These Clinical Trial Results are provided for informational purposes only.

The clinical trial synopses are supplied for information purposes only. The information does not replace the official labelling of a given drug product, which presents benefits and risks of the product for approved use(s) based on an evaluation of an entire research program.

Clinical trials may include approved and non-approved uses, formulations or treatment regimens. The information provided is not intended to promote any product or indication and is not intended to replace the advice of a healthcare professional. If you have questions about this information, please consult a healthcare professional. Before prescribing any Daiichi Sankyo product(s), healthcare professionals should consult prescribing information for the product(s) approved in their country.

2. SYNOPSIS

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Name of Active Ingredients: • Olmesartan medoxomil • Hydrochlorothiazide • Amlodipine besylate		

Title of Study:

Treat-to-target study of olmesartan medoxomil and an add-on treatment algorithm consisting of hydrochlorothiazide and amlodipine besylate in patients with mild to moderate hypertension.

Protocol No. SP-OLM-03-05 OLMETREAT, EudraCT No. 2005-004659-36.

Investigators:

International Coordinating Investigator was [redacted] University of Manchester, Division of Cardiovascular and Endocrine Sciences, 46 Grafton Street, M13 9WL Manchester, United Kingdom.

For a listing of all principal investigators see Appendix 16.1.4.

Study Centre(s):

The trial was located at 58 investigational sites in 9 European countries. The numbers in brackets show the number of active investigational sites in the participating countries: Austria (4), Belgium (6), France (12), Germany (14), Italy (6), The Netherlands (4), Portugal (2), Switzerland (1) and United Kingdom (9).

Publication (reference):

None.

Study Period:	**Phase of Development**:
First patient in: 06 Apr 2006 Last patient out: 08 Apr 2008	Phase IV

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Objectives:

Primary objective:

To evaluate the rates of Subjects Treated to Target (STTT) overall and on each treatment combination step. STTT were defined as patients with mild to moderate hypertension achieving target blood pressure defined as

Non-diabetic patients:
Mean sitting systolic BP (sBP) at trough of ≤130 mmHg **and** mean sitting diastolic BP (dBP) ≤85 mmHg

Diabetic patients:
Sitting systolic BP at trough of <130 mmHg **and** mean sitting diastolic BP <80 mmHg.

Secondary objectives:

- To assess the influence of prognostic factors for the need of a combination therapy (for example: hypertension class [mild/moderate], age [≤65/>65], diabetes [no/yes], gender [female/male], body mass index [BMI]-classes [normal weight/underweight/overweight/obesity], smoking status [non-smoker/exsmoker/smoker], status of pre-treatment [no/yes], target organ damage [TOD] [not known/known]).
- To evaluate the effect of OLM monotherapy and the add-on treatment algorithm overall and on each treatment combination step in terms of normaliser rates, i.e. the percentage of patients achieving a mean sitting sBP at trough of <140 mmHg **and** a mean sitting dBP <90 mmHg for non-diabetic patients or a mean sitting sBP at trough of <130 mmHg **and** a mean sitting dBP <80 mmHg for diabetic patients.
- To evaluate the effect of OLM monotherapy and the add-on treatment algorithm in terms of change of mean sitting sBP and dBP versus baseline at each visit.
- To evaluate the effect of OLM monotherapy and the add-on treatment algorithm in terms of the rate of diastolic responders (defined as a patient who is a normaliser or has a lowering of the mean sitting dBP of ≥10 mmHg at trough) at each visit.
- To evaluate the safety and tolerability of OLM monotherapy and the add-on treatment algorithm consisting of HCTZ and AML after a maximum of 20 weeks of active treatment.

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Other objectives:

In addition, the following questions were addressed as part of the statistical analysis:

- To evaluate the effect of OLM monotherapy and the add-on treatment algorithm in terms of the rate of systolic responders (defined as a patient who is a normaliser or has a lowering of the mean sitting sBP of ≥20 mmHg at trough) at each visit.
- To evaluate the effect of OLM monotherapy and the add-on treatment algorithm in terms of the rate of general responders (defined as a patient who is a normaliser or a diastolic responder or a systolic responder) at each visit.
- To evaluate the effect of OLM monotherapy and the add-on treatment algorithm in terms of changes in hypertension class at each visit.

Trial Hypothesis:

The aim of the study was to estimate the STTT rates and respective confidence intervals at each treatment combination step. Therefore no statistical hypothesis was needed.

Methodology:

This Phase IV trial was a non-comparative, sequential add-on, open-label, multinational, multicentre trial conducted at 58 investigational sites. Washout – Period I (approximately 2 weeks): Period I consisted of a single screening visit for patients not on antihypertensive medication and a washout period for patients on antihypertensive medication(s).

To be eligible for entry into the active treatment phase, all patients had to have a mean sitting sBP ≥140 and <180 mmHg at trough and/or dBP ≥90 and <110 mmHg.
All visits were scheduled at intervals of 4 weeks ± 3 days.
The goal was to reach the target BP, defined as mean sitting sBP of ≤130 mmHg (<130 mmHg for diabetic patients) at trough and mean sitting dBP ≤85 mmHg (< 80 mmHg for diabetic patients) at trough. To achieve this goal, patients were treated with an algorithm consisting of the following sequential steps:
20 mg OLM OD (Period II);
20 mg OLM plus 12.5 mg HCTZ (fixed combination) OD (Period III);
20 mg OLM plus 25 mg HCTZ (fixed combination) OD (Period IV);

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20 mg OLM plus 25 mg HCTZ (fixed combination) plus 5 mg AML OD (Period V);
20 mg OLM plus 25 mg HCTZ (fixed combination) plus 10 mg AML OD (Period VI).

Patients who achieved target blood pressure at any visit during the active treatment period were to be discontinued from the study after conducting the Final Examination Visit (Visit V-FE).

Duration of Treatment:

Duration of every titration step was four weeks, adding up to a maximum of twenty weeks, depending on the time for reaching blood pressure (BP) goal rates.

Number of Patients:

Planned:	720 patients to get approximately 98 patients in the last combination step
Enrolled:	762 patients
Safety Set 1:	694 patients
Safety Set 2:	583 patients
Safety Set 3:	295 patients
Full analysis set:	691 patients
Per protocol set:	457 patients
Not included in Safety Set 1:	68 patients

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Diagnosis and Main Criteria for Inclusion:

Patients with mild to moderate hypertension were included:

- Male or female out-patients aged ≥18 years.
- Treated or non treated patients with mild to moderate essential hypertension: mean sitting sBP ≥140 and <180 mmHg and/or mean sitting dBP ≥90 and <110 mmHg at trough. Pre-treated patients with normal or elevated BP in whom it was medically justifiable to withdraw treatment were also eligible.
- Written informed consent
- Patients without malignant hypertension, history of severe hypertension or mean sitting sBP ≥180 mmHg at trough or mean sitting dBP ≥110 mmHg at trough.
- Patients without unstable BP readings.
- Patients without secondary hypertension.
- Patients without hypotension: sBP <105 mmHg or dBP <60 mmHg.
- Patients without known conditions where excessive blood pressure decrease could have resulted in myocardial infarction or stroke.
- Patients without severe heart failure or other cardiac or valvular diseases.
- Patients without 2nd or 3rd degree AV-block, atrial fibrillation/cardiac arrhythmias, or bradycardia.
- Patients without clinically significant laboratory abnormalities.
- Patients without serious disorders which could have limited the ability to evaluate the efficacy or safety of the test drug(s), including cardiovascular, renal, pulmonary, hepatic, gastrointestinal, endocrine/metabolic, haematological, oncological, neurological and psychiatric diseases.
- Patients without a history of a wasting disease (cancer) within the past 5 years or still requiring treatment.
- Female patients who were not pregnant or nursing
- The participation of female patients of childbearing potential was subject to country specific restrictions and/or requirements regarding contraception.

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Investigational Product and Comparator Information:

Dosage Form: Tablets

Period I (Placebo):	28 tablets
Period II (OLM 20 mg):	42 tablets
Period III (OLM 20 mg plus HCTZ 12.5 mg):	42 tablets
Period IV (OLM 20 mg plus HCTZ 25 mg):	42 tablets
Period V (OLM 20 mg plus HCTZ 25 mg plus AML 5 mg):	42 tablets
Period VI (OLM 20 mg plus HCTZ 25 mg plus AML 10 mg):	42 tablets

Route of Administration: Oral

Lot No.: [redacted]

Batch No.: [redacted] (Placebo)
[redacted] (OLM 20 mg)
(OLM 20 mg plus HCTZ 12.5 mg)
and [redacted] (OLM 20 mg plus HCTZ 25 mg)
[redacted] (ALM 5 mg)
[redacted] IH, [redacted] IH and
[redacted] (AML 10 mg)

Criteria for Evaluation:

Efficacy:

Systolic and diastolic BP: Measurements were taken on the same arm, by the same person, and at the same time of day and were made three times in the sitting position and once standing. Subjects treated to target (STTT) were calculated from the means of the three sitting sBP and dBP measurements.

Safety:

Adverse events (AEs) were documented during the whole study period and were coded according to the Medical Dictionary for Regulatory Activities (MedDRA®) Version 11.0 for analysis. Furthermore, vital signs, 12-lead electrocardiographic examinations (ECG), physical examinations, clinical haematology, blood chemistry and urinalysis results (including urine pregnancy tests if applicable) were documented.

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Statistical Methods:

To analyse the primary efficacy parameter, the STTT rate was estimated overall and on each treatment step, with a two-sided 95% confidence interval using the normal approximation to the binomial distribution. The analysis of the primary endpoint primarily was performed using the full analysis set (FAS) and last observation carried forward (LOCF) approach, but was additionally performed on the per-protocol (PP) set to evaluate the robustness of the results

In an exploratory analysis, potential prognostic factors were assessed by logistic regression to investigate indicators for the need of a double or triple combination therapy, respectively, in order to reach the BP target.

Safety analyses were performed on the safety set that consisted of all patients who received OLM at least once (Safety Set 1), who received HCTZ at least once (Safety Set 2), and who received AML at least once (Safety Set 3), respectively.

Summary:

Efficacy Results:

Between April 2006 and April 2008 this European study recruited 762 patients with mild to moderate hypertension according to the guidelines of the European Society of Cardiology and the European Society of Hypertension (ESC/ESH). Of these patients, 694 started treatment with an add-on treatment algorithm consisting of olmesartan medoxomil (OLM), hydrochlorothiazide (HCTZ) in two different doses, and amlodipine besylate (AML) in two different doses, with the aim to achieve systolic and diastolic target blood pressure. Target blood pressure was defined as a mean sitting systolic BP (SBP) at trough of ≤ 130 mmHg and mean sitting diastolic BP (DBP) ≤ 85 mmHg (non-diabetic patients; diabetic patients: sitting systolic BP at trough of < 130 mmHg and mean sitting diastolic BP < 80 mmHg).

The study was successful in obtaining its primary objective, i.e. to provide data on the rates of subjects who reached the defined blood pressure target overall and at every treatment step (STTT, i.e. Subjects Treated to Target).

Overall, 71.8% of patients reached the defined blood pressure target (95% Confidence Interval CI: 68.4-75.1%; Full Analysis Set FAS; Per Protocol Set PPS: 84.5%; 95% CI: 81.1-87.8%). Approximately every eighth patient achieved the target under monotherapy with OLM 20 mg (12.3%; 95% CI: 9.9–14.7%; FAS). The STTT rates increased under combination therapy with HCTZ (+12.5 mg: 16.4%; 95% CI: 13.6-19.1; +25 mg: 19.2%; 95% CI: 16.3-22.2; FAS). The addition of AML converted further patients to target;

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however, the STTT rates were somewhat smaller than these achieved by the addition of HCTZ (+5 mg: 14.9%; 95% CI: 12.3-17.6%; +10 mg: 8.5%; 95% CI: 6.5-10.6%; FAS). STTT rates for the PPS followed the same pattern, but were up to approximately 5% higher. As the most frequent reason for exclusion from the PPS was non-observance of the visit schedule, this indicates that patient discipline is an important requirement for successful antihypertensive therapy.

Normaliser and responder rates were between 85% and 96% (FAS; PPS: 91% to 98%) and thus higher than STTT rates. This is expected because the definitions differed from and were less strict than those for STTT. However, the same pattern regarding the combination of drugs applied as for STTTs: Additional efficacy by combining OLM with HCTZ and AML, with HCTZ achieving the larger step. Changes of ESC/ESH hypertension classes were in line with the results for STTTs, normaliser and responder rates. Whereas at baseline 98.8% of patients (FAS) suffered from mild to moderate hypertension, this percentage decreased continuously over time. At the last available assessment, only 12.6% of patients were in these two hypertension classes and two third of patients had normal or optimal blood pressure.

The sitting diastolic blood pressure started at a mean baseline value of 94.7±7.0 mmHg and decreased considerably to 79.0±6.9 mmHg at the last available assessment (FAS). Changes were largest early in the study (Baseline to Week 4: -6.4±7.5 mmHg; FAS) and decreased to approximately half this effect at the later visits. At the last available assessment, the decrease vs. baseline was 16.8±7.2 mmHg. The addition of HCTZ and AML to OLM again showed an additional effect, with that of HCTZ being the larger one. However, here the largest single effect of all was that of OLM. This pattern was comparable for sitting systolic blood pressure, which started at 158.1±11.8 mmHg and decreased by 11.97±11.4 mmHg until Week 4 and by 29.6±13.5 mmHg until the last available assessment (FAS), and also for standing blood pressure measurements.

The investigators' efficacy assessment appeared to correlate with the normaliser and responder rates, with 90% good or very good ratings (FAS; PPS: 94%). Only in 3% of patients (FAS; PPS: 2%) investigators rated the treatment algorithm as insufficiently effective.

Data were evaluated for prognostic factors indicating a need for combination therapy. Results varied to a certain extent between analysis populations and the need for double or triple therapy. However, moderate to severe baseline hypertension (Odds ratio OR: 2.45–5.81; FAS) and the presence of diabetes (OR: 2.74-3.60; FAS) indicated an overall need for combination therapy. An abnormal BMI (OR=1.77; FAS) predisposed to a need for double, but not triple therapy, whereas age > 65 years (OR=1.82; FAS) and pre-treatment of hypertension (OR=1.72; PPS) indicated a need for triple, but not double therapy.

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The subject selection criteria in this study generally reflected the requirements of the Summaries of Product Characteristics (SmPCs) of the involved study medication, and there were no criteria which artificially skewed or modelled the patient sample. The demographics of the patients indicate a middle aged (58±12 years), moderately obese (BMI 29±5 kg/m²) population with an approximately even gender balance, frequent dyslipidaemia and diabetes (39% and 13%, respectively) and insufficient antihypertensive therapy (40% untreated), despite a considerable history of hypertension (mean duration 5.7±6.6 years). Accordingly the efficacy results seen in this study appear representative for a typical population of mildly to moderately hypertensive patients seen by European cardiologists, internists or general practitioners.

Safety Results:

Patient exposure to OLM was approximately 164 patient years, to HCTZ (both doses) approximately 113 patient years, and to AML (both doses) approximately 35 patient years. Of all 694 patients receiving one or more of the study drugs, 271 (39%) experienced at least one treatment emergent adverse event (AE), 137 patients (20%) at least one AE considered at least possibly related to one or more of the study drugs. Seven patients experienced a treatment emergent serious AE, and three additional patients a serious AE before the start of study medication. The investigators assessed none of the treatment emergent serious AEs related to the study medication. Considering the nature of the events, existing concomitant diseases, predisposing disorders, temporal implausibility, and a missing pathophysiological link these assessments are plausible.

In 19 patients (3% of patients receiving one or more of the study drugs) a treatment emergent AE resulted in a discontinuation of the study medication. Study medication was more often than not considered responsible for discontinuations due to gastrointestinal symptoms and nervous system and ear disorders (dizziness, syncope, tinnitus). Thus the adverse events resulting in a discontinuation of study medication reflected the known spectrum of side effects of the study drugs and did not indicate novel safety aspects.

The adverse events affecting more than 1% of patients, regardless of their causal connection with the study medication, were respiratory and urinary infections, dizziness, headache, cough, different upper gastrointestinal symptoms, constipation, musculoskeletal pain, joint swelling, and peripheral oedemas, i.e. events typical for a general population, especially one with hypertension.

Drug related AEs affecting at least two patients were checked against the SmPCs for labelledness. With the exception of one case of a benign neoplasm of the testis (orchioncus), where there is insufficient information to verify or dispel the investigator's causality assessment and where there is no known similar

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precedent, all events were labelled in at least one of the study drugs' SmPCs. This is true also for drug related laboratory AEs, which were all covered by the information in the SmPCs.

Laboratory values showed mainly clinically irrelevant (though sometimes statistically significant) changes over the treatment period, which were consistent with known and labelled effects of the study drugs. No changes of laboratory values were considered as serious adverse events or as otherwise significant. No patient discontinued the study due to laboratory adverse events.

Investigators rated the tolerability of the study treatment as good or very good in 93% of patients (FAS; PPS: 97%). Only in 2% of patients (FAS; PPS: 0.4%) the investigators regarded tolerability as insufficient.

Accordingly the adverse events observed and other safety data evaluated in this study do not indicate novel safety aspects of the study medication.

Conclusions:

This study addressed two relevant questions in daily medical practice – is it possible to treat hypertensive patients to internationally recommended target blood pressure values and how has treatment to be structured to achieve this goal?

The study was characterised by wide in- and exclusion criteria to select hypertensive patients representative for the daily population seen by cardiologists, internists or general practitioners, and this is a patient sample with an accumulation of cardiovascular risk factors. Over 80% were overweight or obese, approximately 40% were dyslipidaemic, and almost every seventh patient had a diagnosis of diabetes mellitus. Every fourth patient was 67 years or older and thus elderly or very elderly and 5–6% of patients had target organ damage like atherosclerosis or left ventricular hypertrophy. In every fourth patient hypertension had been known for eight years or longer, with an astonishing 40% of patients hitherto untreated. With only 3–8% creatinine and urea serum values outside the upper normal range at study start, renal dysfunction was less frequent than might be expected in this population. However, patients with more severe renal disorders were excluded a priori from the study because of the known effects of the study medication (Angiotensin receptor blocker, diuretic) on renal function.

Approximately three quarters (72%) of the study patients reached an ambitious blood pressure target, i.e. a trough mean sitting BP $\leq$ 130/85 mmHg for non-diabetics and < 130/80 mmHg for diabetics. Under monotherapy with OLM 20 mg 12% of patients achieved this target. Although the patients suffered from only mild (44%) to moderate (55%) hypertension, with <1% in other categories, the majority required

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combination therapy. In line with ESC/ESH recommendations, a diuretic (HCTZ) and a calcium channel blocker (AML) were chosen as add-on therapy options. Additional 36% of patients achieved the target after adding HCTZ 12.5 or 25 mg to OLM, 23% after the addition of AML 5 or 10 mg to the OLM + HCTZ combination.

Study treatment showed an impressive influence on the distribution of patients to hypertension classes. Whereas at baseline only 0.1% of patients showed normal or optimal blood pressure, the conversion rates to these classes increased to approximately 30% at the later visits. At the last available individual assessment, only 13% of patients still had mild or moderate hypertension, whereas 21% were classified as high normal, 56% as normal and 10% even as optimal, i.e. two third of patients had normal or optimal blood pressure.

The antihypertensive efficacy of the study medication was generally comparable to that in previous studies. In this study OLM 20 mg as monotherapy achieved a reduction of trough sitting BP of approximately 12/6 mmHg, compared to previous data showing a reduction of 10/6 mmHg over placebo). Estimating the effect of HCTZ 25 mg from blood pressure reductions between visits, it reduced trough sitting BP by approximately 17/9 mmHg (previous data: 16/11 mmHg, when added to OLM monotherapy). AML had previously converted additional 20% of patients to target blood pressure when added to OLM/HCTZ treatment, compared to 23% in this study.

Overall blood pressure reduction (30/17 mmHg) and achievement of target blood pressure (72%) were somewhat smaller in this study compared to a previous study with a similar design (34/18 mmHg and 88%, respectively). However, the previous (smaller) study used OLM at a dose of 40 mg, which is somewhat more effective than the 20 mg dose. Furthermore, the current study applied a stricter blood pressure target criterion, in that diabetic patients had to achieve lower values.

The study did not reveal novel safety information. Side effects were in line with previous knowledge and the labelling of the study medication. No serious drug related adverse events occurred. All study medication was generally well tolerated.

Besides confirming the usefulness – and tolerability – of combination therapy for achieving ambitious blood pressure targets (and the feasibility of actually reaching them), the study evaluated risk factors predicting a need for double or triple combination therapy. Such risk factors were moderate to severe hypertension, diabetes, an abnormal BMI, age > 65 years, and pre-treatment of hypertension, the latter possibly related to the severity of hypertension and other cardiovascular risk factors. These predictive factors were present in a considerable proportion of patients. This indicates that many patients even with mild to moderate hypertension may not do sufficiently well on monotherapy but may require a combination

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of different antihypertensive drugs. If the predictive value of these criteria is confirmed, they may help identify patients who should a priori be started on antihypertensive combination therapy.		
Date of the Report: 30 Mar 2009		