Annex 29 **1**
to the Procedure for Conducting Expert Evaluation of Registration Materials Pertinent to Medicinal Products Submitted for the State Registration (Re-Registration) and for Expert Evaluation of Materials about Introduction of Changes to Registration Materials during the Validity Period of Registration Certificate (item 4 section IV)

Preclinical study report

1. Name of medicinal product (registration certificate №, if any):	ATTENTO® PLUS 40/10/25
1) type of medicinal product according to which registration has been conducted or is planned to be conducted	Medicinal product with fixed combination
2) studies conducted	yes
2. Pharmacology:	
1) Primary pharmacodynamics	Not required for products where there is sufficiently documented human experience of their individual and combined use, according to the Guideline on the non-clinical development of fixed combinations of medicinal products, EMEA/CHMP/SWP/258498/2005, 24-Jan-2008
2) Secondary pharmacodynamics	As above
3) Safety pharmacology	As above
4) Pharmacodynamic interactions	As above
3. Pharmacokinetics:	
1) Analytical Methods and validation reports	Method Validation for the quantitation of RNH-6270 (research code of olmesartan, the active metabolite of olmesartan medoxomil), amlodipine, and hydrochlorothiazide in rat plasma by turbo ion spray LC/MS/MS. The method has been validated in the calibration range 10 to 10000 ng/mL for RNH-6270 and hydrochlorothiazide and 1 to 1000 ng/mL for amlodipine, with acceptable values of intra- and inter-assay precision and accuracy.
2) Absorption	Not required for products where there is sufficiently documented human experience of their individual and combined use and without pharmacokinetics interactions, according to the Guideline on the non-clinical development of fixed combinations of medicinal products, EMEA/CHMP/SWP/258498/2005, 24-Jan-2008
3) Distribution	As above
4) Metabolism	As above
5) Excretion	As above
6) Pharmacokinetic Interactions (preclinical)	As above

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7) Other Pharmacokinetic Studies	As above
4. Toxicology:	
1) Single-Dose Toxicity	Not required according to the Questions and Answers on the withdrawal of the "Note for guidance on single dose toxicity", EMA/CHMP/SWP/81714/2010, 24-Jun-2010
2) Repeat-Dose Toxicity	-Study AN07-C0154-R01 (C-B394) with toxicokinetics (Study: AN07-C0169-R01 (080137)): 28-day repeat doses (OM/HCTZ/AML: 0/0/0 (Control), 100/62.5/0, 100/62.5/10, 100/62.5/20, 50/31.25/20, and 0/0/20 administered by gavage in male and female rats. The main aim of this study was the selection of adequate doses to be used in the pivotal 3-month repeat dose study (see below). No death occurred in any group. Body weight gain and food intake were reduced in all groups treated with OM/HCTZ/AML as well as in the 100/62.5/0 group (OM/HCTZ), although with milder effects. Likewise, most of urinalysis, hematological, clinical chemistry findings, and histopathological findings observed in OM/HCTZ/AML-treated groups were also observed in the OM/HCTZ group and in a few cases in the AML group (0/0/20). Some changes seemed to be intensified in the OM/HCTZ groups as compared with OM/HCTZ group, but these changes were mostly related to the severity of suppressed body weight gain. Indeed, toxicokinetic results indicate the exposures to RNH-6270 and HCTZ were increased by co-administration with AM as a consequence of exaggerated pharmacological effects of AML (enhanced absorption of OM and HCTZ due to the delayed gastrointestinal transit) explaining the greater reduction of body weight gain observed in OM/HCTZ/AML-treated groups. This enhanced absorption of OM and HCTZ induced by AML has not been observed in the clinical setting. -Study AN08-C0045-R01 (B-6493) with toxicokinetics (Study: AN08-C0093-R01 (080761)): 3-month repeat doses (OM/HCTZ/AML: 0/0/0 (Control), 100/62.5/0, 100/62.5/10, 100/62.5/20, 30/18.75/20, and 0/0/20 administered by gavage in male and female rats. No treatment-related deaths occurred and no abnormal clinical signs or ophthalmology findings were observed in any dose group. A greater reduction of body weight gain was observed in all OM/HCTZ/AML-treated groups, as compared with OM/HCTZ (100/62.5/0) and AML (0/0/20) groups. In urinalysis an increase in urinary volume and water intake, and a decrease of osmotic pressure, pH and changes

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Annex 30
to the Procedure for Conducting Expert Evaluation of Registration Materials Pertinent to Medicinal Products Submitted for the State Registration (Re-Registration) and for Expert Evaluation of Materials about Introduction of Changes to Registration Materials during the Validity Period of Registration Certificate (item 4 section IV)

1

Clinical study report 1

1. Name of medicinal product (registration certificate №, if available)	ATTENTO ® PLUS 40/10/25 mg
2. Applicant	Menarini International Operations Luxembourg S.A., Luxembourg
3. Manufacturer	Daiichi Sankyo Europe GmbH, Germany (Manufacturing "in bulk", packaging, batch control and release) Berlin-Chemie AG, Germany (Packaging, batch control and release) Menarini - Von Heyden GmbH, Germany (Batch control and release)
4. Studies conducted:	yes
1) type of medicinal product, which has been or will be registered	Medicinal product with fixed combination
5. Title of clinical trial, code number of clinical trial	CS8635-A-E105 An open label, phase I, four-period crossover study in healthy subjects to assess the bioequivalence of the highest and the lowest dose CS-8635 market image formulations to reference trial formulations and dose proportionality of CS-8635 market image formulations
6. Phase of clinical trial	Phase I
7. Period of clinical trial	from 29 Sep 2008 till 03 Mar 2009
8. Countries, where clinical trial has been conducted	Northern Ireland
9. Number of trial subjects	planned: 72 actual: 57 (completed)
10. Objective and secondary endpoints of clinical trial	Primary: To compare the pharmacokinetics (PK) of olmesartan (OM), amlodipine (AML) and hydrochlorothiazide (HCT) when administered as market image formulations (MIF) versus the two reference clinical formulations at the strengths of 40/10/25 (OM/AML/HCT) and 20/5/12.5 mg. Secondary: To determine the dose proportionality of 2 dose levels of CS-8635 MIF; to compare the PK of HCT when administered as a component in Reference Clinical Formulation I (Benicar HCT®) and Reference Clinical Formulation II (HCT); to evaluate the safety and tolerability of the CS-8635

<table>
<tr><td></td><td>MIF at its highest and lowest strengths dose (HD and LD) combinations</td></tr>
<tr><td>11. Clinical trial design</td><td>Phase I, open-label, 4-period crossover study</td></tr>
<tr><td>12. Main inclusion criteria</td><td>Subjects were healthy males and females, 18 to 45 years of age. Female subjects were sterile, post-menopausal or using acceptable contraception.</td></tr>
<tr><td>13. Investigational medicinal product, mode of administration and strength</td><td>Treatment A HD-MIF: CS-8635 40 mg/10 mg/ 25 mg p.o. once daily

Treatment B: LD-MIF: CS-8635 20 mg/5 mg/12.5 mg p.o. once daily</td></tr>
<tr><td>14. Reference product, dose, mode of administration and strength</td><td>Treatment C: HD-RFI: Benicar® HCT 40/25 mg, Antacal® 10 mg p.o. once daily

Treatment D: LD-RFI Benicar® HCT 20/12.5 mg, Antacal® 5 mg p.o. once daily

Treatment: E: HD-RFII Azor ® 40/10 mg; Hydrochlorothiazide 25 mg

Treatment F: LD-RFII Azor® 20/5 mg, hydrochlorothiazide 12.5 mg</td></tr>
<tr><td>15. Concomitant therapy</td><td>None</td></tr>
<tr><td>16. Criteria for evaluation efficacy</td><td>The 90% Confidence Interval (CI) of the ratios of geometric least square means for the PK parameters AUC_{last}, $AUC_{0\text{-}inf}$ and C_{max} for each analyte (OM/AML/HCT) of the CS-8635 MIF to the reference clinical formulations at each strength.</td></tr>
<tr><td>17. Criteria for evaluation safety</td><td>Safety assessments included Adverse Events, clinical laboratory measurements, vital signs, physical examinations and ECGs</td></tr>
<tr><td>18. Statistical methods</td><td>Analysis of Variance (ANOVA) with sequence, treatment, period as factors. Each ANOVA included calculation of least square means (LSM), the difference between treatment LSM, and the standard error associated with the difference.</td></tr>
<tr><td>19. Demographic indices of studied population (sex, age, race, etc.)</td><td>
<table>
<tr><th colspan="2">Demographic Trait</th><th>Cohort 1
Overall</th><th>Cohort 2
Overall</th><th>Overall</th></tr>
<tr><td>Gender N (%)</td><td>Male</td><td>27 (75.0%)</td><td>26 (72.2%)</td><td>53 (73.6%)</td></tr>
<tr><td></td><td>Female</td><td>9 (25.0%)</td><td>10 (27.8%)</td><td>19 (26.4%)</td></tr>
<tr><td>Ethnicity N (%)</td><td>Not Hispanic/Latino</td><td>36 (100.0%)</td><td>36 (100.0%)</td><td>72 (100.0%)</td></tr>
<tr><td>Race N (%)</td><td>Black</td><td>1 (2.8%)</td><td>0 (0.0%)</td><td>1 (1.4%)</td></tr>
<tr><td></td><td>Caucasian</td><td>35 (97.2%)</td><td>36 (100.0%)</td><td>71 (98.6%)</td></tr>
<tr><td>Age (yr)</td><td>Mean ± SD</td><td>28.9 ± 6.62</td><td>28.6 ± 7.80</td><td>28.7 ± 7.19</td></tr>
<tr><td></td><td>Median (Min – Max)</td><td>27.0 (19 – 45)</td><td>28.5 (18 – 44)</td><td>27.5 (18 – 45)</td></tr>
<tr><td>Height (cm)</td><td>Mean ± SD</td><td>175.4 ± 8.49</td><td>172.3 ± 9.44</td><td>173.8 ± 9.05</td></tr>
<tr><td></td><td>Median (Min – Max)</td><td>176.5 (157 – 194)</td><td>174.0 (151 – 191)</td><td>175.0 (151 – 194)</td></tr>
<tr><td>Weight (kg)</td><td>Mean ± SD</td><td>76.84 ± 11.431</td><td>74.60 ± 12.930</td><td>75.72 ± 12.169</td></tr>
<tr><td></td><td>Median (Min – Max)</td><td>78.20 (56.8 – 108.6)</td><td>76.95 (44.0 – 95.4)</td><td>77.75 (44.0 – 108.6)</td></tr>
<tr><td>BMI (kg/m^2)</td><td>Mean ± SD</td><td>24.944 ± 2.9188</td><td>24.955 ± 2.8389</td><td>24.949± 2.8588</td></tr>
<tr><td></td><td>Median (Min – Max)</td><td>25.045 (18.55 – 29.89)</td><td>25.260 (19.30 – 29.92)</td><td>25.090 (18.55 – 29.92)</td></tr>
</table>
</td></tr>
</table>

20. Efficacy results	**Statistical Comparisons of the PK Parameters of HCT between the High Dose CS-8635 MIF and Reference Formulations - Cohort 1**

Parameters	Geometric LSM			Ratio of Geometric LSM and 90% CI (%)	
	Treatment A Test	Treatment C Reference I	Treatment E Reference II	A/C	A/E
AUC_{last} (ng·h/mL)	1152	1133	1194	101.66 (96.83, 106.73)	96.50 (91.83, 101.40)
AUC_{0-inf} (ng·h/mL)	1177	1159	1219	101.57 (96.86, 106.51)	96.58 (92.02, 101.37)
C_{max} (ng/mL)	183.6	178.1	177.9	103.11 (94.13, 112.95)	103.25 (94.01, 113.39)

Source: Table 16.4.1.2.2

Statistical Comparisons of the PK Parameters of HCT between the Low Dose CS-8635 MIF and Reference Formulations - Cohort 2

Parameters	Geometric LSM			Ratio of Geometric LSM and 90% CI (%)	
	Treatment B Test	Treatment D Reference I	Treatment F Reference II	B/D	B/F
AUC_{last} (ng·h/mL)	562.6	576.8	560.5	97.53 (93.53, 101.69)	100.37 (96.30, 104.61)
AUC_{0-inf} (ng·h/mL)	584.8	597.4	580.5	97.89 (94.11, 101.84)	100.75 (96.89, 104.76)
C_{max} (ng/mL)	91.90	86.44	80.94	106.32 (97.33, 116.14)	113.53 (104.03, 123.91)

Source: Table 16.4.1.2.2

Statistical Comparisons of the PK Parameters of HCT between the High Dose Reference Formulations of 25 mg HCT and 40/25 mg Benicar HCT® - Cohort 1

Parameters	Geometric LSM		Ratio of Geometric LSM (C/E) and 90% CI (%)
	Treatment C Test	Treatment E Reference	
AUC_{last} (ng·h/mL)	1133	1194	94.92 (90.25, 99.83)
AUC_{0-inf} (ng·h/mL)	1159	1219	95.09 (90.52, 99.89)
C_{max} (ng/mL)	178.1	177.9	100.13 (91.14, 110.02)

Source: Table 16.4.1.2.3

Statistical Comparisons of the PK Parameters of HCT between the Low Dose Reference Formulations 12.5 mg HCT and 20/12.5 mg Benicar HCT® - Cohort 2

Parameters	Geometric LSM		Ratio of Geometric LSM (D/F) and 90% CI (%)
	Treatment D Test	Treatment F Reference	
AUC_{last} (ng·h/mL)	576.8	560.5	102.92 (98.78, 107.22)
AUC_{0-inf} (ng·h/mL)	597.4	580.5	102.92 (99.02, 106.97)
C_{max} (ng/mL)	86.44	80.94	106.78 (97.88, 116.50)

Source: Table 16.4.1.2.3

21. Safety results	There were no deaths or SAEs during the study. Overall, a total of 263 TEAEs were reported by 59 subjects. 31 Subjects in cohort 1 reported 137 adverse events and a total of 28 subjects from cohort 2. The most frequently reported TEAEs were headache (37.5%), followed by dizziness (33.3%), oropharyngeal pain (20.8%), nausea (16.7%) cough (15.3%) and nasal congestion (12.5%)
22. Conclusion (summary)	The high dose CS-8635 MIF was bioequivalent to the reference formulations of 40/25 mg Benicar HCT® coadministered with 10 mg Antacal® and 40/10 mg Azor® coadministered with 25 mg HCT. The low dose CS-6835 MIF was bioequivalent to the reference formulation of 20/12.5 mg Benicar HCT® coadministered with 5 mg Antacal® and 20/5 mg Azor® coadministered with 12.5 mg HCT:
Applicant (registration	

certificate holder)	(signature) Dr. Kai Schumacher (full name)

Clinical study report 2

1. Name of medicinal product (registration certificate №, if available)	ATTENTO ® PLUS 40/10/25 mg **5**
2. Applicant	Menarini International Operations Luxembourg S.A., Luxembourg
3. Manufacturer	Daiichi Sankyo Europe GmbH, Germany (Manufacturing "in bulk", packaging, batch control and release) Berlin-Chemie AG, Germany (Packaging, batch control and release) Menarini - Von Heyden GmbH, Germany (Batch control and release)
4. Studies conducted:	yes
1) type of medicinal product, which has been or will be registered	Medicinal product with fixed combination
5. Title of clinical trial, code number of clinical trial	CS-8635-A-U103 A randomized, open-label, single-dose crossover study to determine the bioavailability of olmesartan, amlodipine and hydrochlorothiazide administered together as CS-8635 pilot formulation A or separately as Benicar HCT® (olmesartan and hydrochlorothiazide) plus Antacal® (amlodipine) in healthy subjects.
6. Phase of clinical trial	Phase I
7. Period of clinical trial	10 Jan 2008 to 03 Apr 2008
8. Countries, where clinical trial has been conducted	USA
9. Number of trial subjects	planned: 41 actual:28 (completed)
10. Objective and secondary endpoints of clinical trial	Primary: to determine the relative bioavailability of olmesartan, amlodipine and hydrochlorothiazide when administered as a fixed dose formulation (CS-8635 pilot formulation A) and as two-tablet regime (Benicar HCT® plus Antacal®). Secondary: to assess the safety and tolerability of CS-8635 pilot formulation A).
11. Clinical trial design	Open-label, randomized, 2-way crossover study
12. Main inclusion criteria	Subjects enrolled were healthy adult men and women aged 18-45 years (inclusive) who satisfied all inclusion/exclusion criteria
13. Investigational medicinal product, mode of administration and strength	Treatment A: CS-8635 (olmesartan medoxomil 40 mg/amlodipine besylate 10 mg/HCT 25 mg) pilot formulation A
14. Reference product, dose, mode of administration and strength	Benicar HCT® 40/25 mg tablets Antacal ® 10 mg tablets
15. Concomitant therapy	None
16. Criteria for evaluation efficacy	AUC0-t, AUC, 0-Inf, AUC%extr, Cmax, Tmax, Lambda Z, t1/2 and CL/F
17. Criteria for evaluation safety	Number and severity of TEAEs, physical examination, vital signs, 12-lead ECGs and laboratory

measurements

18. Statistical methods

An analysis of variance (ANOVA) was performed on the ln-transformed AUC0-last, AUC0-Inf and Cmax for olmesartan, amlodipine and hydrochlorothiazide. The ANOVA model included sequence, treatment and period as fixed effects.

19. Demographic indices of studied population (sex, age, race, etc.)

Trait		Treatment Sequence AB (N = 21)	BA (N = 20)	Overall (N = 41)
Gender N(%)	Male	18 (85.7%)	18 (90.0%)	36 (87.8%)
	Female	3 (14.3%)	2 (10.0%)	5 (12.2%)
Race N(%)	American Indian/ Alaskan Native	1 (4.8%)	0	1 (2.4%)
	Asian	0	2 (10.0%)	2 (4.9%)
	Black or African American	10 (47.6%)	16 (80.0%)	26 (63.4%)
	White	10 (47.6%)	2 (10.0%)	12 (29.3%)
Ethnicity N(%)	Hispanic or Latino	7 (33.3%)	4 (20.0%)	11 (26.8%)
	Not Hispanic or Latino	14 (66.7%)	16 (80.0%)	30 (73.2%)
Age (yr)	Mean ± SD	34.5 ± 7.97	30.0 ± 6.36	32.3 ± 7.49
	Median (Min – Max)	38.0 (21-44)	28.5 (22-42)	33.0 (21-44)
Height (cm)	Mean ± SD	176.2 ± 10.30	179.1 ± 8.57	177.6 ± 9.49
	Median (Min – Max)	178.0 (156-198)	179.5 (161-193)	178.0 (156-198)
Weight (kg)	Mean ± SD	84.08 ± 14.060	83.99 ± 13.379	84.03 ± 13.560
	Median (Min – Max)	82.70 (63.4-108.2)	85.50 (61.2-106.5)	84.90 (61.2-108.2)
BMI (kg/m^2)	Mean ± SD	27.08 ± 3.885	26.16 ± 3.384	26.63 ± 3.634
	Median (Min – Max)	28.81 (19.1-32.0)	26.68 (19.7-31.2)	27.25 (19.1-32.0)

20. Efficacy results

Olmesartan	Treatment A N = 31	Treatment B N = 30
AUC_{last} (ng·h/mL) Arithmetic Mean ±SD	6632.3 ± 1715.48	6745.2 ± 1916.63
Geometric Mean (CV%)	6423.9 (25.7%)	6538.0 (24.8%)
AUC_{0-inf} (ng·h/mL)* Arithmetic Mean ±SD	6706.8 ± 1798.62	6793.5 ± 1911.67
Geometric Mean (CV%)	6493.7 (25.9%)	6588.7 (24.3%)
C_{max} (ng/mL) Arithmetic Mean ±SD	986.3 ± 316.35	988.8 ± 270.97
Geometric Mean (CV%)	941.4 (31.5%)	958.7 (25.0%)
T_{max} (h) Median (Min, Max)	1.9830 (0.983, 4.00)	1.742 (1.00, 3.00)
$t_{\frac{1}{2}}$ (h)* Arithmetic Mean ±SD	18.457 ± 10.2844	17.238 ± 8.3481
CL/F* (L/h) Arithmetic Mean ±SD	6.351 ± 1.5706	6.227 ± 1.3211

	Geometric LSMEANS				
PK Parameter	Treatment A (Test)	Treatment B (Reference)	Ratio of LSMEANS (%) (A/B)	90% C.I. for Ratio (%)	Intra-Subject CV (%)
AUC_{0-inf}	6457	6393	101.00	(95.51, 106.80)	12.2
AUC_{last}	6405	6341	101.01	(95.70, 106.61)	12.0
C_{max}	941.6	929.1	101.35	(94.05, 109.22)	16.7

Amlodipine	Treatment A N = 31	Treatment B N = 30
AUC_{last} (ng·h/mL) Arithmetic Mean ±SD	359.5 ± 90.69	331.8 ± 90.92
Geometric Mean (CV%)	347.4 (28.1%)	319.4 (29.1%)
AUC_{0-Inf} (ng·h/mL) Arithmetic Mean ±SD	406.5 ± 114.61	373.1 ± 110.16
Geometric Mean (CV%)	389.7 (31.2%)	356.8 (31.7%)
C_{max} (ng/mL) Arithmetic Mean ±SD	7.117 ± 1.8022	6.797 ± 1.7252
Geometric Mean (CV%)	6.896 (26.4%)	6.601 (24.8%)
T_{max} (h) Median (Min, Max)	8.017 (5.98, 12.0)	7.509 (6.00, 16.0)
$t_{\frac{1}{2}}$ (h) Arithmetic Mean ±SD	43.57 ± 10.973	43.15 ± 8.853
CL/F (L/h) Arithmetic Mean ±SD	26.92 ± 9.289	29.39 ± 9.566

	Geometric LSMEANS				
PK Parameter	Treatment A (Test)	Treatment B (Reference)	Ratio of LSMEANS (%) (A/B)	90% C.I. for Ratio (%)	Intra-Subject CV (%)
AUC_{0-inf}	387.6	362.4	106.96	(102.93, 111.13)	8.5
AUC_{last}	346.0	323.2	107.05	(102.97, 111.30)	8.6
C_{max}	6.878	6.599	104.22	(99.59, 109.06)	10.0

Hydrochlorothiazide	Treatment A N=31	Treatment B N=31
AUC_{last} (ng·h/mL) Arithmetic Mean ±SD Geometric Mean (CV%)	1177.3 ± 234.22 1152.0 (22.1%)	1170.6 ± 229.05 1147.0 (21.4%)
AUC_{0-inf} (ng·h/mL) Arithmetic Mean ±SD Geometric Mean (CV%)	1202.8 ± 233.90 1178.7 (21.3%)	1195.2 ± 229.33 1172.0 (21.0%)
C_{max} (ng/mL) Arithmetic Mean ±SD Geometric Mean (CV%)	186.48 ± 53.543 178.48 (31.9%)	177.05 ± 40.209 172.14 (25.5%)
T_{max} (h) Median (Min, Max)	1.4830 (0.983, 3.00)	1.5000 (0.983, 3.00)
$t_{\frac{1}{2}}$ (h) Arithmetic Mean ±SD	10.843 ± 1.7363	10.457 ± 1.2373
CL/F (L/h) Arithmetic Mean ±SD	21.70 ± 5.130	21.81 ± 5.126

	Geometric LSMEANS				
PK Parameter	Treatment A (Test)	Treatment B (Reference)	Ratio of LSMEANS (%) (A/B)	90% C.I. for Ratio (%)	Intra-Subject CV (%)
AUC_{0-inf}	1158	1169	99.03	(93.69, 104.67)	12.4
AUC_{last}	1132	1145	98.87	(93.29, 104.78)	13.0
C_{max}	176.0	172.4	102.09	(92.50, 112.69)	22.5

21. Safety results	The concomitant oral administration of olmesartan medoxomil 40 mg, amlodipine besylate 10 mg, and hydrochlorothiazide 25 mg was safe and well tolerated in this group of healthy subjects and no differences in the frequency of TEAEs between the two formulations were observed.
22. Conclusion (summary)	The triple fixed dose combination (CS-8635 pilot formulation A) is bioequivalent to the Benicar HCT® plus Antacal® regimen.
Applicant (registration certificate holder)	 (signature) Dr. Kai Schumacher (full name)

Clinical study report 3

1. Name of medicinal product (registration certificate №, if available)	ATTENTO ® PLUS 40/10/25 mg
2. Applicant	Menarini International Operations Luxembourg S.A., Luxembourg
3. Manufacturer	Daiichi Sankyo Europe GmbH, Germany (Manufacturing "in bulk", packaging, batch control and release) Berlin-Chemie AG, Germany (Packaging, batch control and release) Menarini - Von Heyden GmbH, Germany (Batch control and release)
4. Studies conducted:	yes
1) type of medicinal product, which has been or will be registered	Medicinal product with fixed combination
5. Title of clinical trial, code number of clinical trial	CS-8635-A-U104 A randomized, open-label, single-dose crossover study to determine the bioavailability of olmesartan, amlodipine and hydrochlorothiazide administered together as CS-8635 pilot formulation B or separately as Benicar HCT® (olmesartan and hydrochlorothiazide) plus Antacal® (amlodipine) in healthy subjects.
6. Phase of clinical trial	Phase I
7. Period of clinical trial	17 Jan 2008 to 14 Feb 2008
8. Countries, where clinical trial has been conducted	USA
9. Number of trial subjects	planned: 32 actual: 28 (completed)
10. Objective and secondary endpoints of clinical trial	Primary: to determine the relative bioavailability of olmesartan, amlodipine and hydrochlorothiazide when administered as a fixed dose triple component formulation (CS-8635 pilot formulation B) and as two tablet regimen (Benicar HCT® plus Antacal®). Secondary: to assess the safety and tolerability of CS-8635 pilot formulation B
11. Clinical trial design	Open-label, randomized, 2-way crossover study
12. Main inclusion criteria	Subjects enrolled were healthy adult men and women aged 18-45 years (inclusive) who satisfied all inclusion/exclusion criteria
13. Investigational medicinal product, mode of administration and strength	Treatment A: A single dose of CS-8635 pilot formulation B tablet (olmesartan medoxomil 40 mg/amlodipine besylate 10 mg/hydrochlorothiazide 25 mg)
14. Reference product, dose, mode of administration and strength	Treatment B: a single oral dose of Benicar HCT® (olmesartan medoxomil 40 mg/hydrochlorothiazide 25 mg) plus Antacal® (amlodipine besylate 10 mg)
15. Concomitant therapy	None
16. Criteria for evaluation efficacy	AUC_{0-t}, AUC, $_{0-Inf}$, AUC%extr, C_{max}, T_{max}, Lambda Z, $t_{1/2}$ and CL/F
17. Criteria for evaluation safety	Number and severity of TEAEs, physical examination, vital signs, 12-lead ECGs and laboratory measurements

18. Statistical methods

An analysis of variance (ANOVA) was performed on the ln-transformed $AUC_{0\text{-last}}$, $AUC_{0\text{-Inf}}$ and C_{max} for olmesartan, amlodipine and hydrochlorothiazide. The ANOVA model included sequence, treatment and period as fixed effects.

19. Demographic indices of studied population (sex, age, etc.)

Trait		Treatment Sequence AB (N = 16)	BA (N = 16)	Overall (N = 32)
Gender N(%)	Male	12 (75.0%)	13 (81.3%)	25 (78.1%)
	Female	4 (25.0%)	3 (18.8%)	7 (21.9%)
Race N(%)	American Indian/ Alaskan Native	1 (6.3%)	2 (12.5%)	3 (9.4%)
	Asian	1 (6.3%)	0	1 (3.1%)
	Black or African American	10 (62.5%)	11 (68.8%)	21 (65.6%)
	White	4 (25.0%)	4 (25.0%)	8 (25.0%)
Ethnicity N(%)	Hispanic or Latino	7 (43.8%)	7 (43.8%)	14 (43.8%)
	Not Hispanic or Latino	9 (56.3%)	9 (56.3%)	18 (56.3%)
Age (yr)	Mean ± SD	31.1 ± 7.85	32.1 ± 7.61	31.6 ± 7.62
	Median (Min – Max)	30.5 (21-42)	29.5 (23-45)	30.5 (21-45)

20. Efficacy results

Olmesartan	Treatment A N = 30	Treatment B N = 30
AUC_{last} (ng·h/mL) Arithmetic Mean ±SD	6710.5 ± 1777.29	6043.3 ± 1455.81
Geometric Mean (CV%)	6493.8 (26.4%)	5874.0 (24.8%)
$AUC_{0\text{-}Inf}$ (ng·h/mL)* Arithmetic Mean ±SD	6588.0 ± 1732.22	6092.5 ± 1483.37
Geometric Mean (CV%)	6384.0 (25.7%)	5919.1 (25.0%)
C_{max} (ng/mL) Arithmetic Mean ±SD	1006.5 ± 337.39	899.1 ± 277.48
Geometric Mean (CV%)	957.4 (32.5%)	856.9 (32.9%)
T_{max} (h) Median (Min, Max)	2.000 (1.00, 4.00)	1.992 (1.00, 4.00)
$t_{\frac{1}{2}}$ (h)* Arithmetic Mean ±SD	21.022 ± 14.2767	21.874 ± 14.6826
CL/F* (L/h) Arithmetic Mean ±SD	6.456 ± 1.5728	6.961 ± 1.7548

	Geometric LSMEANS				
PK Parameter	Treatment A (Test)	Treatment B (Reference)	Ratio of LSMEANS (%) (A/B)	90% C.I. for Ratio (%)	Intra-Subject CV (%)
$AUC_{0\text{-}Inf}$	6418	5903	108.73	(100.75, 117.33)	16.2
AUC_{last}	6496	5849	111.06	(103.44, 119.24)	15.9
C_{max}	952.7	858.5	110.97	(99.86, 123.32)	23.9

Amlodipine	Treatment A N = 30	Treatment B N = 30
AUC_{last} (ng·h/mL) Arithmetic Mean ±SD	325.6 ± 87.74	308.9 ± 79.03
Geometric Mean (CV%)	315.5 (25.6%)	300.1 (24.6%)
$AUC_{0\text{-}Inf}$ (ng·h/mL) Arithmetic Mean ±SD	355.8 ± 102.19	338.3 ± 96.37
Geometric Mean (CV%)	343.2 (27.4%)	326.4 (27.3%)
C_{max} (ng/mL) Arithmetic Mean ±SD	7.035 ± 2.0205	6.799 ± 1.5532
Geometric Mean (CV%)	6.779 (27.9%)	6.631 (23.0%)
T_{max} (h) Median (Min, Max)	8.009 (6.00, 12.00)	7.050 (4.00, 12.00)
$t_{\frac{1}{2}}$ (h) Arithmetic Mean ±SD	38.43 ± 6.728	38.41 ± 7.517
CL/F (L/h) Arithmetic Mean ±SD	30.15 ± 7.863	31.70 ± 8.366

	Geometric LSMEANS				
PK Parameter	Treatment A (Test)	Treatment B (Reference)	Ratio of LSMEANS (%) (A/B)	90% C.I. for Ratio (%)	Intra-Subject CV (%)
$AUC_{0\text{-}Inf}$	346.5	324.6	106.74	(102.21, 111.48)	9.6
AUC_{last}	318.6	298.2	106.84	(102.37, 111.51)	9.5
C_{max}	6.867	6.523	105.29	(100.77, 110.00)	9.7

	<table><tr><th>Hydrochlorothiazide</th><th>Treatment A N = 30</th><th>Treatment B N = 30</th></tr><tr><td>AUC_{last} (ng·h/mL) Arithmetic Mean ±SD Geometric Mean (CV%)</td><td>1171.6 ± 233.23 1148.9 (20.5%)</td><td>1188.4 ± 267.64 1160.9 (22.1%)</td></tr><tr><td>AUC_{0-inf} (ng·h/mL) Arithmetic Mean ±SD Geometric Mean (CV%)</td><td>1198.8 ± 236.04 1176.1 (20.2%)</td><td>1212.0 ± 267.40 1185.2 (21.6%)</td></tr><tr><td>C_{max} (ng/mL) Arithmetic Mean ±SD Geometric Mean (CV%)</td><td>179.96 ± 54.987 172.13 (31.1%)</td><td>178.9 ± 62.74 170.2 (31.8%)</td></tr><tr><td>T_{max} (h) Median (Min, Max)</td><td>1.5000 (0.967, 4.00)</td><td>1.5000 (0.983, 3.00)</td></tr><tr><td>$t_{\frac{1}{2}}$ (h) Arithmetic Mean ±SD</td><td>10.831 ± 1.3403</td><td>10.508 ± 1.3201</td></tr><tr><td>CL/F (L/h) Arithmetic Mean ±SD</td><td>21.68 ± 4.474</td><td>21.55 ± 4.491</td></tr></table> <table><tr><th></th><th colspan="5">Geometric LSMEANS</th></tr><tr><th>PK Parameter</th><th>Treatment A (Test)</th><th>Treatment B (Reference)</th><th>Ratio of LSMEANS (%) (A/B)</th><th>90% C.I. for Ratio (%)</th><th>Intra-Subject CV (%)</th></tr><tr><td>AUC_{0-inf}</td><td>1174</td><td>1169</td><td>100.39</td><td>(95.70, 105.32)</td><td>10.6</td></tr><tr><td>AUC_{last}</td><td>1147</td><td>1145</td><td>100.11</td><td>(95.34, 105.12)</td><td>10.8</td></tr><tr><td>C_{max}</td><td>171.2</td><td>169.5</td><td>101.01</td><td>(91.05, 112.06)</td><td>23.5</td></tr></table>
21. Safety results	The concomitant oral administration of olmesartan medoxomil 40 mg, amlodipine besylate 10 mg, and hydrochlorothiazide 25 mg was safe and well tolerated in this group of healthy subjects, and no differences in the frequency of TEAEs between the two formulations were observed.
22. Conclusion (summary)	The triple fixed dose combination (CS-8635 pilot formulation B) is bioequivalent to the Benicar HCT® plus Antacal® regimen
Applicant (registration certificate holder)	(signature) Dr. Kai Schumacher (full name)

Clinical study report 4

1. Name of medicinal product (registration certificate №, if available)	ATTENTO ® PLUS 40/10/25 mg **11**
2. Applicant	Menarini International Operations Luxembourg S.A., Luxembourg
3. Manufacturer	Daiichi Sankyo Europe GmbH, Germany (Manufacturing "in bulk", packaging, batch control and release) Berlin-Chemie AG, Germany (Packaging, batch control and release) Menarini - Von Heyden GmbH, Germany (Batch control and release)
4. Studies conducted:	yes
1) type of medicinal product, which has been or will be registered	Medicinal product with fixed combination
5. Title of clinical trial, code number of clinical trial	CS-8663-A-E102 A randomized, open-label, single-dose, three-way crossover study to determine the bioequivalence of 10 mg amlodipine besylate, Istin® (UK) vs. 10 mg amlodipine besylate, Norvasc® (US) and amlodipine besylate, Antacal® (Italy).
6. Phase of clinical trial	Phase I
7. Period of clinical trial	17 Dec 2004 to 28 Feb 2005
8. Countries, where clinical trial has been conducted	Germany
9. Number of trial subjects	planned:18 actual: 18 (completed)
10. Objective and secondary endpoints of clinical trial	Primary: to determine the bioequivalence of three marketed amlodipine besylate formulations: Istin® 10 mg (Pfizer, UK), Norvasc® 10 mg (Pfizer US) and Antacal® 10 mg (Pfizer Italy), each equivalent to 10 mg amlodipine. Secondary: to assess the safety and tolerability of a single dose of amlodipine besylate equivalent to 10 mg amlodipine, Istin® 10 mg (Pfizer, UK), Norvasc® 10 mg (Pfizer US) and Antacal® 10 mg (Pfizer Italy).
11. Clinical trial design	Randomised, open-label, single center study with a three way crossover design.
12. Main inclusion criteria	Subjects enrolled were healthy adult men and women aged 18-45 years (inclusive) who satisfied all inclusion/exclusion criteria
13. Investigational medicinal product, mode of administration and strength	Treatment A: Istin® 10 mg (amlodipine besylate equivalent to 10 mg amlodipine) tablets (UK formulation)
14. Reference product, dose, mode of administration and strength	Treatment B. Norvasc® 10 mg (amlodipine besylate equivalent to 10 mg amlodipine) tablets (US formulation) Treatment C. Antacal® 10 mg (amlodipine besylate equivalent to 10 mg amlodipine) tablets (Italian formulation)
15. Concomitant therapy	None
16. Criteria for evaluation efficacy	$AUC_{0\text{-}Inf}$, $AUC_{0\text{-}t}$, C_{max}, T_{max}, $t_{1/2}$, CL/F and Vss/F
17. Criteria for evaluation safety	Physical examination, vital signs, 12-lead ECGs, adverse events (AE), laboratory parameters
18. Statistical methods	90% CIs for the difference between treatment LSMs were derived from the Analysis of Variance (ANOVA) on the ln-

	transformed PK parameters AUC_{0-t}, AUC_{0-Inf} and C_{max} for amlodipine.
19. Demographic indices of studied population (sex, age, race, etc.)	

Trait		Overall (N=18)
Age (yr)	Mean	36.7
	SD	11.5
	Median	38
	Minimum	19
	Maximum	55
Height (cm)	Mean	176.1
	SD	10.6
	Median	176
	Minimum	161
	Maximum	199
Weight (kg)	Mean	75.23
	SD	12.76
	Median	74.5
	Minimum	54.7
	Maximum	100.7
BMI (kg/m²)	Mean	24.13
	SD	2.35
	Median	24.7
	Minimum	19.4
	Maximum	28.0

20. Efficacy results

Amlopidine (N=18)	Treatment A[1] (N=18)	Treatment B[2] (N=18)	Treatment C[3] (N=18)
AUC_{0-t} [ng.h/mL]			
Arithmetic Mean ±SD	167.8 (43.3)	168.1 (44.8)	171.3 (47.5)
Geometric Mean (CV%)	162.8 (11.0)	162.4 (11.8)	164.4 (13.2)
AUC_{0-Inf} [ng.h/mL]			
Arithmetic Mean ±SD	177.4 (43.7)	177.5 (45.3)	182.1 (48.7)
Geometric Mean (CV%)	172.5 (10.6)	172.0 (11.3)	175.5 (12.5)
C_{max} (ng/mL)			
Arithmetic Mean ±SD	3.74 (0.94)	3.47 (0.82)	3.77 (0.83)
Geometric Mean (CV%)	3.63 (10.82)	3.39 (9.69)	3.68 (10.32)
T_{max} (h)			
Median (Min – Max)	8.0 (4.0; 10.1)	8.6 (4.0; 16.0)	8.6 (7.0; 14.0)
$T_{1/2}$ (h)			
Arithmetic Mean ±SD	43.6 (11.0)	41.9 (7.37)	42.4 (6.24)
CL/f [mL/min]			
Arithmetic Mean ±SD	993 (236.4)	1000 (262.3)	989 (302.0)
Vss/f [L]			
Arithmetic Mean ±SD	3702 (1170)	3536 (794)	3573 (1060)

Parameter	Comparison	Ratio of LSM (%)	90% CI (%) (Lower , Upper)
AUC_{0-t} [ng.h/mL]	Treatment A[1] vs. B[2]	99.2	(94.1 , 104.7)
	Treatment A[1] vs. C[3]	98.8	(93.6 , 104.2)
	Treatment B[2] vs. C[3]	99.5	(94.3 , 105.0)
AUC_{0-Inf} [ng.h/mL]	Treatment A[1] vs. B[2]	98.9	(94.0 , 104.2)
	Treatment A[1] vs. C[3]	98.1	(93.2 , 103.3)
	Treatment B[2] vs. C[3]	99.2	(94.2 , 104.4)
C_{max} [ng/mL]	Treatment A[1] vs. B[2]	108.6	(100.9 , 116.8)
	Treatment A[1] vs. C[3]	98.0	(90.8 , 105.7)
	Treatment B[2] vs. C[3]	90.3	(83.7 , 97.3)

21. Safety results	Nine (50.0%) and 8 (44.4%) subjects experienced at least one TEAE after receiving the UK formulation (Istin® 10 mg) and the US formulation (Norvasc® 10 mg), respectively, and 6 subjects (33.3%) after the administration of the Italian formulation (Antacal® 10 mg). TEAEs were most frequently related to the nervous system such as headache and dizziness. One subject had a TEAE (headache) classified as severe, all other AEs were of mild to moderate severity.
22. Conclusion (summary)	The three different formulations of amlodipine besylate 10 mg (equivalent to 10 mg amlodipine) were bioequivalent. Single, oral doses of amlodipine besylate equivalent to 10 mg of amlodipine appeared to be well tolerated by the healthy subjects in this study.
Applicant (registration certificate holder)	(signature) Dr. Kai Schumacher (full name)

Clinical study report 5

1. Name of medicinal product (registration certificate №, if available)	ATTENTO ® PLUS 40/10/25 mg
2. Applicant	Menarini International Operations Luxembourg S.A., Luxembourg
3. Manufacturer	Daiichi Sankyo Europe GmbH, Germany (Manufacturing "in bulk", packaging, batch control and release) Berlin-Chemie AG, Germany (Packaging, batch control and release) Menarini - Von Heyden GmbH, Germany (Batch control and release)
4. Studies conducted:	yes
1) type of medicinal product, which has been or will be registered	Medicinal product with fixed combination
5. Title of clinical trial, code number of clinical trial	CS8663-A-U109 A randomized, single-dose, open-label, 2-way crossover study to determine the bioavailability of olmesartan and amlodipine from a fifth fixed-dose combination formulation relative to Olmetec® and Antacal® in healthy subjects
6. Phase of clinical trial	Phase I
7. Period of clinical trial	10 Oct 2005 to 31 Oct 2005
8. Countries, where clinical trial has been conducted	USA
9. Number of trial subjects	planned: 28 actual:26 (completed)
10. Objective and secondary endpoints of clinical trial	To determine the bioavailability of olmesartan and amlodipine from a fixed-dose combination relative to co-administration (free combination) of separate entities as their marketed formulations (Olmetec® and Antacal®, respectively).
11. Clinical trial design	Single-center, single-dose, randomized, open-label, 2-way crossover study.
12. Main inclusion criteria	Subjects enrolled were healthy adult men and women aged 18-45 years (inclusive) who satisfied all inclusion/exclusion criteria
13. Investigational medicinal product, mode of administration and strength	Treatment A: CS-8663 40/10 mg (olmesartan medoxomil 40 mg/amlodipine besylate 10 mg) oral tablet.
14. Reference product, dose, mode of administration and strength	Treatment B: Olmetec® (olmesartan medoxomil) 40 mg oral tablets and Antacal® (amlodipine besylate) 10 mg oral tablets.
15. Concomitant therapy	None
16. Criteria for evaluation efficacy	AUC_{0-t}, Auc_{0-Inf}, C_{max}, T_{max}, kel and $t_{1/2}$
17. Criteria for evaluation safety	Adverse events, clinical laboratory measurements, vital signs, physical examinations and 12-lead ECGs.
18. Statistical methods	90% Cis for the difference between treatments LSM were derived from the Analysis of Variance (ANOVA) on the ln-transformed PK parameters AUC_{0-t}, AUC_{0-Inf} and C_{max} for olmesartan and amlodipine.

19. Demographic indices of studied population (sex, age, race, etc.)

Trait		Gender: Male (N = 13)	Female (N = 15)	Overall (N=28)
Gender (N%)	Male			13 (46.4%)
	Female			15 (53.6%)
Race (N%)	Caucasian	1 (7.7%)	0	1 (3.6%)
	Hispanic	12 (92.3%)	15 (100.0%)	27 (96.4%)
Age (yr)	Mean	30.6	27.9	29.2
	SD	9.48	6.46	7.97
	Median	29.0	26.0	27.5
	Minimum	19	19	19
	Maximum	44	38	44
Height (cm)	Mean	171.00	159.67	164.93
	SD	8.103	5.740	8.911
	Median	172.00	159.00	164.00
	Minimum	154.0	151.0	151.0
	Maximum	181.0	171.0	181.0
Weight (kg)	Mean	78.17	71.67	74.69
	SD	11.497	10.512	11.268
	Median	84.10	70.80	74.85
	Minimum	56.2	50.3	50.3
	Maximum	90.9	88.5	90.9
BMI (kg/m²)	Mean	26.59	28.04	27.37
	SD	2.071	3.254	2.817
	Median	26.40	29.70	27.70
	Minimum	23.7	21.2	21.2
	Maximum	29.7	31.5	31.5

20. Efficacy results

Olmesartan	Test[a] (n = 26)	Reference[b] (n = 27)
AUC_{0-t} (ng·h/mL)		
Arithmetic Mean ±SD	5554.0 ± 1315.07	5571.1 ± 1308.37
Geometric Mean (CV%)	5398.7 (25.0%)	5420.9 (24.5%)
AUC_{0-inf} (ng·h/mL)		
Arithmetic Mean ±SD	5589.2 ± 1323.20	5622.8 ± 1320.87
Geometric Mean (CV%)	5433.6 (25.0%)	5470.5 (24.6%)
AUC_{0-t} / AUC_{0-inf}		
Arithmetic Mean ±SD	0.9938 ± 0.00475	0.9916 ± 0.00989
C_{max} (ng/mL)		
Arithmetic Mean ±SD	858.3 ± 207.53	835.7 ± 197.97
Geometric Mean (CV%)	832.6 (26.2%)	810.9 (26.5%)
T_{max} (h)		
Median (Min – Max)	2.000 (1.02 – 4.00)	2.000 (1.50 – 3.03)
T½ (h)		
Arithmetic Mean ±SD	10.670 ± 2.7829	11.723 ± 4.3060

Parameters	Geometric LSM: Test[a] (n = 26)	Geometric LSM: Reference[b] (n = 27)	Ratio (T/R) of LSM (%)	90% CI (Lower, Upper) (%)
AUC_{0-t} (ng·h/mL)	5374.2	5418.6	99.18	(93.38, 105.3)
AUC_{0-inf} (ng·h/mL)	5407.5	5468.3	98.89	(93.21, 104.9)
C_{max} (ng/mL)	833.3	810.3	102.85	(94.81, 111.6)

[a] CS-8663 Formulation G Oral Tablet (olmesartan medoxomil 40 mg and amlodipine besylate 10 mg)
[b] Olmesartan medoxomil 40 mg (Olmetec®) oral tablet in combination with amlodipine besylate 10 mg (Antacal®) oral tablet
Source: Table 14.2.1.5.

Amlodipine	Test[a] (n = 26)	Reference[b] (n = 27)
AUC_{0-t} (pg·h/mL)		
Arithmetic Mean ±SD	433740.9 ± 98822.72	423175.4 ± 103092.2
Geometric Mean (CV%)	422166.6 (24.7%)	410104.7 (26.5%)
AUC_{0-inf} (pg·h/mL)		
Arithmetic Mean ±SD	523343.2 ± 138211.0	501798.5 ± 141550.7
Geometric Mean (CV%)	503682.2 (30.0%)	481699.1 (31.1%)
AUC_{0-t} / AUC_{0-inf}		
Arithmetic Mean ±SD	0.8408 ± 0.06775	0.8551 ± 0.06613
Range (Min – Max)	0.693 – 0.962	0.652 – 0.948
C_{max} (pg/mL)		
Arithmetic Mean ±SD	7695.8 ± 1561.42	7556.3 ± 1792.97
Geometric Mean	7538.0 (21.3%)	7353.5 (24.2%)
T_{max} (h)		
Median (Min – Max)	8.025 (6.00 – 12.0)	8.00 (6.00 – 12.0)
T½ (h)		
Arithmetic Mean ±SD	54.43 ± 13.630	51.59 ± 12.897

Parameters	Geometric LSM: Test[a] (n = 26)	Geometric LSM: Reference[b] (n = 27)	Ratio (T/R) of LSM (%)	90% CI (Lower, Upper) (%)
AUC_{0-t} (pg·h/mL)	424784.8	410898.8	103.38	(100.1, 106.8)
AUC_{0-inf} (pg·h/mL)	505286.7	482249.3	104.78	(100.8, 109.0)
C_{max} (pg/mL)	7642.9	7353.6	103.93	(99.87, 108.2)

[a] CS-8663 Formulation G Oral Tablet (olmesartan medoxomil 40 mg and amlodipine besylate 10 mg)
[b] Olmesartan medoxomil 40 mg (Olmetec®) oral tablet in combination with amlodipine besylate 10 mg (Antacal®) oral tablet
Source: Table 14.2.1.11.

21. Safety results

One subject was withdrawn due to pregnancy and later experienced a spontaneous abortion that was captured as SAE. A total of 30 TEAEs occurred in 11 subjects (39.3%). The frequency of subjects reporting AEs was roughly equal between treatments with 6 subjects (22.2%) with AEs after receiving CS-8663 tablets and 5 (18.5%) after receiving Olmetec® 40 mg and Antacal® 10 mg tablets.

22. Conclusion (summary)

The fixed dose combination of olmesartan medoxomil 40 mg and amlodipine besylate tablet (CS-8663

	formulation G) is bioequivalent to the co-administration of Olmetec® 40 mg and Antacal® 10 mg tablets. Single, oral doses of CS-8663 oral tablets appeared to be safe and well tolerated by the healthy male and female subjects in this study.
Applicant (registration certificate holder)	(signature) Dr. Kai Schumacher (full name)

Clinical study report 6

1. Name of medicinal product (registration certificate №, if available)	ATTENTO ® PLUS 40/10/25 mg **16**
2. Applicant	Menarini International Operations Luxembourg S.A., Luxembourg
3. Manufacturer	Daiichi Sankyo Europe GmbH, Germany (Manufacturing "in bulk", packaging, batch control and release) Berlin-Chemie AG, Germany (Packaging, batch control and release) Menarini - Von Heyden GmbH, Germany (Batch control and release)
4. Studies conducted:	yes
1) type of medicinal product, which has been or will be registered	Medicinal product with fixed combination
5. Title of clinical trial, code number of clinical trial	CS-8663-A-U111 A parallel-group, open-label, randomized, crossover study to determine the bioavailability of a fixed-dose combination tablet of olmesartan medoxomil and amlodipine besylate relative to Olmetec® and Antacal® in healthy subjects.
6. Phase of clinical trial	Phase I
7. Period of clinical trial	23 Jan 2006 to 22 Mar 2006
8. Countries, where clinical trial has been conducted	USA
9. Number of trial subjects	planned: 60 actual:58 (completed)
10. Objective and secondary endpoints of clinical trial	To determine the bioavailability of olmesartan and amlodipine from a fixed-dose combination formulation intended for commercial use relative to combination of the separate entities as their marketed formulations. The bioavailability was determined for two strengths: Olmesartan 10 mg and amlodipine 5 mg; olmesartan 40 mg and amlodipine 10 mg.
11. Clinical trial design	Single-center, single-dose, randomized, open-label, 2-way crossover study
12. Main inclusion criteria	Subjects enrolled were healthy adult men and women aged 18-45 years (inclusive) who satisfied all inclusion/exclusion criteria.
13. Investigational medicinal product, mode of administration and strength	Treatment A: CS-8663 oral tablet (fixed-dose combination of olmesartan medoxomil 10 mg and amlodipine besylate 5 mg) Treatment C: CS-8663 oral tablet (fixed-dose combination of olmesartan medoxomil 40 mg and amlodipine besylate 10 mg)
14. Reference product, dose, mode of administration and strength	Treatment B: Olmesartan medoxomil 10 mg (Olmetec®) in combination with amlodipine besylate 5 mg (Antacal®) Treatment D: Olmesartan medoxomil 40 mg (Olmetec®) in combination with amlodipine besylate 10 mg (Antacal®)
15. Concomitant therapy	None
16. Criteria for evaluation efficacy	AUC_{0-t}, AUC_{0-Inf}, C_{max}, T_{max}, kel, $t_{1/2}$
17. Criteria for evaluation safety	Adverse events, clinical laboratory measurements,

	vital signs, physical examinations and 12-lead ECGs.
18. Statistical methods	90% CIs for the difference between treatment LSMs were derived from the Analysis of Variance (ANOVA) on the ln transformed PK parameters AUC_{0-t}, AUC_{0-Inf} and C_{max} for olmesartan and amlodipine in each cohort.
19. Demographic indices of studied population (sex, age, race, etc.)	
20. Efficacy results	

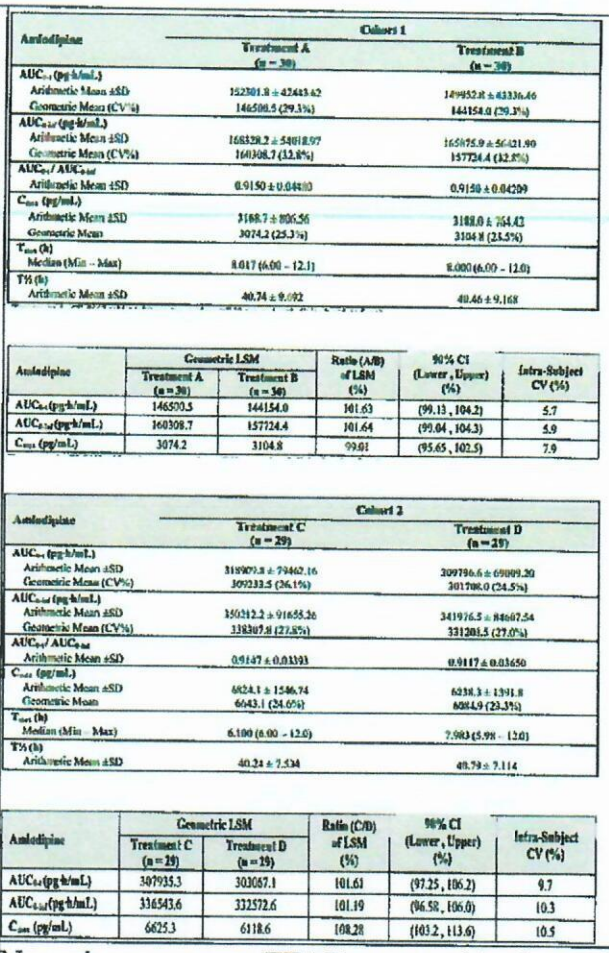
Trait		Cohort 1 Males (N=23)	Cohort 1 Females (N=7)	Cohort 1 Overall (N=30)	Cohort 2 Males (N=26)	Cohort 2 Females (N=4)	Cohort 2 Overall (N=30)	Study Overall (N=60)
Gender	Male			23 (76.7%)			26 (86.7%)	49 (81.7%)
	Female			7 (23.3%)			4 (13.3%)	11 (18.3%)
Race	Black	15 (65.2%)	2 (28.6%)	17 (56.7%)	19 (73.1%)	3 (75.0%)	22 (73.3%)	39 (65.0%)
	Caucasian	4 (17.4%)	2 (28.6%)	6 (20.0%)	4 (15.4%)	0	4 (13.3%)	10 (16.7%)
	Hispanic	4 (17.4%)	3 (42.9%)	7 (23.3%)	2 (7.7%)	0	2 (6.7%)	9 (15.0%)
	Other	0	0	0	1 (3.8%)	1 (25.0%)	2 (6.7%)	2 (3.3%)
Age (yr)	Mean	32.0	32.6	32.2	30.7	27.0	30.2	31.2
	SD	5.64	8.38	6.22	7.67	6.68	7.55	6.93
	Median	32	35	32	29	28	29	29.5
	Minimum	23	23	23	21	19	19	19
	Maximum	43	42	43	45	35	45	45
Height (cm)	Mean	175.43	162.57	172.43	177.00	162.75	175.2	173.77
	SD	7.885	4.791	9.085	7.054	6.238	8.438	8.796
	Median	176	163	173	178.5	162	176.5	175
	Minimum	156	154	154	165	156	156	154
	Maximum	193	168	193	188	171	188	193
Weight (kg)	Mean	79.18	76.50	78.57	82.43	65.98	80.24	79.41
	SD	11.832	12.919	11.915	11.901	11.337	12.953	12.368
	Median	79.4	80.8	79.5	83.1	66.35	80	79.5
	Minimum	59.5	50.5	50.5	61	52	52	50.5
	Maximum	103.1	97	103.1	101.6	79.2	101.6	103.1
BMI (kg/m²)	Mean	25.72	28.96	26.48	26.27	24.83	26.08	26.28
	SD	3.475	3.674	3.727	3.373	3.907	3.411	3.548
	Median	25.8	30.7	26.45	25.9	23.8	25.55	25.95
	Minimum	19.4	21.4	19.4	19.8	21.3	19.8	19.4
	Maximum	31.7	31.7	31.7	31.5	30.4	31.5	31.7

Olmesartan	Cohort 1 Treatment A (n = 30)	Cohort 1 Treatment B (n = 30)
AUC_{0-t} (ng·h/mL)		
Arithmetic Mean ±SD	1871.5 ± 407.38	1738.6 ± 391.02
Geometric Mean (CV%)	1824.7 (23.95%)	1690.3 (23.0%)
AUC_{0-Inf} (ng·h/mL)		
Arithmetic Mean ±SD	1901.9 ± 403.11	1778.3 ± 403.09*
Geometric Mean (CV%)	1857.1 (23.1%)	1734.5 (23.2%)*
AUC_{0-t} / AUC_{total}		
Arithmetic Mean ±SD	0.9827 ± 0.01704	0.9835 ± 0.00916*
C_{max} (ng/mL)		
Arithmetic Mean ±SD	347.5 ± 80.00	306.0 ± 80.55
Geometric Mean (CV%)	338.0 (24.8%)	295.7 (27.3%)
T_{max} (h)		
Median (Min - Max)	1.559 (1.00 – 4.02)	2.000 (1.00 – 4.02)
T½ (h)		
Arithmetic Mean ±SD	14.355 ± 7.5439	13.639 ± 5.6033*

Olmesartan	Geometric LSM Treatment A (n = 30)	Geometric LSM Treatment B (n = 30)	Ratio (A/B) of LSM (%)	90% CI (Lower, Upper) (%)	Intra-Subject CV (%)
AUC_{0-t} (ng·h/mL)	1824.7	1696.3	107.57	(99.67, 116.1)	17.5
AUC_{0-Inf} (ng·h/mL)	1857.1	1729.4*	107.39	(99.42, 116.0)	17.4
C_{max} (ng/mL)	338.0	295.7	114.30	(106.6, 122.5)	15.9

Olmesartan	Cohort 2 Treatment C (n = 29)	Cohort 2 Treatment D (n = 29)
AUC_{0-t} (ng·h/mL)		
Arithmetic Mean ±SD	5994.9 ± 1782.10	5383.2 ± 1297.31
Geometric Mean (CV%)	5760.8 (29.2%)	5223.1 (26.0%)
AUC_{0-Inf} (ng·h/mL)		
Arithmetic Mean ±SD	6168.7 ± 1789.50*	5491.5 ± 1327.74
Geometric Mean (CV%)	5942.1 (28.2%)*	5325.7 (26.3%)
AUC_{0-t} / AUC_{total}		
Arithmetic Mean ±SD	0.9849 ± 0.01555*	0.9809 ± 0.01646
C_{max} (ng/mL)		
Arithmetic Mean ±SD	938.7 ± 240.44	859.1 ± 182.23
Geometric Mean (CV%)	907.5 (27.7%)	839.3 (25.7%)
T_{max} (h)		
Median (Min – Max)	2.000 (1.00 – 4.02)	1.517 (1.00 – 3.10)
T½ (h)		
Arithmetic Mean ±SD	15.630 ± 7.0027*	17.213 ± 8.1291

Olmesartan	Geometric LSM Treatment C (n = 29)	Geometric LSM Treatment D (n = 29)	Ratio (C/D) of LSM (%)	90% CI (Lower, Upper) (%)	Intra-Subject CV (%)
AUC_{0-t} (ng·h/mL)	5790.3	5164.8	112.11	(103.3, 121.6)	18.1
AUC_{0-Inf} (ng·h/mL)	5976.7*	5265.7	113.50	(104.7, 123.0)	17.4
C_{max} (ng/mL)	911.9	831.0	109.73	(101.8, 118.3)	16.8

Amlodipine	Cohort 1	
	Treatment A (n = 30)	Treatment B (n = 30)
AUC_{t} (pg·h/mL)		
Arithmetic Mean ±SD	152301.8 ± 42443.62	149452.8 ± 43336.46
Geometric Mean (CV%)	146500.5 (29.3%)	144154.0 (29.3%)
AUC_{0-tld} (pg·h/mL)		
Arithmetic Mean ±SD	168329.2 ± 54018.97	165875.9 ± 56421.90
Geometric Mean (CV%)	160308.7 (32.6%)	157724.4 (32.8%)
AUC_{t} / AUC_{0-tld}		
Arithmetic Mean ±SD	0.9150 ± 0.04480	0.9150 ± 0.04209
C_{max} (pg/mL)		
Arithmetic Mean ±SD	3168.7 ± 805.56	3188.0 ± 764.42
Geometric Mean	3074.2 (25.3%)	3104.8 (23.5%)
T_{max} (h)		
Median (Min - Max)	8.017 (6.00 - 12.1)	8.000 (6.00 - 12.0)
T½ (h)		
Arithmetic Mean ±SD	40.74 ± 9.092	40.46 ± 9.168

Amlodipine	Geometric LSM		Ratio (A/B) of LSM (%)	90% CI (Lower , Upper) (%)	Intra-Subject CV (%)
	Treatment A (n = 30)	Treatment B (n = 30)			
AUC_{t} (pg·h/mL)	146500.5	144154.0	101.63	(99.13 , 104.2)	5.7
AUC_{0-tld} (pg·h/mL)	160308.7	157724.4	101.64	(99.04 , 104.3)	5.9
C_{max} (pg/mL)	3074.2	3104.8	99.01	(95.65 , 102.5)	7.9

Amlodipine	Cohort 2	
	Treatment C (n = 29)	Treatment D (n = 29)
AUC_{t} (pg·h/mL)		
Arithmetic Mean ±SD	318909.8 ± 79462.16	309786.6 ± 69009.20
Geometric Mean (CV%)	309233.5 (26.1%)	301708.0 (24.5%)
AUC_{0-tld} (pg·h/mL)		
Arithmetic Mean ±SD	350312.2 ± 91655.26	341976.5 ± 84607.54
Geometric Mean (CV%)	338307.8 (27.8%)	331201.5 (27.0%)
AUC_{t} / AUC_{0-tld}		
Arithmetic Mean ±SD	0.9147 ± 0.03393	0.9117 ± 0.03650
C_{max} (pg/mL)		
Arithmetic Mean ±SD	6824.1 ± 1546.74	6238.3 ± 1391.8
Geometric Mean	6643.1 (24.6%)	6084.9 (23.3%)
T_{max} (h)		
Median (Min - Max)	6.100 (6.00 - 12.0)	7.983 (5.98 - 12.0)
T½ (h)		
Arithmetic Mean ±SD	40.24 ± 7.534	40.79 ± 7.114

Amlodipine	Geometric LSM		Ratio (C/D) of LSM (%)	90% CI (Lower , Upper) (%)	Intra-Subject CV (%)
	Treatment C (n = 29)	Treatment D (n = 29)			
AUC_{t} (pg·h/mL)	307935.3	303067.1	101.61	(97.25 , 106.2)	9.7
AUC_{0-tld} (pg·h/mL)	336543.6	332572.6	101.19	(96.58 , 106.0)	10.3
C_{max} (pg/mL)	6625.3	6118.6	108.28	(103.2 , 113.6)	10.5

21. Safety results	No serious or severe TEAEs occurred in the study. Most TEAEs were mild, and no moderate TEAEs were related to the study treatments. One subject was withdrawn due to a TEAE (swelling to left lower jaw/parotitis) and moderate eosinophilia; these TEAEs were considered unrelated to treatment. No TEAE was considered definitely or probably related to the study treatments.
22. Conclusion (summary)	The lower strength of CS-8663 oral tablet (fixed dose combination of olmesartan medoxomil 10 mg and amlodipine besylate 5 mg) was bioequivalent to co-administered Olmetec® 10 mg and Antacal® 5 mg under fasting conditions. The higher strength of CS-8663 oral tablet (fixed dose combination of olmesartan medoxomil 40 mg and amlodipine besylate 10 mg) was bioequivalent to co-administered Olmetec® 40 mg and Antacal® 10 mg under fasting conditions.
Applicant (registration certificate holder)	(signature) Dr. Kai Schumacher (full name)

Clinical study report 7

1. Name of medicinal product (registration certificate №, if available)	ATTENTO ® PLUS 40/10/25 mg
2. Applicant	Menarini International Operations Luxembourg S.A., Luxembourg
3. Manufacturer	Daiichi Sankyo Europe GmbH, Germany (Manufacturing "in bulk", packaging, batch control and release) Berlin-Chemie AG, Germany (Packaging, batch control and release) Menarini - Von Heyden GmbH, Germany (Batch control and release)
4. Studies conducted:	yes
1) type of medicinal product, which has been or will be registered	Medicinal product with fixed combination
5. Title of clinical trial, code number of clinical trial	CS-8635-A-U301 A randomized, double-blind, parallel group study evaluating the efficacy and safety of co-administration of a triple combination therapy of olmesartan medoxomil (OM), amlodipine besylate (AML) and hydrochlorothiazide (HCT) in subjects with hypertension
6. Phase of clinical trial	Phase III
7. Period of clinical trial	12 May 2008 to 27 Feb 2009
8. Countries, where clinical trial has been conducted	USA (317 study sites)
9. Number of trial subjects	planned: 2492 actual:2116 (completed Period II)
10. Objective and secondary endpoints of clinical trial	The main objective of this trial was to determine if co-administration of OM, AML, and HCT had a clinical significant benefit versus respective dual therapy components in controlling blood pressure in subjects with hypertension.
11. Clinical trial design	This was a 52-week, multi-center, randomized, double-blind, parallel group trial consisting of 3 periods as follows: **Washout – Period I** (maximum 3 weeks): to be eligible for randomization, all subjects had to have a SeDBP≥140 mmHg and SeSBP≥100 mmHg or SeSBP≥160 mmHg and SeDBP≥90 mmHg at two consecutive visits during Period 1 and the difference in mean SeSBP/SeDBP must have been ≤20/10 mmHg between the 2 qualifying visits. **Double-blind treatment – Period II** (Day 1 to week 12): Period II consisted of a 12-week treatment period. On day 1, subjects who met all inclusion criteria and none of the exclusion criteria were randomized to 1 of the 4 treatment groups (OM 40 mg + AML 10 mg, OM 40 mg + HCT 25 mg, AML 10 mg + HCT 25 mg, or OM 40 mg + AML 10 mg + HCT 25 mg), which reflected the treatment they received from week 4 to week 12. **Open-label Treatment – Period III** (week 12 to week 52): Period III consisted of a 40-week open-label treatment period to assess long-term safety

	and efficacy of the triple combination. After completing period II, all subjects were switched to the combination of OM 40 mg + AML 5 mg + HCT 12.5 mg. After week 14, subjects who did not achieve the BP goal had their dosage adjusted to OM 40 mg + AML 10 mg + HCT 25 mg at the discretion of the investigator.
12. Main inclusion criteria	This study enrolled male and female subjects 18 years or older with hypertension (defined as mean sitting trough cuff blood pressure [BP] ≥140/100 mmHg or mean sitting trough cuff BP ≥160/90 mmHg). Newly diagnosed hypertensive subjects (naïve subjects) as well as subjects on antihypertensive therapy could be included in the study.
13. Investigational medicinal product, mode of administration and strength	Olmesartan medoxomil (OM) 40 mg + amlodipine besylate (AML 10 mg) + hydrochlorothiazide (HCT) 25 mg
14. Reference product, dose, mode of administration and strength	• OM 40 mg + AML 10 mg • OM 40 mg + HCT 25 mg, • AML 10 mg + HCT 25 mg
15. Concomitant therapy	Standard antihypertensive therapy was allowed at study start and discontinued during the washout period.
16. Criteria for evaluation efficacy	Primary: Change from baseline in sitting diastolic blood pressure (SeDBP) at week 12 with the last observation carried forward (LOCF) Secondary: • Change from baseline in sitting systolic blood pressure (SeSBP) at week 12 with LOCF • Change from baseline in SeDBP and SeSBP at weeks 6, 8, 10 and 12 • Change in SeDBP and SeSBP from baseline at week 2 (to compare the placebo and each dual combination treatment) • Proportion of subjects who reached the BP goal (<140/90 mmHg, <130/80 mmHg in subjects with diabetes, chronic renal disease, or chronic cardiovascular disease) • Proportion of subjects who reached BP targets at weeks 6, 8, 10 and 12 with LOCF (i.e. <130/85 mmHg, <130/80 mmHg, <120/80 mmHg, SeDBP <90 mmHg and SeSBP<140 mmHg. • Change from baseline in 24-hour ABPM following 12 weeks of treatment in a subset (60 subjects per treatment arm) with both

	baseline and end of week 12 ABPM.
17. Criteria for evaluation safety	Safety assessments included TEAEs, clinical laboratory test results, vital signs, physical examinations and 12-lead ECGs
18. Statistical methods	The primary efficacy analysis (period II) consisted of comparisons between treatment groups for change from baseline to week 12 in SeDBP. The treatment comparisons were performed using an Analysis of Covariance (ANCOVA) model with fixed effects of treatment. Diabetic status, age group, race and baseline SeDPB as covariates.
19. Demographic indices of studied population (sex, age, race, etc.)	
20. Efficacy results	

	OM40/ AML10 (N = 628)	OM40/ HCTZ25 (N = 637)	AML10/ HCTZ25 (N = 600)	OM40/ AML10/ HCTZ25 (N = 627)
Age (years)				
N	628	637	600	627
Mean (SD)	55.1 (10.93)	55.9 (10.78)	54.6 (10.82)	54.7 (11.22)
Age Group (n, %) [1]				
<65 years	508 (80.9)	505 (79.3)	504 (84.0)	504 (80.4)
≥65 years	120 (19.1)	132 (20.7)	96 (16.0)	123 (19.6)
≥75 years	25 (4.0)	19 (3.0)	17 (2.8)	18 (2.9)
Gender (n, %) [1]				
Male	325 (51.8)	339 (53.2)	334 (55.7)	320 (51.0)
Female	303 (48.2)	298 (46.8)	266 (44.3)	307 (49.0)
Ethnicity (n, %) [1]				
Hispanic or Latino	90 (14.3)	85 (13.3)	98 (16.3)	96 (15.3)
Not Hispanic or Latino	538 (85.7)	551 (86.5)	502 (83.7)	531 (84.7)
Race (n, %) [1,2]				
Caucasian/White	432 (68.8)	422 (66.2)	395 (65.8)	415 (66.2)
Black/African or African American	181 (28.8)	200 (31.4)	192 (32.0)	184 (29.3)
Asian	13 (2.1)	10 (1.6)	7 (1.2)	19 (3.0)
American Indian or Alaskan Native	3 (0.5)	1 (0.2)	4 (0.7)	1 (0.2)
Native Hawaiian or Other Pacific Islander	0 (0.0)	1 (0.2)	1 (0.2)	2 (0.3)
Other	0 (0.0)	4 (0.6)	5 (0.8)	6 (1.0)
Weight (kg)				
N	628	637	600	627
Mean (SD)	95.9 (22.63)	96.1 (22.55)	96.1 (23.41)	96.0 (23.24)
Height (cm)				
N	628	637	600	627
Mean (SD)	170.1 (10.37)	170.3 (10.52)	170.4 (10.96)	170.0 (10.50)
BMI (kg/m²) [3]				
N	628	637	600	627
Mean (SD)	33.1 (7.27)	33.1 (7.25)	33.0 (7.05)	33.2 (6.99)

Table S1. Change in Seated Diastolic and Systolic Blood Pressure (mmHg) Baseline to Week 12 with LOCF – Full Analysis Set

	OM40/ AML10 (N = 624)	OM40/ HCTZ25 (N = 627)	AML10/ HCTZ25 (N = 593)	OM40/ AML10/ HCTZ25 (N = 614)
Seated Diastolic Blood Pressure				
n [1]	624	627	593	614
Baseline [2]				
Mean (SD)	101.0 (7.81)	100.6 (8.16)	101.2 (7.58)	100.9 (7.46)
Change from Baseline				
Mean (SD)	-17.8 (9.47)	-16.5 (10.84)	-14.8 (8.78)	-21.5 (10.25)
LS Mean (SE)	-18.0 (0.45)	-16.9 (0.45)	-15.1 (0.46)	-21.8 (0.45)
P-value [3]	<0.0001	<0.0001	<0.0001	<0.0001
	Between treatment comparisons [4]			
Comparisons	LS Mean (SE)		P-value	
OM40/AML10/HCTZ25 vs. OM40/AML10	-3.8 (0.53)		<0.0001	
OM40/AML10/HCTZ25 vs. OM40/HCTZ25	-4.9 (0.53)		<0.0001	
OM40/AML10/HCTZ25 vs. AML10/HCTZ25	-6.7 (0.54)		<0.0001	
Seated Systolic Blood Pressure				
n [1]	624	627	593	614
Baseline [2]				
Mean (SD)	168.2 (13.50)	169.0 (14.88)	168.9 (14.47)	168.0 (13.40)
Change from Baseline				
Mean (SD)	-31.1 (15.44)	-31.2 (18.58)	-28.9 (15.12)	-38.1 (17.40)
LS Mean (SE)	-30.0 (0.74)	-29.7 (0.73)	-27.5 (0.76)	-37.1 (0.74)
P-value [3]	<0.0001	<0.0001	<0.0001	<0.0001
	Between treatment comparisons [4]			
Comparisons	LS Mean (SE)		LS Mean (SE)	
OM40/AML10/HCTZ25 vs. OM40/AML10	-7.1 (0.87)		<0.0001	
OM40/AML10/HCTZ25 vs. OM40/HCTZ25	-7.4 (0.86)		<0.0001	
OM40/AML10/HCTZ25 vs. AML10/HCTZ25	-9.6 (0.88)		<0.0001	

Figure S1. Mean Change in Seated Diastolic Blood Pressure (mmHg) Over Time by Randomized Treatment Group – Full Analysis Set

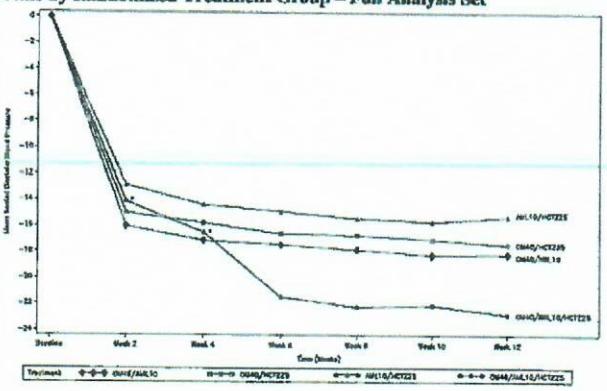


Table S2. Number (%) of Subjects Reaching Blood Pressure Treatment Goal at Week 12 with LOCF – Full Analysis Set

	OM40/ AML10 (N = 624)	OM40/ HCTZ25 (N = 627)	AML10/ HCTZ25 (N = 593)	OM40/ AML10/ HCTZ25 (N = 614)
Number achieving goal (n)	287	292	207	395
Percent achieving goal (n/N)	46.0	46.6	34.9	64.3
P-value for comparison to OM40/AML10/HCTZ25 [1]	<0.0001	<0.0001	<0.0001	

Table S3. Change in Mean 24-Hour Ambulatory Blood Pressure (mmHg) Baseline to Week 12/Early Termination – ABPM Analysis Set

	OM40/ AML10 (N = 112)	OM40/ HCTZ25 (N = 116)	AML10/ HCTZ25 (N = 95)	OM40/ AML10/ HCTZ25 (N = 117)
24-Hour Diastolic Blood Pressure				
n [1]	96	101	83	100
Baseline [2]				
Mean (SD)	88.6 (10.41)	88.7 (10.22)	88.6 (10.07)	87.2 (9.38)
Change from Baseline				
Mean (SD)	-13.9 (8.09)	-14.5 (8.73)	-10.7 (7.46)	-18.0 (8.11)
LS Mean (SE)	-13.8 (0.69)	-14.3 (0.68)	-10.5 (0.75)	-18.5 (0.68)
P-value [3]	<0.0001	<0.0001	<0.0001	<0.0001
	Between treatment comparisons [4]			
Comparisons	LS Mean (SE)		P-value	
OM40/AML10/HCTZ25 vs. OM40/AML10	-4.7 (0.97)		<0.0001	
OM40/AML10/HCTZ25 vs. OM40/HCTZ25	-4.2 (0.96)		<0.0001	
OM40/AML10/HCTZ25 vs. AML10/HCTZ25	-8.0 (1.01)		<0.0001	
24-Hour Systolic Blood Pressure				
n [1]	96	101	83	100
Baseline [2]				
Mean (SD)	149.7 (13.91)	147.3 (13.63)	147.0 (12.13)	147.4 (13.58)
Change from Baseline				
Mean (SD)	-23.5 (11.80)	-23.9 (12.10)	-18.5 (10.67)	-30.3 (13.85)
LS Mean (SE)	-22.6 (1.09)	-24.2 (1.06)	-19.0 (1.17)	-30.6 (1.07)
P-value [3]	<0.0001	<0.0001	<0.0001	<0.0001
	Between treatment comparisons [4]			
Comparisons	LS Mean (SE)		LS Mean (SE)	
OM40/AML10/HCTZ25 vs. OM40/AML10	-8.0 (1.53)		<0.0001	
OM40/AML10/HCTZ25 vs. OM40/HCTZ25	-6.4 (1.51)		<0.0001	
OM40/AML10/HCTZ25 vs. AML10/HCTZ25	-11.6 (1.59)		<0.0001	

21. Safety results	There did not appear to be a new or unexpected safety issues relative to each dual component therapy that were caused by the concomitant use of OM 40 mg + AML 10 mg + HCT 10 mg. There were no meaningful differences in the number of subjects experiencing drug-related TEAEs, SAEs, or in the number of subjects that needed to be withdrawn due to TEAEs across the different treatment groups. In total, 585 (25.4%) subjects had a drug-related TEAE. The percentage of subjects with a drug-related TEAE ranged from 20.9% to 29.7%. In total, 35 subjects had an SAE; only 1 subject (on OM 40 mg + AML10 mg) had an SAE that was considered treatment-related. This was a case of angina pectoris which was considered probably treatment-related.
22. Conclusion (summary)	The combination of OM, AML and HCT reduced both mean SeDBP and mean SeSBP to a significantly greater extend compared to each of the possible dual therapy components that made up the triple combination. The combination of OM 40

	mg + AML 10 mg + HCT 25 mg resulted in the greatest mean reductions in both SeDBP and SeSBP. The greater blood pressure reduction with triple combination therapy compared to the component dual combination therapies observed with the cuff BP measurement was confirmed by the analysis of the 24-hour ambulatory BP measurements. The comparisons of the mean reductions in SeDBP and SeSBP, and both diastolic and systolic 24-hours ABPM between the triple combination therapy and the component dual combination therapies were all statistically significant as well as clinically meaningful.
Applicant (registration certificate holder)	(signature) Dr. Kai Schumacher (full name)

Clinical study report 8

1. Name of medicinal product (registration certificate №, if available)	ATTENTO ® PLUS 40/10/25 mg
2. Applicant	Menarini International Operations Luxembourg S.A., Luxembourg
3. Manufacturer	Daiichi Sankyo Europe GmbH, Germany (Manufacturing "in bulk", packaging, batch control and release) Berlin-Chemie AG, Germany (Packaging, batch control and release) Menarini - Von Heyden GmbH, Germany (Batch control and release)
4. Studies conducted:	yes
1) type of medicinal product, which has been or will be registered	Medicinal product with fixed combination
5. Title of clinical trial, code number of clinical trial	CS-8663-A-U301 A randomized, double-blind, placebo-controlled factorial study evaluating the efficacy and safety of co-administration of olmesartan medoxomil plus amlodipine compared to monotherapy in patients with mild to severe hypertension. Results of the open-label treatment period – week 8 to week 52.
6. Phase of clinical trial	Phase III
7. Period of clinical trial	02 May 2005 to 09 Jan 2007
8. Countries, where clinical trial has been conducted	USA (172 study sites)
9. Number of trial subjects	planned:1684 actual:1400 (completed)
10. Objective and secondary endpoints of clinical trial	Period III (open-label extension period): • To gain long-term efficacy and safety experience with the co-administration of OM + AML (plus the addition of HCT, if needed). • To evaluate the number (%) of patients achieving BP control (defined as BP < 140/90 mmHg, < 130/80 in diabetic patients).
11. Clinical trial design	A 52-week, multi-center, randomized, double-blind, placebo-controlled, parallel group factorial trial consisting of 3 periods as follows: **Washout – Period I** (approx. 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 randomization, all patients had to have a mean SeDBP ≥95 mmHg and ≤120 mmHg at the randomization visit 3. **Double-blind treatment – Period II** (day 1 to

	week 8): Period II consisted of an 8-week treatment period. Patients who met all the inclusion criteria and none of the exclusion criteria were randomized equally to 1 of the 12 treatment arms as follows: Placebo; Olmesartan medoxomil (OM) 10 mg, OM 20 mg, OM 40 mg, Amlodipine besylate (AML) 5 mg, AML 10 mg, OM 10 mg + AML 5 mg, OM 20 mg + AML 5 mg, OM 10 mg + AML 10 mg, OM 20 mg + AML 10 mg, or OM 40 mg + AML 10 mg. **Open label treatment – Period III** (week 8 through week 52): Period III consisted of a 44-week, open-label treatment period. After completing Period II, all patients were switched to the combination of OM 40 mg + AML 5 mg. Those patients whose BP was not adequately controlled were titrated to OM 40 mg + AML 10 mg. Patients whose BP was still not adequately controlled were offered HCT 12.5 mg and subsequently 25 mg as required to reach BP control.
12. Main inclusion criteria	This study enrolled male and female subjects 18 years or older with hypertension (defined as mean sitting trough cuff blood pressure [BP] ≥140/100 mmHg or mean sitting trough cuff BP ≥160/90 mmHg). Newly diagnosed hypertensive subjects (naïve subjects) as well as subjects on antihypertensive therapy could be included in the study.
13. Investigational medicinal product, mode of administration and strength	• Olmesartan medoxomil (OM) 40 mg + amlodipine besylate (AML) 5 mg
14. Reference product, dose, mode of administration and strength	• OM 40 mg + AML 10 mg • OM 40 mg + AML) 10 mg + hydrochlorothiazide (HCT) 12.5 mg • OM 40 mg + AML 10 mg + HCT 25 mg
15. Concomitant therapy	Standard antihypertensive therapy was allowed at study start and discontinued during the washout period.
16. Criteria for evaluation efficacy	• Mean SeDBP following 44 weeks of titration treatment from OM 40 + AML 5 mg to OM 40 mg + AML 10 mg and to OM 40 + AML 10 mg + HCT 12.5/25 mg, respectively. • Number (%) of patients achieving BP control (defined as BP < 140/90 mmHg, < 130/80 in diabetic patients).
17. Criteria for evaluation safety	Frequency, seriousness and severity of TEAEs

18. Statistical methods	Efficacy evaluations consisted of summary statistics presented for SeDBP and SeSBP by dosing regimen at each open-label visit. Summary statistics were also presented for the titration effect corresponding to changes in the dosing regimen for SeDBP and SeSBP. The titration effect was calculated as the BP value at the last visit on the new dosing regimen minus the BP value at the last visit of the previous dosing regimen. Additionally, the number and percentage of patients achieving BP treatment goal were summarized for each dosing regimen.
19. Demographic indices of studied population (sex, age, race, etc.)	

Baseline Characteristics	Patients Entering Period III (N = 1684)
Age (years)[1]	
N	1684
Mean (SD)	54.1 (10.98)
Age Group (n, %)[2]	
<65 years	1353 (80.3)
≥65 years and <75 years	277 (16.4)
≥75 years	54 (3.2)
Gender (n, %)[2]	
Male	927 (55.0)
Female	757 (45.0)
Ethnicity (n, %)[2]	
Hispanic or Latino	214 (12.7)
Not Hispanic or Latino	1468 (87.2)
Race (n, %)[2]	
Caucasian	1205 (71.6)
Black	413 (24.5)
Asian	33 (2.0)
American Indian/Alaskan Native	10 (0.6)
Native Hawaiian/Pacific Islander	1 (0.1)
Other	31 (1.8)
Weight (kg)[3]	
N	1683
Mean (SD)	95.1 (21.77)
Height (cm)	
N	1672
Mean (SD)	170.2 (10.40)
Body mass index (kg/m²)[4]	
N	1671
Mean (SD)	33.4 (7.08)

20. Efficacy results	

Table 7: Seated Diastolic Blood Pressure (mmHg) by Week and Dosing Regimen – All Patients Entering Period III

Week	OM40/ AML5	OM40/ AML10	OM40/ AML10/ HCTZ12.5	OM40/ AML10/ HCTZ25	Other[4]
Baseline[1]					
N	1683				
Mean ± SD	101.5 ± 4.97				
Week 10					
N	1640	11			3
Mean ± SD	86.0 ± 9.28	92.8 ± 8.07			75.3 ± 3.61
n (%) to BP goal[2]	792 (48.3)	2 (18.2)			3 (100.0)
Week 12					
N	882	694	32		14
Mean ± SD	82.1 ± 7.69	87.0 ± 8.26	92.6 ± 7.88		82.5 ± 7.55
n (%) to BP goal[2]	643 (72.9)	247 (35.6)	1 (3.1)		10 (71.4)
Week 18					
N	697	435	391	30	22
Mean ± SD	81.7 ± 7.68	83.7 ± 7.95	85.8 ± 8.67	85.0 ± 7.39	84.4 ± 7.59
n (%) to BP goal[2]	526 (75.5)	247 (56.8)	145 (37.1)	7 (23.3)	13 (59.1)
Week 26					
N	564	391	308	232	31
Mean ± SD	80.9 ± 7.71	82.4 ± 7.61	83.6 ± 8.11	85.0 ± 8.09	85.0 ± 7.15
n (%) to BP goal[2]	450 (79.8)	271 (69.3)	167 (54.2)	68 (29.3)	15 (48.4)
Week 34					
N	479	360	279	316	37
Mean ± SD	80.1 ± 7.62	81.7 ± 7.30	81.5 ± 7.65	83.7 ± 8.08	81.8 ± 8.12
n (%) to BP goal[2]	412 (86.0)	268 (74.4)	192 (68.8)	131 (41.5)	23 (62.2)
Week 42					
N	431	335	258	355	47
Mean ± SD	79.2 ± 7.01	80.5 ± 7.67	80.1 ± 7.52	82.5 ± 8.42	80.9 ± 6.93
n (%) to BP goal[2]	387 (89.8)	268 (80.0)	199 (77.1)	185 (52.1)	35 (74.5)
Week 52					
N	412	312	248	372	56
Mean ± SD	79.8 ± 7.51	81.3 ± 7.56	80.5 ± 8.49	82.7 ± 8.38	79.1 ± 9.64
n (%) to BP goal[2]	355 (86.2)	244 (78.2)	171 (69.0)	180 (48.4)	40 (71.4)
Week 52/ET					
N	525	378	287	419	63
Mean ± SD	81.0 ± 8.46	82.4 ± 8.14	81.0 ± 8.78	83.4 ± 8.72	79.4 ± 9.90
n (%) to BP goal[2]	420 (80.0)	267 (70.6)	191 (66.6)	194 (46.3)	43 (68.3)
Week 54/Follow-up[3]					
N	398	303	242	365	51
Mean ± SD	82.6 ± 9.03	84.3 ± 9.17	85.0 ± 10.41	87.4 ± 9.85	84.5 ± 10.14
n (%) to BP goal[2]	263 (66.1)	172 (56.8)	108 (44.6)	103 (28.2)	31 (60.8)

- A total of 525 patients remained on OM 40 mg + AML 5 mg and had a mean SeDBP of 81 0 mmHg and a mean

	SeSBP of 127 mmHg. 80.0% of these patients reached their BP goal • A total of 378 patients were on OM 40 mg + AML 10 mg and had a mean SeDPB of 82.4 mmHg and a mean SeSBP of 130.9 mmHg. 70.6% of these patients reached their BP goal. • A total of 287 patients were on OM 40 mg + AML 10 mg + HCT 12.5 mg and had a mean SeDBP of 130.7 mmHg. 66.6% of these patients reached their BP goal. • A total of 419 patients were on OM 40 mg + AML 10 mg + HCT 25 mg and had a mean SeDBP of 83.4 mmHg and a mean SeSBP of 136.8. 46.3% of these patients reached their BP goal.
21. Safety results	No new safety issues were identified during the course of this study with any of the combination therapies. During the open-label extension phase TEAEs were experienced by 622 (37.0%) patients on OM 40 mg + AML 5 mg, 455 (40,5%) patients on OM 40 mg + AML 10 mg, 312 (42.2%) patients on OM 40 mg + AML 10 mg + HCT 12.5 mg, and 248 (56.4%) patients on OM 40 mg + AML 10 mg + HCT 25 mg.
22. Conclusion (summary)	From the mean baseline blood pressure of 163.6/101.5 mmHg, BP reductions were observed across all combination treatment regimens to week 52, with 66.7% of the study cohort achieving treatment goal. The mean BP for the total patient cohort at week 52 was 131.2/81.9 mmHg. At this time point, the lowest mean BP (127.6/81.0 mmHg) and the greatest percentage of patients reaching goal BP were in the group still receiving OM 40 mg + AML 5 mg, whose amlodipine dose had not been increased and who did not receive hydrochlorothiazide. The groups of patients who required titration of the AML dose or the addition of HCT were more severe hypertensive patients and/or were more resistant to antihypertensive effects of treatment.
Applicant (registration certificate holder)	(signature) Dr. Kai Schumacher (full name)

Clinical study report 9

1. Name of medicinal product (registration certificate №, if available)	ATTENTO ® PLUS 40/10/25 mg
2. Applicant	Menarini International Operations Luxembourg S.A., Luxembourg
3. Manufacturer	Daiichi Sankyo Europe GmbH, Germany (Manufacturing "in bulk", packaging, batch control and release) Berlin-Chemie AG, Germany (Packaging, batch control and release) Menarini - Von Heyden GmbH, Germany (Batch control and release)
4. Studies conducted:	yes
1) type of medicinal product, which has been or will be registered	Medicinal product with fixed combination
5. Title of clinical trial, code number of clinical trial	CS-8663 –A-E303 Add-on study of olmesartan medoxomil in patients with moderate to severe hypertension not achieving target blood pressure on Amlodipine 5 mg alone. Results of the open-label treatment period – period IV
6. Phase of clinical trial	Phase III
7. Period of clinical trial	03 Oct 2005 to 08 May 2007
8. Countries, where clinical trial has been conducted	Belgium, Finland, Germany, Italy, the Netherlands, Poland, Russia, the United Kingdom, Ukraine (75 study sites)
9. Number of trial subjects	planned:692 actual:673 (completed)
10. Objective and secondary endpoints of clinical trial	To demonstrate the additional antihypertensive efficacy in lowering SeDBP gained by adding olmesartan medoxomil (OM) 10 mg, 20 mg, or 40 mg to the treatment regimen in patients with moderate to severe hypertension not adequately controlled on amlodipine (AML) 5 mg alone assessed by conventional BP measurements after 8 weeks of double-blind treatment.
11. Clinical trial design	A 52-week, phase III, randomised, parallel-group, multi-center, multi-national trial consisting of 4 periods: **Period I**: an 8-week, open-label treatment period with AML 5 mg monotherapy **Period II**: an 8-week, double-blind treatment period with randomization to a fixed combination of OM and AML **Period III**: an 8 week, double-blind treatment period with dose up-titration if needed. **Period IV**: a 28-week, open-label, long-term extension period with possible dose titration.
12. Main inclusion criteria	Patients enrolled into the study were male and female patients ≥18 years with moderate to severe hypertension. To enter period I, patients must have had a mead SeDBP≥100 mmHg and

	a mean SeSBP≥160 mmHg. To enter period II, patients must have had a mean SeDBP≥90 mmHg and a mean SeSBP≥140 mmHg. To enter Period III, patients must not have reached their BP goal of 140/90 mmHg (130/80 in diabetic patients) in Period II. To enter Period IV, patients must not have reached their BP goal of 140/90 mmHg (130/80 in diabetic patients) in Period III.
13. Investigational medicinal product, mode of administration and strength	Period I. AML 5 mg Period II: Placebo + AML 5 mg Period III: Placebo + AML 5 mg, OM 10 mg + AML 5 mg, OM 20 mg + AML 5 mg, OM 40 mg + AML 5 mg Period IV: OM 40 mg + AML 5 mg
14. Reference product, dose, mode of administration and strength	Period I: none Period II: , OM 10 mg + AML 5 mg, OM 20 mg + AML 5 mg, OM 40 mg + AML 5 mg Period III: OM 20 mg + AML 5 mg, OM 40 mg + AML 5 mg, OM 40 + AML 5 mg Period IV: OM 40 mg + AML 10 mg; OM 40 mg + AML 10 mg + HCT 12.5 mg; OM 40 mg + AML 10 mg + HCT 25 mg
15. Concomitant therapy	Standard antihypertensive therapy was allowed at study start and discontinued during the washout period.
16. Criteria for evaluation efficacy	• Mean SeDBP at weeks 28, 34, 43 and 52 • Mean SeSBP at weeks 28, 34, 43 and 52 • Mean changes in SeDBP and SeSBP during period IV with titration from one dose regimen to the next. • Number (%) of patients achieving BP goal (140/90 mmHg; 130/80 mmHg in diabetic patients) • Number (%) of patients reaching BP thresholds (<120/80 mmHg, <130/80 mmHg, <130/85 mmHg and 140/90 mmHg) during Period IV
17. Criteria for evaluation safety	Safety assessments included TEAEs, clinical laboratory test results, vital signs, physical examinations and 12-lead ECGs
18. Statistical methods	Mean SeDBP and SeSBP values were summarised at weeks 28, 34, 43 and 52 by treatment regimen for patients who entered

	Period IV. Descriptive statistics were computed for the titration effect, quantifying the mean change in SeDBP and SeSBP when the dose regimen was titrated from OM 40 mg + AML mg to OM 40 mg + AML 10 mg, from OM 40 mg + AML 10 mg to OM 40 mg + AML 10 mg + HCT 12.5 mg and from OM 40 mg + AML 10 mg + HCT 12.5 mg to OM 40 mg + AML 10 mg + HCT 25 mg.
19. Demographic indices of studied population (sex, age, race, etc.)	

Characteristic	All Patients Who Entered Period IV (N = 692)
Gender n (%)	
Male	430 (62.1)
Female	262 (37.9)
Ethnic origin n (%)	
Caucasian	690 (99.7)
Other	2 (0.3)
Age (years)	
n	692
Mean (SD)	55.7 (9.52)
Age group n (%)	
<65 years	547 (79.0)
≥65 years	145 (21.0)
≥65 years to <75 years	137 (19.8)
≥75 years	8 (1.2)
Weight (kg)	
n	692
Mean (SD)	84.3 (13.64)
Height (cm)	
n	692
Mean (SD)	170.8 (8.83)
Body mass index (kg/m²)	
n	692
Mean (SD)	28.8 (3.86)

20. Efficacy results

Time Point Statistic	OM40/ AML5	OM40/ AML10	OM40/ AML10/ HCTZ12.5	OM40/ AML10/ HCTZ25
Week 8 (baseline)				
N entering Period IV	692			
Sitting DBP mean (SD)	97.0 (5.11)			
Sitting SBP mean (SD)	154.5 (10.89)			
Week 28				
N	665	20		
Sitting DBP mean (SD)	84.1 (7.63)	89.7 (7.44)		
Sitting SBP mean (SD)	133.4 (12.68)	141.8 (14.45)		
n (%) to BP goal [1]	468 (70.4)	9 (45.0)		
Week 34				
N	546	114	13	4
Sitting DBP mean (SD)	83.6 (7.04)	90.6 (6.33)	89.6 (8.00)	86.3 (4.91)
Sitting SBP mean (SD)	132.3 (10.68)	143.2 (13.26)	143.1 (10.82)	140.8 (10.64)
n (%) to BP goal [1]	403 (73.8)	38 (33.3)	5 (38.5)	1 (25.0)
Week 43				
N	467	135	66	5
Sitting DBP mean (SD)	82.9 (6.08)	86.0 (6.42)	87.8 (6.57)	89.7 (8.66)
Sitting SBP mean (SD)	131.3 (10.55)	136.9 (11.10)	140.9 (10.62)	144.3 (13.29)
n (%) to BP goal [1]	364 (77.9)	76 (56.3)	23 (34.8)	2 (40.0)
Week 52 [2]				
N	431	142	68	27
Sitting DBP mean (SD)	83.2 (6.47)	85.3 (6.63)	87.3 (5.99)	89.7 (5.42)
Sitting SBP mean (SD)	131.6 (10.18)	134.8 (9.79)	138.3 (10.52)	145.6 (14.48)
n (%) to BP goal [1]	321 (74.5)	84 (59.2)	32 (47.1)	9 (33.3)
Week 52/ET				
N	452	144	68	27
Sitting DBP mean (SD)	83.1 (6.56)	85.4 (6.82)	87.3 (5.99)	89.7 (5.42)
Sitting SBP mean (SD)	131.4 (10.74)	135.0 (9.95)	138.3 (10.52)	145.6 (14.48)
n (%) to BP goal [1]	336 (74.3)	85 (59.0)	32 (47.1)	9 (33.3)

- Of the 691 patients exposed to OM 40 mg + AML 5 mg, 537 (77.7%) reached the <140/90 mmHg threshold, 361 (52.2%) reached the <130/85mmHg threshold. 229 (33.1%9 reached the <130/80 mmHg threshold and 91 (13.2%) reached the <120/80 mg threshold.
- Of the 243 patients exposed to OM 40 mg + AML 10 mg, 131 (53.9%) reached the <140/90 mmHg threshold, 50 (20.6%) reached the <130/85 mmHg threshold; 20 (8.2%) reached the <130/80 mmHg threshold and 6 (2.5%)

	reached the <120/80 mmHg threshold. • Of the 93 patients exposed to OM 40 mg + AML 10 mg + HCT 12.5 mg, 47 (50.5%) reached the <140/90 mmHg threshold, 10 (10.8%) reached the <130/85 mmHg threshold; 5 (5.4%) reached the <130/80 mmHg threshold and 1 (1.1%) reached the <120/80 mmHg threshold. • Of the 28 patients exposed to OM 40 mg + AML 10 mg + HCT 25 mg, 11 (39.3%) reached the <140/90 mmHg threshold, 1 (3.6%) reached the <130/85 mmHg threshold; none reached the lower BP thresholds.
21. Safety results	In total, 228 (33.0%) patients on Om 40 mg + AML 5 mg, 60 (24.7%) patients on OM 40 mg + AML 10 mg, 17 (18.3%) patients on OM 40 mg + AML 10 mg + HCT 12.5 mg, and 7 (25.0%) patients on OM 40 mg + AML 10 mg + HCT 25 mg had a TEAE during Period IV. 42 (6.1%) patients on OM 40 mg + AML 5 mg, 11 (4.5%) patients on OM 40 mg + AML 10 mg, 3 (3.2%) patients on OM 40 mg + AML 10 mg + HCT 12.5 mg and 1 (3.6%) patient on OM 40 mg + AML 10 mg + HCT 25 mg had a TEAE that was considered to be related to the study medication. Most TEAEs were mild to moderate in severity.
22. Conclusion (summary)	Long term treatment with OM + AML demonstrated maintenance of BP-lowering effects observed in earlier periods of the study. No new safety concerns with combination treatment with OM + AML with the possible addition of HCT were identified that were unexpected for these classes of drugs. Overall, the incidence of adverse events was low with all of the evaluated treatment regimens. Long-term treatment with OM + AML or the triple combination of OM + AML + HCT was safe and well tolerated.
Applicant (registration certificate holder)	(signature) Dr. Kai Schumacher (full name)

Clinical study report 10

1. Name of medicinal product (registration certificate №, if available)	ATTENTO ® PLUS 40/10/25 mg
2. Applicant	Menarini International Operations Luxembourg S.A., Luxembourg
3. Manufacturer	Daiichi Sankyo Europe GmbH, Germany (Manufacturing "in bulk", packaging, batch control and release) Berlin-Chemie AG, Germany (Packaging, batch control and release) Menarini - Von Heyden GmbH, Germany (Batch control and release)
4. Studies conducted:	yes
1) type of medicinal product, which has been or will be registered	Medicinal product with fixed combination
5. Title of clinical trial, code number of clinical trial	CS-8635-A-U101 A randomized, open-label, single dose, crossover study of olmesartan, amlodipine, and hydrochlorothiazide, to determine the bioavailability when administered as Benicar HCT® plus Norvasc® together versus separately in healthy volunteers
6. Phase of clinical trial	Phase I
7. Period of clinical trial	25 Jun 2007 to 03 Sep 2007
8. Countries, where clinical trial has been conducted	USA
9. Number of trial subjects	planned: 36 actual:32 (completed)
10. Objective and secondary endpoints of clinical trial	Primary; to determine bioavailability of olmesartan, amlodipine and hydrochlorothiazide when administered together as Benicar HCT® and Norvasc® and when administered alone. Secondary: to evaluate the safety and tolerability when Benicar® is coadministered with Norvasc®.
11. Clinical trial design	Open-label, randomised, single-dose 3 way crossover study.
12. Main inclusion criteria	Subjects enrolled were healthy men and women, aged 18-45 years (inclusive), who satisfied all inclusion/exclusion criteria
13. Investigational medicinal product, mode of administration and strength	Benicar HCT® (olmesartan medoxomil/hydrochlorothiazide)
14. Reference product, dose, mode of administration and strength	Norvasc® (amlodipine besylate)
15. Concomitant therapy	None
16. Criteria for evaluation efficacy	The following PK parameters were calculated for olmesartan, amlodipine and hydrochlorothiazide: AUC_{0-t}, AUC_{0-Inf}, AUC%extr, C_{max}, T_{max}, Lambda Z, $t_{1/2}$ and CL/F
17. Criteria for evaluation safety	Number and severity of TEAEs, physical examinations, vital signs, 12-lead ECGs, laboratory measurements.
18. Statistical methods	An analysis of variance (ANOVA) was performed on the ln-transformed AUC_{0-t}, AUC_{0-Inf} and C_{max} for OM, AML and HCT. The ANOVA model included sequence, treatment and period as fixed effects.

19. Demographic indices of studied population (sex, age, race, etc.)

Trait		Overall (n = 36)
Gender (N%)	Male	28 (77.8%)
	Female	8 (22.2%)
Ethnicity (N%)	Hispanic or Latino	11 (30.6%)
	Not Hispanic or Latino	25 (69.4%)
Race (N%)	American Indian/Alaskan Native	2 (5.6%)
	Asian	1 (2.8%)
	Black or African American	26 (72.2%)
	White	7 (19.4%)
Age (yr)	Mean ± SD	30.5 ± 7.66
	Median (Min – Max)	30.5 (19 –45)
Height (cm)	Mean ± SD	176.5 ± 9.85
	Median (Min – Max)	177.0 (156 – 193)
Weight (kg)	Mean ± SD	80.83 ± 12.559
	Median (Min – Max)	79.25 (53.6 – 107.6)
BMI (kg/m^2)	Mean ± SD	25.86 ± 2.829
	Median (Min – Max)	26.43 (19.4 – 31.0)

20. Efficacy results

Olmesartan	Treatment A N = 34	Treatment B N = 35
AUC_{0-t} (ng·h/mL) Arithmetic Mean ±SD	6134.4 ± 1676.74	6399.5 ± 1816.81
Geometric Mean (CV%)	5938.7 (25.8%)	6068.9 (38.3%)
AUC_{0-inf} (ng·h/mL) Arithmetic Mean ±SD	6249.8 ± 1678.98	6501.9 ± 1837.56
Geometric Mean (CV%)	6055.8 (25.5%)	6189.9 (35.8%)
C_{max} (ng/mL) Arithmetic Mean ±SD	912.5 ± 305.57	1016.3 ± 317.94
Geometric Mean (CV%)	871.2 (30.7%)	957.4 (40.2%)
T_{max} (h) Median (Min, Max)	1.983 (1.00, 4.00)	1.983 (1.00, 3.00)
$t_{½}$ (h) Arithmetic Mean ±SD	17.394 ± 7.8206	16.257 ± 8.6458
CL/F (L/h) Arithmetic Mean ±SD	6.804 ± 1.6651	6.958 ± 3.6439

	Geometric LSMEANS			
PK Parameter	Treatment A (Test)	Treatment B (Reference)	Ratio of LSMEANS (%) (A/B)	90% C.I. for Ratio (%)
AUC_{0-inf}	5989	6184	96.84	(89.14, 105.20)
AUC_{0-t}	5876	6068	96.83	(88.49, 105.96)
C_{max}	866.2	954.1	90.79	(83.24, 99.01)

Amlodipine	Treatment A N = 33*	Treatment C N = 34
AUC_{0-t} (ng.h/mL) Arithmetic Mean ±SD	339.1 ± 89.12	334.7 ± 95.38
Geometric Mean (CV%)	327.7 (27.5%)	321.3 (30.1%)
AUC_{0-inf} (ng.h/mL) Arithmetic Mean ±SD	381.9 ±112.01	378.3 ± 126.45
Geometric Mean (CV%)	365.8 (31.0%)	358.6 (34.2%)
C_{max} (ng/mL) Arithmetic Mean ±SD	7.456 ±1.9622	7.013 ± 2.0320
Geometric Mean (CV%)	7.224 (25.7%)	6.747 (28.7%)
T_{max} (h) Median (Min, Max)	7.017 (5.98, 12.0)	7.000 (5.97, 12.0)
$t_{½}$ (h) Arithmetic Mean ±SD	45.18 ±12.802	44.11 ± 12.909
CL/F (L/h) Arithmetic Mean ±SD	28.63 ± 9.356	29.43 ± 10.022

	Geometric LSMEANS			
PK Parameter	Treatment A (Test)	Treatment C (Reference)	Ratio of LSMEANS (%) (A/C)	90% C.I. for Ratio (%)
AUC_{0-inf}	365.6	361.8	101.05	(95.89, 106.49)
AUC_{0-t}	328.4	324.6	101.19	(96.71, 105.87)
C_{max}	7.186	6.768	106.18	(101.97, 110.56)

	Hydrochlorothiazide / **Treatment A N = 34** / **Treatment B N = 35** AUC_{0-t} (ng.h/mL) Arithmetic Mean ±SD: 1043.4 ± 224.90 / 1052.7 ± 231.13 Geometric Mean (CV%): 1020.7 (21.6%) / 1021.8 (27.4%) AUC_{0-inf} (ng.h/mL) Arithmetic Mean ±SD: 1069.3 ± 224.78 / 1079.8 ± 229.12 Geometric Mean (CV%): 1047.1 (21.0%) / 1050.9 (25.8%) C_{max} (ng/mL) Arithmetic Mean ±SD: 161.51 ± 53.714 / 164.78 ± 57.837 Geometric Mean (CV%): 153.90 (31.8%) / 155.34 (37.0%) T_{max} (h) Median (Min, Max): 1.5000 (0.983, 4.00) / 1.5000 (0.983, 4.00) $t_{½}$ (h) Arithmetic Mean ±SD: 10.800 ± 1.4435 / 10.866 ± 2.0647 CL/F (L/h) Arithmetic Mean ±SD: 24.38 ± 5.164 / 24.70 ± 8.513 **Geometric LSMEANS** **PK Parameter** / **Treatment A (Test)** / **Treatment B (Reference)** / **Ratio of LSMEANS (%) (A/B)** / **90% C.I. for Ratio (%)** AUC_{0-inf}: 1051 / 1050 / 100.06 / (95.01, 105.39) AUC_{0-t}: 1025 / 1021 / 100.33 / (94.93, 106.05) C_{max}: 154.9 / 155.1 / 99.89 / (91.97, 108.48)
21. Safety results	No serious or severe TEAEs occurred during the study. Overall, 16 subjects (44.4%) reported 62 TEAEs. No TEAE was considered definitely or probably drug-related. Overall, there was no clear difference for TEAEs between treatments A, B, and C.
22. Conclusion (summary)	The pharmacokinetics of olmesartan in the fixed dose combination (Benicar HCT®) are not affected by the co-administration of amlodipine. The PK of amlodipine are not affected by the fixed dose combination (Benicar HCT®). The PK of hydrochlorothiazide in the fixed dose combination (Benicar HCT®) are not affected by the co-administration of amlodipine. The concomitant administration of amlodipine besylate 10 mg, olmesartan medoxomil 40 mg and hydrochlorothiazide 25 mg was safe and well tolerated in this group of healthy male and female subjects.
Applicant (registration certificate holder)	(signature) Dr. Kai Schumacher (full name)

Clinical study report 11

1. Name of medicinal product (registration certificate №, if available)	ATTENTO ® PLUS 40/10/25 mg
2. Applicant	Menarini International Operations Luxembourg S.A., Luxembourg
3. Manufacturer	Daiichi Sankyo Europe GmbH, Germany (Manufacturing "in bulk", packaging, batch control and release) Berlin-Chemie AG, Germany (Packaging, batch control and release) Menarini - Von Heyden GmbH, Germany (Batch control and release)
4. Studies conducted:	yes
1) type of medicinal product, which has been or will be registered	Medicinal product with fixed combination
5. Title of clinical trial, code number of clinical trial	866-126 A randomized, open-label, three-way crossover bioequivalence study of CS-866 tablets plus hydrochlorothiazide capsules or tablets and CS-866/hydrochlorothiazide combination tablets in healthy adult volunteers.
6. Phase of clinical trial	Phase I
7. Period of clinical trial	10 Aug 2001 to 28 Aug 2001
8. Countries, where clinical trial has been conducted	USA
9. Number of trial subjects	planned: 33 actual:30(completed)
10. Objective and secondary endpoints of clinical trial	To determine the bioequivalence of the clinical trial supply of CS-866 tablets and hydrochlorothiazide (HCT) capsules or tablets administered orally in combination versus oral administration of the market-image single-tablet formulation of CS-866/HCT.
11. Clinical trial design	A randomized, open-label, 3-way crossover comparison of single oral doses of CS-866 (20 mg) in combination with HCT (12.5 mg) administered to healthy male and female volunteers.
12. Main inclusion criteria	Volunteers for the study were healthy male and non-pregnant female subjects between 18-45 years (inclusive) who were practicing an acceptable form of birth control (females only), were within acceptable body weights and height ranges, had not used tobacco products in the last 12 months, had a negative urine drug/alcohol screen, and signed an informed consent form.
13. Investigational medicinal product, mode of administration and strength	20 mg CS-866/12.5 mg HCT market image combination tablet, single-dose, p.o. (formulation C)
14. Reference product, dose, mode of administration and strength	20 mg CS-866 investigational tablet + 12.5 mg HCT capsule, single-dose, p.o. (formulation A) 20 mg CS-866 investigational tablet + 12.5 mg NCT tablet, single-dose, p.o. (formulation B)
15. Concomitant therapy	None

16. Criteria for evaluation efficacy	$AUC_{0\text{-}lqc}$, $AUC_{0\text{-}lqc}$, C_{max}, k_{el} and $t_{1/2}$ for the CS-866 metabolite RNH-6270 and HCT
17. Criteria for evaluation safety	Physical examinations, vital signs, clinical adverse events and hematology, blood chemistry and urinalysis test results.
18. Statistical methods	Ln-transformed $AUC_{0\text{-}lqc}$, $AUC_{0\text{-}Inf}$ and C_{max} were analysed by ANOVA: The formulation differences and their corresponding 90% CIs were obtained from the analysis and were exponentiated to obtain the formulation bioequivalence ratios and their corresponding 90% CIs.
19. Demographic indices of studied population (sex, age, race, etc.)	ALL SUBJECTS TOTAL N (%) 33 (100%) GENDER N (%) MALE 17 (52%) FEMALE 16 (48%) RACE N (%) CAUCASIAN 12 (36%) BLACK 14 (42%) ASIAN 1 (3%) HISPANIC 5 (15%) OTHER 1 (3%) FRAME SIZE N (%) SMALL 2 (6%) MEDIUM 26 (79%) LARGE 5 (16%) AGE (yr) MEAN (SD) 26.5 (7.87) RANGE 18.0 - 44.0 HEIGHT (in) MEAN (SD) 66.0 (4.07) RANGE 59.0 - 73.0 WEIGHT (lb) MEAN (SD) 156.1 (25.96) RANGE 114.0 -212.0
20. Efficacy results	The CS-866/HCT market image combination tablet (formulation C) and the investigational CS-866 tablet in combination with marketed HCT capsule (formulation A: US) or tablet (formulation B; Europe) were bioequivalent. The ratio point estimates for RNH-6270 were 1.04, 1.04 and 1.08 for $AUC_{0\text{-}lqc}$, $AUC_{0\text{-}Inf}$ and C_{max}, respectively, between formulations C and A. The 90% CI for all 3 ratios were contained within the standard bounds for bioequivalence. Similarly, RNH-6270 ratio point estimates were 1.07, 1.07 and 1.08 for $AUC_{0\text{-}lqc}$, $AUC_{0\text{-}Inf}$ and C_{max}, respectively between formulations C and B, and the 90% CI for all 3 ratios were contained well within the bounds for bioequivalence. Please see the summary PK for RNH-6270 below: TABLE 7.2.8.1 SUMMARY OF PLASMA PHARMACOKINETIC PARAMETERS FOR RNH-6270 FORMULATION A (N=30) / FORMULATION B (N=30) / FORMULATION C (N=30) / FORM C TO FORM A COMPARISON RATIO POINT ESTIMATE (N=30) / FORM C TO FORM A COMPARISON 90% CI (N=30) / FORM C TO FORM B COMPARISON RATIO POINT ESTIMATE (N=30) / FORM C TO FORM B COMPARISON 90% CI (N=30) PARAMETER / MEAN (SD) / MEAN (SD) / MEAN (SD) AUC 0-lqc (ng/mL)*hr 3463.96 (736.59) 3372.77 (781.04) 3602.66 (917.46) 1.04 0.90 - 1.19 1.07 1.01 - 1.13 AUC 0-Inf (ng/mL)*hr 3561.43 (843.38) 3459.21 (805.15) 3696.51 (872.01) 1.04 0.98 - 1.10 1.07 1.01 - 1.13 Cmax (ng/mL) 559.67 (123.83) 559.67 (110.09) 600.00 (136.61) 1.08 1.02 - 1.15 1.08 1.01 - 1.15 Tmax (hr) 2.00* 1.50* 2.00* - - - - t 1/2 (hr) 21.44 (17.60) 21.59 (19.47) 20.44 (16.37) - - - - Bioequivalence also was observed for HCT, with ratio point estimates and 90% CI of the ratios between formulations similar to those observed for RNH-6270. Please see the summary PK for HCT below:

	TABLE 7.2.3.2 SUMMARY OF PLASMA PHARMACOKINETIC PARAMETERS FOR HYDROCHLOROTHIAZIDE (HCTZ) PARAMETER — FORMULATION A (N=30) MEAN (SD) — FORMULATION B (N=30) MEAN (SD) — FORMULATION C (N=30) MEAN (SD) — FORM C TO FORM A COMPARISON RATIO POINT ESTIMATE (N=30) — FORM C TO FORM A COMPARISON 90% CI (N=30) — FORM C TO FORM B COMPARISON RATIO POINT ESTIMATE (N=30) — FORM C TO FORM B COMPARISON 90% CI (N=30) AUC 0-tqc (ng/mL)*hr — 507.33 (155.53) — 484.62 (137.05) — 522.00 (121.38) — 1.04 — 0.98 - 1.10 — 1.07 — 1.01 - 1.15 AUC 0-Inf (ng/mL)*hr — 588.79 (140.16) — 565.79 (134.78) — 584.55 (117.96) — 1.06 — 0.99 - 1.10 — 1.06 — 1.02 - 1.14 Cmax (ng/mL) — 90.34 (29.93) — 88.84 (27.54) — 94.30 (31.97) — 1.06 — 0.98 - 1.15 — 1.06 — 0.98 - 1.15 Tmax (hr) — 2.00* — 1.50* — 1.50* — - — - — - t 1/2 (hr) — 11.20 (7.22) — 10.58 (2.62) — 11.02 (2.05) — - — - — -
21. Safety results	10 TEAEs were reported by 7 (21.9%) subjects who received 20 mg CS-866+12.5 mg HCT (formulation A), 23 TEAEs were reported by 6 (19.4%) subjects who received 20 mg CS-866+12.5 mg HCT tablet (formulation B) and 17 TEAEs were reported by 12 subjects who received the market image combination tablet (formulation C) Headache, dizziness and nausea were the most common TEAEs overall. One subject who experienced 14 of the 23 TEAEs after receiving formulation B was withdrawn due to nausea and vomiting. No serious TEAEs were reported.
22. Conclusion (summary)	The study demonstrated that the market-image combination tablet formulation of CS-866/HCT was bioequivalent to the clinical supplies used in US clinical studies (CS-866 + HCT capsules) and European clinical studies (CS-866 investigational tablets + HCT tablets). The 90% CI surrounding the ratio point estimates for $AUC_{0\text{-}tqc}$, $AUC_{0\text{-}Inf}$ and C_{max} for RNH-6270 and for HCT all were within the standard bounds (0.80, 1.25) for bioequivalence.
Applicant (registration certificate holder)	_____ (signature) Dr. Kai Schumacher (full name)

Clinical study report 12

1. Name of medicinal product (registration certificate №, if available)	ATTENTO ® PLUS 40/10/25 mg
2. Applicant	Menarini International Operations Luxembourg S.A., Luxembourg
3. Manufacturer	Daiichi Sankyo Europe GmbH, Germany (Manufacturing "in bulk", packaging, batch control and release) Berlin-Chemie AG, Germany (Packaging, batch control and release) Menarini - Von Heyden GmbH, Germany (Batch control and release)
4. Studies conducted:	yes
1) type of medicinal product, which has been or will be registered	Medicinal product with fixed combination
5. Title of clinical trial, code number of clinical trial	866-138 A randomized, open-label, three-way crossover bioequivalence study of 40 mg CS-866 tablets plus 12.5 mg hydrochlorothiazide capsules or tablets and 40/12.5 mg CS-866/hydrochlorothiazide combination tablets in healthy adult volunteers.
6. Phase of clinical trial	Phase I
7. Period of clinical trial	18 Dec 2002 to 07 Jan 2003
8. Countries, where clinical trial has been conducted	USA
9. Number of trial subjects	planned: 42 actual: 38 (completed)
10. Objective and secondary endpoints of clinical trial	To determine the bioequivalence of the market-image, single tablet treatment of CS-866-hydrochlorothiazide (Test, treatment C) to the clinical supply of CS-866 (olmesartan medoxomil) tablets + hydrochlorothiazide capsules (Reference, treatment A) and the clinical supply of CS-866 + hydrochlorothiazide tablets (Reference, treatment B).
11. Clinical trial design	A randomized, open-label, 3-way crossover comparison of single oral doses of CS-866 (40 mg) in combination with HCT (12.5 mg) administered to healthy male and female volunteers.
12. Main inclusion criteria	Volunteers for this study were healthy male and non-pregnant female subjects between 19-45 years (inclusive) who were practicing an acceptable form of birth control (females only), were within acceptable body weight and height ranges, had not used tobacco products in the last 12 months, had a negative urine drug/alcohol screen and signed an informed consent.
13. Investigational medicinal product, mode of administration and strength	Treatment C: 40/12.5 mg CS-866/HCT market-image combination tablet, single dose, p.o.
14. Reference product, dose, mode of administration and strength	Treatment A: 40 mg CS-866 investigational tablet + 12.5 mg HCT capsules, single dose, p.o. Treatment B: CS-866 Investigational tablet + 12.5 mg HCT tablet, single dose, p.o.
15. Concomitant therapy	None
16. Criteria for evaluation efficacy	$AUC_{0\text{-}Inf}$, $AUC_{0\text{-}lqc}$, C_{max}, T_{max}, k_{el}, $t_{1/2}$ of RNH-6270 (the active metabolite of CS-866).

17. Criteria for evaluation safety	Physical examination findings, vital sig measurement, clinical adverse events and serum chemistry test results.
18. Statistical methods	Ln-transformed $AUC_{0\text{-}lqc}$, $AUC_{0\text{-}Inf}$ and C_{max} were analyzed by ANOVA. The treatment differences and their corresponding 90%CIs were obtained from the analyses and were exponentiated to obtain treatment bioequivalence ratios and their corresponding 90% CIs.
19. Demographic indices of studied population (sex, age, race, etc.)	
20. Efficacy results	

	ALL SUBJECTS
TOTAL	
N (%)	42 (100%)
GENDER N (%)	
MALE	27 (64%)
FEMALE	15 (36%)
RACE N (%)	
CAUCASIAN	32 (76%)
BLACK	3 (7%)
ASIAN	2 (5%)
HISPANIC	3 (7%)
OTHER^	2 (5%)
FRAME SIZE N (%)	
SMALL	4 (10%)
MEDIUM	30 (71%)
LARGE	8 (19%)
AGE (yr)	
MEAN (SD)	28.4 (7.60)
RANGE	19.0 - 44.0
HEIGHT (in)	
MEAN (SD)	68.1 (4.17)
RANGE	60.0 - 76.0
WEIGHT (lb)	
MEAN (SD)	154.1 (25.87)
RANGE	115.0 -218.0

RNH-6270 PK Parameters

Parameter	Treatment A (n=40)[1] Mean (SD) Geomean (%CV) Median	Treatment B (n=40)[1] Mean (SD) Geomean (%CV) Median	Treatment C (n=40)[1] Mean (SD) Geomean (%CV) Median
$AUC_{0\text{-}lqc}$ (ng.h/mL)	6632.70 (1704.33) 6406.51 (28.04) 6628.59	6601.34 (2056.43) 6312.44 (30.75) 6311.93	6362.25 (1525.58) 6188.20 (24.21) 6137.50
$AUC_{0\text{-}\infty}$ (ng.h/mL)	6758.62 (1698.51) 6539.03 (27.22) 6694.36	6742.66 (2090.74) 6445.73 (30.99) 6609.46	6569.04 (1587.33) 6384.67 (24.62) 6342.09
C_{max} (ng/mL)	1048.08 (289.24) 1010.07 (28.89) 989.36	1050.03 (331.47) 1006.05 (29.67) 977.20	1070.66 (269.76) 1038.95 (25.12) 985.31
$C_{max}/AUC_{0\text{-}\infty}$ (1/h)	0.16 (0.03)	0.16 (0.03)	0.17 (0.03)
T_{max} (hrs)	2.00*	2.00*	1.50*
$T_{1/2}$ (hrs)	19.31 (15.97) 13.44	19.03 (13.39) 13.87	21.44 (21.02) 14.30

Parameter	Treatment C vs. Treatment A Ratio Point Estimate (90% CI)[1]	Treatment C vs. Treatment B Ratio Point Estimate (90% CI)[1]
$AUC_{0\text{-}lqc}$	0.97 (0.90, 1.04)	0.97 (0.91, 1.05)
$AUC_{0\text{-}\infty}$	0.98 (0.91, 1.05)	0.99 (0.92, 1.06)
C_{max}	1.03 (0.96, 1.11)	1.03 (0.96, 1.11)
$C_{max}/AUC_{0\text{-}\infty}$	1.05 (1.00, 1.11)	1.04 (0.98, 1.10)

HCTZ PK Parameters

Parameter	Treatment A (n=40)[1] Mean (SD) Geomean (%CV) Median	Treatment B (n=40)[1] Mean (SD) Geomean (%CV) Median	Treatment C (n=40)[1] Mean (SD) Geomean (%CV) Median
$AUC_{0\text{-}lqc}$ (ng.h/mL)	493.41 (100.12) 483.51 (20.74) 481.93	489.24 (121.77) 475.07 (24.86) 471.22	472.11 (108.48) 460.60 (22.71) 456.24
$AUC_{0\text{-}\infty}$ (ng.h/mL)	541.88 (95.94) 533.54 (18.11) 531.93	542.54 (120.95) 530.08 (21.92) 524.44	521.79 (104.98) 512.02 (19.74) 508.59
C_{max} (ng/mL)	80.39 (21.71) 77.67 (27.64) 78.29	79.98 (29.71) 74.76 (33.09) 71.46	78.18 (22.12) 75.24 (28.63) 76.01
$C_{max}/AUC_{0\text{-}\infty}$ (1/h)	0.15 (0.03)	0.14 (0.03)	0.15 (0.03)
T_{max} (hrs)	1.75*	1.75*	1.50*
$T_{1/2}$ (hrs)	9.63 (1.83) 9.60	10.18 (1.72) 10.07	10.01 (1.96) 9.98

Parameter	Treatment C vs. Treatment A Ratio Point Estimate (90% CI)[1]	Treatment C vs. Treatment B Ratio Point Estimate (90% CI)[1]
$AUC_{0\text{-}lqc}$	0.95 (0.90, 1.00)	0.97 (0.92, 1.02)
$AUC_{0\text{-}\infty}$	0.96 (0.92, 1.00)	0.96 (0.92, 1.01)
C_{max}	0.97 (0.90, 1.04)	1.01 (0.93, 1.08)
$C_{max}/AUC_{0\text{-}\infty}$	1.01 (0.95, 1.07)	1.04 (0.99, 1.10)

21. Safety results	A total of 16 TEAEs were experienced by 11 (27.5%) subjects who received 40 mg CS-866 + 12.5 mg HCT capsules (treatment A), 15 TEAEs were experienced by 10 (23.8%) subjects who received 40 mg CS-866 + 12.5 HCT tablets (treatment B), and 11 TEAEs were experienced by 8 (20.6%) subjects who received 40/12.5 market-image combination tablet (treatment C). No TEAE was judged to be severe in severity. The most common TEAEs were dizziness and headache. Only one subject was withdrawn from the study due to an adverse event (tachycardia), and no serious adverse event occurred.
22. Conclusion (summary)	The total exposure and peak exposure of RNH-6270 were bioequivalent between the 40/12.5 mg CS-866/HCT market image tablet (treatment C), the 40 mg CS-866 + 12.5 mg HCT capsule US clinical supplies (treatment A) and the 40 mg CS-866 + 12.5 mg HCT tablet European clinical supply (treatment B). The total exposure and peak exposure to HCT were bioequivalent between the 40/12.5 mg CS-866/HCT market image tablet (treatment C), the 40 mg CS-866 + 12.5 mg HCT capsule US clinical supplies (treatment A) and the 40 mg CS-866 + 12.5 mg HCT tablet European clinical supply (treatment B).
Applicant (registration certificate holder)	(signature) Dr. Kai Schumacher (full name)

Clinical study report 13

1. Name of medicinal product (registration certificate №, if available)	ATTENTO ® PLUS 40/10/25 mg **41**
2. Applicant	Menarini International Operations Luxembourg S.A., Luxembourg
3. Manufacturer	Daiichi Sankyo Europe GmbH, Germany (Manufacturing "in bulk", packaging, batch control and release) Berlin-Chemie AG, Germany (Packaging, batch control and release) Menarini - Von Heyden GmbH, Germany (Batch control and release)
4. Studies conducted:	yes
1) type of medicinal product, which has been or will be registered	Medicinal product with fixed combination
5. Title of clinical trial, code number of clinical trial	CS8635-A-U102 A randomized, open-label, single-dose crossover study to determine the bioavailability of olmesartan, amlodipine and hydrochlorothiazide when administered as CS-8663 plus Hydrochlorothiazide together versus separately in healthy subjects
6. Phase of clinical trial	Phase I
7. Period of clinical trial	21 June 2007 to 09 Aug 2007
8. Countries, where clinical trial has been conducted	USA
9. Number of trial subjects	planned: 36 actual:29 (completed)
10. Objective and secondary endpoints of clinical trial	Primary: to determine the bioavailability of olmesartan, amlodipine and hydrochlorothiazide when administered together as CS-8663 (olmesartan plus amlodipine besylate) and hydrochlorothiazide, and when administered alone Secondary: to evaluate the safety and tolerability when CS-8663 is co-administered with hydrochlorothiazide
11. Clinical trial design	Open label, randomized, single-dose, 3-way crossover study
12. Main inclusion criteria	Subjects enrolled were healthy adult men and women, aged 19-45 years (inclusive) who satisfied all inclusion/exclusion criteria
13. Investigational medicinal product, mode of administration and strength	CS-8663 (olmesartan medoxomil and amlodipine besylate) 40 mg/10 mg oral tablet
14. Reference product, dose, mode of administration and strength	Hydrochlorothiazide 25 mg oral tablet
15. Concomitant therapy	None
16. Criteria for evaluation efficacy	AUC_{0-t}, AUC, $_{0-Inf}$, AUC%extr, C_{max}, T_{max}, Lambda Z, $t_{1/2}$ and CL/F
17. Criteria for evaluation safety	Number and severity of TEAEs, physical examination, vital signs, 12-lead ECGs and laboratory measurements
18. Statistical methods	An analysis of variance (ANOVA) was performed on ln-transformed AUC_{0-t}, AUC_{0-Inf} and C_{max}. The ANOVA model included sequence, treatment and period as fixed effects

19. Demographic indices of studied population (sex, age, race, etc.)

Trait		Overall (n = 36)
Gender (N%)	Male	30 (83.3%)
	Female	6 (16.7%))
Ethnicity (N%)	Hispanic or Latino	8 (22.2%)
	Not Hispanic or Latino	28 (77.8%)
Race (N%)	Asian	1 (2.8%)
	Black or African American	27 (75.0%)
	White	8 (22.2%)
Age (yr)	Mean ± SD	31.1 ± 7.75
	Median (Min – Max)	30.5 (19 – 45)
Height (cm)	Mean ± SD	173.5 ± 8.47
	Median (Min – Max)	173.5 (156 – 188)
Weight (kg)	Mean ± SD	78.4 ± 12.578
	Median (Min – Max)	76.5 (54.0 – 104.8)
BMI (kg/m^2)	Mean ± SD	26.03 ± 3.628
	Median (Min – Max)	26.22 (19.0 – 31.9)

20. Efficacy results

Olmesartan	Treatment A N = 33*	Treatment B N = 30
AUC_{0-t} (ng.h/mL)		
Arithmetic Mean ±SD	6976.9 ± 1709.89	6776.1 ± 1503.53
Geometric Mean (CV%)	6759.8 (26.8%)	6617.3 (22.5%)
AUC_{0-inf} (ng.h/mL)		
Arithmetic Mean ±SD	7113.4 ± 1748.65	6879.1 ± 1506.23
Geometric Mean (CV%)	6896.2 (26.3%)	6721.5 (22.3%)
C_{max} (ng/mL)		
Arithmetic Mean ±SD	1070.1 ± 304.01	1055.1 ± 306.40
Geometric Mean (CV%)	1028.6 (29.6%)	1013.6 (29.6%)
T_{max} (h)		
Median (Min, Max)	1.9830 (0.983, 3.98)	2.000 (1.00, 4.00)
$t_{\frac{1}{2}}$ (h)		
Arithmetic Mean ±SD	15.835 ± 6.1931	15.560 ± 6.1679
CL/F (L/h)		
Arithmetic Mean ±SD	6.001 ± 1.6977	6.093 ± 1.3700

	Geometric LSMEANS			
PK Parameter	Treatment A (Test)	Treatment B (Reference)	Ratio of LSMEANS (%) (A/B)	90% C.I. for Ratio (%)
AUC_{0-inf}	6912	6537	105.74	(99.15, 112.77)
AUC_{0-t}	6763	6395	105.76	(99.01, 112.97)
C_{max}	1020	975.8	104.56	(96.84, 112.90)

Amlodipine	Treatment A N = 33	Treatment B N = 30
AUC_{0-t} (ng.h/mL)		
Arithmetic Mean ±SD	359.4 ± 127.09	364.7 ± 110.24
Geometric Mean (CV%)	338.0 (37.0%)	347.2 (33.9%)
AUC_{0-inf} (ng.h/mL)		
Arithmetic Mean ±SD	410.0 ± 170.89	416.0 ± 139.30
Geometric Mean (CV%)	378.7 (42.0%)	392.1 (37.2%)
C_{max} (ng/mL)		
Arithmetic Mean ±SD	7.301 ± 2.0067	7.782 ± 2.4615
Geometric Mean (CV%)	7.027 (29.1%)	7.426 (31.9%)
T_{max} (h)		
Median (Min, Max)	7.017 (5.98, 16.0)	7.983 (5.98, 12.0)
$t_{\frac{1}{2}}$ (h)		
Arithmetic Mean ±SD	44.36 ± 10.765	46.36 ± 11.213
CL/F (L/h)		
Arithmetic Mean ±SD	28.51 ± 11.213	27.23 ± 10.559

	Geometric LSMEANS			
PK Parameter	Treatment A (Test)	Treatment B (Reference)	Ratio of LSMEANS (%) (A/B)	90% C.I. for Ratio (%)
AUC_{0-inf}	383.3	386.4	99.18	(95.50, 103.00)
AUC_{0-t}	343.7	341.4	100.68	(97.37, 104.11)
C_{max}	7.269	7.399	98.25	(93.62, 103.11)

Hydrochlorothiazide	Treatment A N = 32	Treatment C N = 33
AUC_{0-t} (ng.h/mL)		
Arithmetic Mean ±SD	1054.7 ± 202.82	1127.8 ± 251.41
Geometric Mean (CV%)	1036.4 (19.1%)	1102.0 (21.9%)
AUC_{0-inf} (ng.h/mL)		
Arithmetic Mean ±SD	1081.4 ± 202.63	1153.5 ± 249.21
Geometric Mean (CV%)	1063.5 (18.7%)	1128.7 (21.3%)
C_{max} (ng/mL)		
Arithmetic Mean ±SD	158.46 ± 50.355	162.92 ± 45.449
Geometric Mean (CV%)	150.38 (34.9%)	156.92 (28.3%)
T_{max} (h)		
Median (Min, Max)	1.742 (1.00, 8.97)	1.9830 (0.983, 4.03)
$t_{\frac{1}{2}}$ (h)		
Arithmetic Mean ±SD	11.151 ± 1.6693	10.839 ± 1.4503
CL/F (L/h)		
Arithmetic Mean ±SD	23.90 ± 4.426	22.62 ± 4.718

	Geometric LSMEANS

PK Parameter	Treatment A (Test)	Treatment C (Reference)	Ratio of LSMEANS (%) (A/C)	90% C.I. for Ratio (%)
AUC_{0-inf}	1083	1131	95.74	(92.79, 98.79)
AUC_{0-t}	1056	1104	95.64	(92.64, 98.74)
C_{max}	152.7	158.7	96.24	(88.85, 104.24)

21. Safety results	No serious TEAEs or deaths occurred during the study. Overall, 20 subjects reported 60 TEAEs. No TEAE was considered definitely or probably drug-related. Differences were noted between Treatments A, B and C with respect to the overall number of subjects with at least 1 TEAE, with a slight increase apparent in Treatment B (olmesartan and amlodipine combination therapy): Within each treatment, 8 (24.2%) subjects in Treatment A and 10 (31.3%) subjects in Treatment B experienced TEAEs that were considered related to the study drugs. Only 3 (8.8%) subjects in Treatment C experienced TEAEs related to the study drug.
22. Conclusion (summary)	The pharmacokinetics (PK) of olmesartan administered as the fixed dose combination (CS-8663) are not affected by co-administration of hydrochlorothiazide. The PK of amlodipine administered as the fixed dose combination (CS-8663) are not affected by the co-administration of hydrochlorothiazide. The PK of hydrochlorothiazide are not affected by the co-administration of the fixed dose combination of olmesartan medoxomil and amlodipine besylate (CS-8663). The concomitant oral administration of amlodipine besylate 10 mg, olmesartan medoxomil 40 mg and hydrochlorothiazide 25 mg was safe and well tolerated in this group of healthy male and female subjects.
Applicant (registration certificate holder)	_____ (signature) __Dr. Kai Schumacher_____ (full name)

{Procedure amended by new annex 30 according to MoH Ukraine Order № 1528 of 27.06.2019 }