 (12.4%)	30 (30.6%)	11 (16.9%)

There was a dose dependency trend in the percentage of subjects experiencing ARs within the three fixed combination groups and more obvious one in the two amlodipine monotherapy groups.

Overall, the most common treatment emergent AR was peripheral oedema, followed by headache and dizziness. No particular differences in the incidence of specific types of ARs were observed between groups. The general incidence of TEARs was in line with expectations and corresponds to the literature data.

SAFETY RESULTS (continued):

Subjects experienced mostly mild ARs (just for 3 subjects severe ARs were reported). Relatedness to the study drug for ARs was reported mostly as 'Possible' and only for 7 subjects ARs were judged as certainly related to the study drug.

There were altogether 49 unexpected adverse reactions which occurred in 46 subjects yielding an overall incidence of 5.4 %. The incidence per therapeutic group ranged from 0,8 % in OA 40/5 group to 12.3 % in O 20 group. In the majority of cases the AR were reported as a single event.

Laboratory parameters results were comparable between the treatment groups. The average of the mean values of all parameters at baseline were quite similar in all treatment groups and no relevant differences were observed in the mean change from baseline (week 0) at the end of therapy (week 8). Similarly, the safety results of assessed key ECG parameters, vital signs and physical findings were similar in all treatment groups. No significant decrease or increase in average values of key ECG parameters (PR interval, QRS duration and QTc interval), average values of heart rate, average body weight and body temperature was observed.

Few AEs resulted in the premature discontinuation of patients belonging to treatment groups OAFC 20/5, O20, O40, A10 and a total of 9 subjects (1.1%) reported ARs which led to their discontinuation from the study.

There was a single drug related serious AR reported (a syncope in the OA 20/5 group followed by a short hospitalisation) which has recovered quickly with no sequel.

No deaths occurred in the study.

Overall, the safety profile can be considered similar between all treatment groups.

CONCLUSIONS:

In conclusion, the results of KKL172014 show that fixed combination is the effective treatment which was demonstrated by a significant difference versus placebo. The superiority of fixed combination over the monotherapies could not been demonstrated by the primary efficacy endpoint and secondary efficacy endpoints analysis due to the limitations related to study population configuration and to study hypotheses testing.

The safety analysis demonstrated unequivocally that fixed combination is safe and well tolerated in the patients with primary arterial hypertension.

DATE OF THE FINAL INTEGRATED STUDY REPORT: May 19, 2016

2 Appendix 1: Signature page

Study title:
The efficacy and safety of olmesartan medoxomil/amlodipine fixed combination in patients with grade 1 to grade 2 arterial hypertension. An international randomized, double-blind, 10-week multi-factorial clinical study.

I, the undersigned, have written this summary of integrated clinical study report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study

June 16, 2016

Marko Boh, MD, MSc
Sponsor representative

Date

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