Annex 29
to the Procedure for Conducting Expert
Evaluation of Registration Materials
Pertinent to Medicinal Products
Submitted for the State Registration (ReRegistration) 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	ATTENTO® PLUS 40/10/25
certificate №, if any):	
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 intraand inter-assay precision and accuracy.
	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)	
(Presimination)	AAMACKIHA A.B BIPA

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



Annex 30
to the Procedure for Conducting Expert
Evaluation of Registration Materials
Pertinent to Medicinal Products
Submitted for the State Registration (ReRegistration) 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. 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
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	CS8635-A-E105
trial	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



	MIF at	its highest and	l lowest streng	ths dose (HD a	and LD)
11 (1)		nations			
11. Clinical trial design	Phase .	I, open-label, 4	-period crosso	ver study	
12. Main inclusion criteria	Female	Subjects were healthy males and females, 18 to 45 years of age. Female subjects were sterile, post-menopausal or using acceptable contraception.			years of age.
13. Investigational					
medicinal product, mode of administration and strength	daily	ent A HD-MII	1: CS-8635 40	mg/10 mg/ 25	mg p.o. once
	daily	ent B: LD-MII			
14. Reference product,	Treatm	ent C: HD-RF	I: Benicar® Ho	CT 40/25 mg,	Antacal® 10
dose, mode of administration and strength	mg p.o	once daily			
	Treatm mg p.o	ent D: LD-RFI . once daily	Benicar® HC	T 20/12.5 mg,	Antacal® 5
	Treatment: E: HD-RFII Azor ® 40/10 mg; Hydrochlord 25 mg				hlorothiazide
	Treatm 12.5 m	ent F: LD-RFI	I Azor® 20/5 1	ng, hydrochlor	rothiazide
<ol><li>Concomitant therapy</li></ol>	None				
16. Criteria for evaluation efficacy	The 90% Confidence Interval (CI) of the ratios of geometric least square means for the PK parameters AUC last, AUC <sub>0-inf</sub> and C <sub>max</sub> for each analyte (OM/AML/HCT) of the CS-8635 MIF to				AUC <sub>0-inf</sub> and 8635 MIF to
		rence clinical t			
17. Criteria for evaluation safety	Safety a measur	assessments inc ements, vital si	cluded Adverse gns, physical e	e Events, clinic	cal laboratory
18. Statistical methods	Analysi period a square	is of Variance (as factors. Each means (LSM), standard error	(ANOVA) with ANOVA included the difference	h sequence, tre uded calculati between treatr	eatment, on of least nent LSM,
<ol> <li>Demographic indices of studied population (sex,</li> </ol>	Den	nographic Trait	Cahart I Overali	Cohart 2 Overall	Overall
age, race, etc.)	Gender	Male	27 (75.0%)	26 (72.2%)	53 (73.6%)
	N (%) Ethnicity	Pemale	9 (25.0%)	10 (27.8%)	19 (26.4%)
	N (%)	Not Hispanic/Latino	36 (100.0%)	36 (100.0%)	72 (100.0%)
	Race N (%)	Black Caucasian	1 (2.8%) 35 (97.2%)	0 (0.0%) 36 (100.0%)	1 (1.4%)
	Age	Mean ± SD	28.9 ± 6.62	28.6 ± 7.80	71 (98.6%) 28.7 ± 7.19
	(yr)	Median (Min - Max)	27.0 (19 - 45)	28.5 (18 44)	27.5 (18 – 45)
	Height (cm)	Mean + SD	175.4 ± 8.49	172.3 ± 9.44	173.8 ± 9.05
	Weight	Median (Min – Max) Mean ± SD	176.5 (157 – 194) 76.84 ± 11.431	174.0 (151 - 191) 74.60 ± 12.930	175.0 (151 – 194)
	(kg)	Median (Min – Max)	78.20 (56.8 - 108.6)	76.95 (44.0 - 95.4)	75.72 ± 12.169 77.75 (44.0 – 108.6)
	ВМІ	Mean ± SD	24.944 ± 2.9188	24.955 ± 2.8389	24.949± 2.8588
	(kg/m²)	Median (Min – Max)	25.045 (18.55 – 29.89)	25.260 (19.30 - 29.92)	25.090 (18.55 – 29.92)



#### 20. Efficacy results Statistical Comparisons of the PK Parameters of HCT between the High Dose CS-8635 MIF and Reference Formulations - Cohort 1 Ratio of Geometrie LSM and 90% CI (%) Treatment A Treatment C Treatment E AC Test Reference I Reference II AUC 101.66 96.50 1152 1133 1194 (ng-h/mL) (96.83, 106.73) (91.83, 101,40) AUC 101.57 96.58 1177 1159 1219 (ng·h/mL) (96.86, 106.51) (92.02, 101.37) 103.11 103 25 183.6 178.1 177.9 (ng/mL) (94.13, 112.95) (94.01, 113.39) Statistical Comparisons of the PK Parameters of HCT between the Low Dose CS-8635 MIF and Reference Formulations - Cohort 2 Ratio of Geometric LSM Geometric LSM and 90% CI (%) Treatment B Treatment D Treatment F Test Reference I Reference II AUC. 97.53 100.37 562.6 576.8 560.5 (ng-h/mL) (93.53, 101.69) (96.30, 104.61) AUC ... 97.89 100.75 584.8 597.4 580.5 (ng·h/mL) (94.11, 101.84) (96.89, 104.76) Coux (ag/mL) 106.32 113.53 91.90 86.44 80.94 (97.33, 116.14) (104.03, 123.91) 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 Geometric LSM Ratio of Genmetric LSM (C/E) **Parameters** Treatment C Treatment E and 96% CI (%) Reference AUC ... 04 02 1133 1194 (ng-h/mL) (90.25, 99.83) AUC. 95.09 1150 1219 (ng-b/mL) (90.52, 99.89) 100.13 178.1 (ng/ml.) (91.14, 110.02) 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 Geometric LSM Ratio of Geometric LSM (D/F) and 98% CI (%) **Parameters** Treatment D Treatment F Test Reference AUChas 102.92 560.5 (ng-h/mL) (98.78, 107.22) AUC 102.92 597.4 580.5 (ng-h/mL) (99.02, 106.97) C<sub>aux</sub> (ng/mL) 106.78 80.94 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



(signature)

Dr. Kai Schumacher

(full name)

KOTI A

ATTENTO ® PLUS 40/10/25 mg 5
Menarini International Operations Luxembourg S.A., Luxembourg
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)
yes
Medicinal product with fixed combination
fCS-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.
Phase I
10 Jan 2008 to 03 Apr 2008
USA
planned: 41 actual:28 (completed)
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).
Open-label, randomized, 2-way crossover study
Subjects enrolled were healthy adult men and women aged 18-45 years (inclusive) who satisfied all inclusion/exclusion criteria
Treatment A: CS-8635 (olmesartan medoxomil 40 mg/amlodipine
besylate 10 mg/HCT 25 mg) pilot formulation A
Benicar HCT® 40/25 mg tablets
Antacal ® 10 mg tablets
None
AUC0-t, AUC, 0-Inf, AUC%extr, Cmax, Tmax, Lambda Z, t1/2 and CL/F
Number and severity of TEAEs, physical examination, vital signs, 12-lead ECGs and laboratory

#### 18. Statistical methods

measurements

An analysis of variance (ANOVA) was performed on the In-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.)

	(22)		Treatment Sequence	has a second and a second	
Trait	AB (N=21)	BA (N = 29)	Overall (N=41)		
Gender	Male	18 (85.7%)	18 (90.0%)	36 (87.8%)	
N(%)	Female	3 (14.3%)	2(10.0%)	5 (12.2%)	
	American Indian/ Alaskan Native	1 (4.8%)	0	1 (2.4%)	
Race N(%)	Asian	0	2 (10.0%)	2(4.9%)	
14(10)	Black or African American	10 (47.6%)	16 (80.0%)	26 (63.4%)	
	White	10 (47.6%)	2 (10.0%)	12 (29.3%)	
Ethnicity	Hispanic or Latino	7 (33.3%)	4 (20.0%)	11 (26.8%)	
N(%) Not Hispanic or Latino		14 (66.7%)	16 (80.0%)	30 (73,2%)	
Age ±SD			34.5 ± 7.97	30.0 ± 6.36	32.3 ±7.49
(yr)	Median (Min – Max)	38.0 (21-44)	28.5 (22-42)	33.0 (21-44)	
Height	Mean ± SD	176.2 ± 10.30	179.1 ±8.57	177.6 ± 9.49	
(cm)	Median (Min - Max)	178.0 (156-198)	179_5 (161-193)	178.0 (156-198)	
Weight	Mem ± SD	84,08 ± 14.060	83.99 ± 13.379	84.03 ± 13.560	
(kg)	Median (Min – Max)	82.70 (63.4-108.2)	85.50 (61.2-106.5)	84.90 (61.2-108.2)	
ВМІ	Mean ± SD	27.08 ± 3.885	26.16 ± 3.384	26.63 ±3.634	
(kg/m²)	Median (Min - Max)	28.81 (19.1-32.0)	26.68 (19.7-31.2)	27.25 (19.1-32.0)	

20. Efficacy results

Olmesarian	Tresiment A N = 3t	Trestment B N = 36
AUCho (ng-h/mL) Anthretic Mean ±SD	6632.3 ± 1775.48	6745.2 ± 1916.63
Geometric Mean (CV%)	6423.9 (25.7%)	653 8.0 (24,6%)
AUC+64 (ng-h/mL)* Anthmetic Mean ±SD Geometric Mean (CV%)	6706.8 ± 1798.62 6493.7 (25.9%)	6793.5 ± 1911.67 6588.7 (24.3%)
C <sub>met</sub> (ag/mL) Arithmetic Mean ±SD Grometric Mean (CV%)	986.3 ± 316.35 941.4 (31.5%)	988.8 ± 270.97 958.7 (25,0%)
T <sub>max</sub> (h) Median (Min, Max)	1.9830 (0.983, 4.00)	1.742 (1.00, 3.00)
t <sub>h</sub> (h) <sup>6</sup> Arithmetic Mean ±SD	12.457 ± 10.2844	17.238 ± N.3481
CL/F* (L/h) Arhimetic Mean ±SD	6.331 ± 1.5706	6.227 ± 1,3211

	Geometrie	LSMEANS			
PK Parameter	Treatment A (Test)	Trentment B (Reference)	Ratio of LSMEANS (%) (A/B)	90% C.I. for Ratio (%)	latra-Subject CV (%)
AUCsec	6457	6393	101.00	(95.51, 106.80)	12.2
AUC	6405	6341	101.01	(95.70, 106.61)	12.0
Cma	941.6	929.1	101,35	(94.05, 109.22)	16.7

Amladipine	Treatment A N = 31	Treatment B N = 30
AUChai (ng-h/mL)		
Arithmetic Mean ±SD	359.5 ± 90.69	$331.8 \pm 90.92$
Geometric Mean (CV%)	347.4 (28.1%)	319.4 (29.1%)
AUC to the (ng h/mL)		
Arithmetic Mean ±SD	406.5 ± 1.14.61	373.1 ± 110.16
Geometric Mean (CV%)	389.7 (31.2%)	356.8 (31.7%)
C <sub>max</sub> (ng/mL)		
Arithmetic Mean ±SD	7.117 ± 1,8022	6.797 ± 1.7252
Geometrie Mean (CV%)	6.896 (26.4%)	6.601 (24.8%)
T <sub>max</sub> (h)		
Median (Min, Max)	8.017 (5.98, 12.0)	7.509 (6.00, 16.0)
t <sub>s</sub> (h) Arithmetic Mean ±SD	43.57 ± 10.973	43.15±8.853
CUF (Uh)		10.15 1 4.05
Arithmetic Mean ±SD	26.92 ± 9.289	29.39 ± 9.566

	Geometric	LSMEANS			-
PK Parameter	Trestment A (Test)	Trestment B (Reference)	Ratio of LSMEANS (%) (A/B)	98% C.I. for Ratio (%)	futra-Subjec CV (%)
AUCein	387.6	362.4	106.96	(102.93, 111.15)	8.5
AUC	346.0	323,2	107.05	(102.97, 111.30)	8.6
C···	6.878	6.599	104.22	(99.59, 109.06)	10.0



	Hydrochia	prethiazide		stancat A V=31	Trents		
	AUCton (ng fin Arithmetic M Geometric M	can ±SD con (CV%)		1 + 234.22 0 (22.1%)		1170.6 ± 229.05 1147.0 (21.4%)	
	Arithmetic M Geometric M	AUC <sub>star</sub> (sg-ts/mL) Arithmetic Mean ±SD 1202.8 ± 233.90 Geometric Mean (CV%) 1178.7 (21.3%)			1195.2 ± 229.33 1172.0 (21.0%)		
	C <sub>max</sub> (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 <sub>max</sub> (h) Median (Min. t <sub>M</sub> (h) Arithmetic M			0.983, 3.00)	1.5000 (0.9)		
	CL/F (L/h) Arithmetic Mi			3 ± 1.7363 0 ± 5.130	10.457 ±		
		Geometric	LSMEANS			1	
	PK Parameter	Treatment A (Test)	Treatment B (Reference)	Ratio of LSMEANS (%) (A/B)	90% C.L. for Ratio	Intra-Subject CV (%)	
	AUC <sub>0-inf</sub>	1158	1169	99.03	(93.69, 104.67)	12.4	
	AUC <sub>inst</sub>	1132	172.4	98.87	(93.29, 104.78) (92.50, 112.69)	13.0	
21. Safety results	medoxor hydroch tolerated	mil 40 r lorothia l in this ces in th	ng, aml zide 25 group o e frequ	odipine long was of healthy ency of	ation of old besylate 10 safe and way subjects a FEAEs bet	mg, and rell and no	
22. Conclusion (summary)	The triple fixed dose combination (CS-8635 pilot formulation A) is bioequivalent to the Benicar HCT plus Antacal® regimen.			5 pilot icar HCT@			
Applicant (registration certificate holder)		/	7	) commi	lan		
	(signature) Dr. Kai Schumacher						
	(full name)						



1. Name of medicinal product	ATTENTO ® PLUS 40/10/25 mg
(registration certificate №, if available)	
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	100 (100 pt 100
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-
11 01 1 1 1 1 1 1	8635 pilot formulation B
<ul><li>11. Clinical trial design</li><li>12. Main inclusion criteria</li></ul>	Open-label, randomized, 2-way crossover study 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 ana	lveie of	fyariar	ca (ANI	27/4)			
	An analysis of variance (ANOVA) was performed on the ln-transformed AUC <sub>0-last</sub> ,							
	AUCourand C for olmosorten amodicining							
	AUC <sub>0-Inf</sub> and C <sub>max</sub> for olmesartan, amlodipine a							
	hydrochlorothiazide. The ANOVA model							
	included sequence, treatment and period as fixed							
	effects.							
9. Demographic indices of studied	Trait AB BA Corr							
opulation (sex, age, race, etc.)		Trait			BA (N = 16)	Overall (N = 32)		
. ( , , , , , , , , , , , , , , , , , ,	N(%)	Gender Male N(%) Female			13 (RL3%) 3 (18.8%)	25 (78.1%) 7 (21.9%)		
		unerican Indian/ Uaskan Native		1 (6.3%)	2 (12.5%)	3 (9.4%)		
	N/40 13	ksian Black or African A	merican	1 (6.3%)	0	1 (3.1%)		
	l i	Vhite Ispanie or Latino		4 (25.0%)	4 (25.0%)	21 (65.6%) 8 (25.0%)		
	N(%)	let Hispanic or La		7 (43.8%) 9 (56.3%)	7 (43.8%) 9 (56.3%)	18 (56.3%)		
	Age ±	SD		31.1 ±7.85	32.1 ±7.61	31.6 ± 7.62		
		dedian Min – Max)		30,5 (21-42)	(23-45)	30.5		
O. Efficacy results	Olme	cartan		mest A	Treatment	В		
	AUCint (ng th		N	= 30	N=30			
	Arithmetic M Geometric M	ean ±SD		1777.29	6043.3 ± 1455			
	AUCour(ngth	/mil.)*		(26.4%)	5874.0 (24.8	76)		
	Arithmetic M Geometric M	run (CV%)		(25.7%)	6092.5 ± 1483 5919.1 (25.0			
	C <sub>max</sub> (ng/mL) Arithmetic M			± 337.39				
	Geometric Mo			32.5%)	899.1 ± 277.48 856.9 (32.9%)			
		Tuest (h) Median (Min, Max)		.00, 4.00)	1.992 (1.00, 4.00)			
	t <sub>H</sub> (h)* Arithmetic Me	72± nm		14.2767				
	CL/F* (L/b)				21.874 ± 14.6826			
	Arithmetic Me	Arithmetic Mean ±SD 6.456			± 1.5728 6.961 ± 1.7548			
		Geometric LSMEANS						
				Ratio of		Intra-		
	PK Parameter	Treatment A		LSMEANS (%	6) 90% C.I. for Rat			
	AUC <sub>0-bf</sub>	(Test) 6418	(Reference)	(A/B) 108.73	(%)	(%)		
	AUCtox	6496	5849	111.06	(103,44, 119,24	-		
	C <sub>max</sub>	952.7	858.5	110.97	(99.86, 123.32)			
		Amionipine		atment A Treatm N = 30 N =				
	AUC <sub>lust</sub> (ng-h/s Avithmetic Me Geometric Me	an ±SD		± 87.74 (25.6%)	308.9 ± 79.03 300.1 (24.6%)			
	AUCulat (ng-b/ Arithmetic Me Geometric Me	an ±SD	355.8	± 102.19 (27.4%)	338.3 ± 96.37			
	Camb (ng/mL) Arithmetic Me Geometric Me	an ±SD	7.035	± 2.0205 (27.9%)	326.4 (27.3%) 6.799 ± 1.5532			
	T <sub>max</sub> (h) Median (Min,			(27.9%) 6.631 (23.0%) 6.00, 12.00) 7.050 (4.00, 12.0				
	h, (h) Arithmetic Me	an ±SD	38.43	± 6.728	38.41±7			
		CLIF (LA) Arithmetic Mean 2SD 30.15 ± 7.863				366		
		Geometri	LSMEANS					
		Cometric	CENTRALICO			Intra-		
				Ratio of		Subject		
	PK Parameter	Treatment A (Test)	Treatment B (Reference)	LSMEANS (%) (A/B)	90% C.L for Ratio (%)	(%)		
	PK Parameter				7,000,000			
		(Test)	(Reference)	(A/B)	(%)	(%)		



	Rydrochlarothiazide  AUC <sub>tot</sub> (ng-h/mt.) Aribinetic Mesn (CV-th) Aribinetic Mesn (CV-th) AUC <sub>tot</sub> (ng-h/mt.) Aribinetic Mesn (EV-th) Connetic Mesn (CV-th) Arithmetic Mesn (CV-th) Arithmetic Mesn ±SD CLF (L/h) Arithmetic Mesn ±SD CLF (L/h) Arithmetic Mesn ±SD			tment A = 30	Treatment   N = 30	3	
			2SD 1171.6 ± 233.23 (CV%) 1148.9 (20.5%) L) ±SD 1198.8 ± 236.04 (CV%) 1176.1 (20.2%) ±SD 179.96 ± 34.987 (CV%) 172.13 (31.1%) xx) 1.5000 (0.967, 4.00) ±SD 10.831 ± 1.3403		1189.4±267.64 1160 9 (22.1%) 1212.0±267.40 1185.2 (21.6%) 178.9±62.74 170.2 (31.8%) 1.5001 (0.983, 3.00) 10.508±1.3201 21.55±4.491		
			LSMEANS				
	PK Parameter	Treatment A (Test)	Treatment B (Reference)	Ratio of LSMEANS (%) (A/B)	90% C.I. for Ratio	Intra- Subject CV (%)	
	AUC <sub>d-of</sub>	1174	1169	100.39	(95.70, 105.32)	10.6	
	Cmar	171.2	169.5	101.01	(95.34, 105.12) (91.05, 112.06)	23.5	
21. Safety results	The concomitant oral administration of olmesartan medoxomil 40 mg, amlodipine besylate 10 mg, and hydrochlorothiazide 25 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.					25 mg of	
22. Conclusion (summary)	The triple fixed dose combination (CS-8635 pil formulation B) is bioequivalent to the Benicar HCT® plus Antacal® regimen					635 pilo micar	
Applicant (registration certificate holder)	- 6	/11	0/	www.l	0		
	(signature) Dr. Kai Schumacher						
	(full nar			,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,			



1 Name of medicinal and dust	ATTENITO ® DI LIG 40/10/05
(registration certificate №, if	ATTENTO ® PLUS 40/10/25 mg 11
available)	
2. Applicant	Menarini International Operations Lywersham C.A. I.
3. Manufacturer	Menarini International Operations Luxembourg S.A., Luxembourg
3. Wandiacturei	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,	Medicinal product with fixed combination
which has been or will be	and the product with fixed combination
registered	
5. Title of clinical trial, code	CS-8663-A-E102
number of clinical trial	
	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	Germany
trial has been conducted	
9. Number of trial subjects	planned:18
	actual: 18 (completed)
10. Objective and secondary	Primary: to determine the bioequivalence of three marketed amlodipine
endpoints of clinical trial	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	Treatment A: Istin® 10 mg (amlodipine besylate equivalent to 10 mg
product, mode of	amlodipine) tablets (UK formulation)
administration and strength	
14. Reference product, dose,	Treatment B. Norvasc® 10 mg (amlodipine besylate equivalent to 10 mg
mode of administration and	amlodipine) tablets (US formulation)
strength	
	Treatment C. Antacal® 10 mg (amlodipine besylate equivalent to 10 mg
	amlodipine) tablets (Italian formulation)
15. Concomitant therapy	None
16. Criteria for evaluation	AUC <sub>0-Inf</sub> , AUC <sub>0-t</sub> , C <sub>max</sub> , T <sub>max</sub> , t <sub>1/2</sub> , CL/F and Vss/F
efficacy	
17. Criteria for evaluation	Physical examination, vital signs, 12-lead ECGs, adverse events (AE),
safety	laboratory parameters
18. Statistical methods	90% CIs for the difference between treatment LSMs were derived from the
	Analysis of Variance (ANOVA) on the In-

19. Demographic indices of	amlodipine.					
studied population (sex, age		Fruit Mean	Over (N=1	<b>(1)</b>		
race, etc.)	Age (yr)	SD Median Minimum	36, 11, 38, 19	5		
		Maximum Mean SD	55 176.	1		
	Height (em)	Median Minimum Maximum	176 161 199			
	Weight (kg)	Mean SD Median Minimum	75.2 12.7 74.5 54.7	6		
	BMI (kg/m²)	Meximum Mean SID Median Minimum	24.1 2.35 24.7 19.4	3		
20. Efficacy results		Maximum	28.0			
o. Efficacy results	Amlapidine (N=18) AUC <sub>54</sub> [ng.h/mL]	Treatment A <sup>1</sup> (N=18)	Treatment B¹ (N=18)	Treatment C <sup>3</sup> (N=18)		
	Arithmetic Mean ±SD Geometric Mean (CV%)	167.8 (43.3) 162.8 (11.0)	168.1 (44.8) 162.4 (11.8)	171.3 (47.5) 164.4 (13.2)		
	AUCom [ng.h/mL]					
	Arithmetic Mean ±SD Geometric Mean (CV%) C <sub>max</sub> (ng/mL)	177.4 (43.7) 172.5 (10.6)	177.5 (45.3) 172.0 (11.3)	182.1 (48.7) 175.5 (12.5)		
	Arithmetic Mean ±SD Geometric Mean (CV%)	3.74 (0.94) 3.63 (10.82)	3.47 (0.82) 3.39 (9.69)	3.77 (0.83) 3.68 (10.32)		
	T <sub>max</sub> (h) Median (Min – Max)	8.0 (4.0; 10.1)	8.6 (4.0; 16.0)	8.6 (7.0; 14.0)		
	T <sub>1/2</sub> (h) Arithmetic Mean ±SD CLf [mL/min]	43.6 (11.0)	41.9 (7.37)	42.4 (6.24)		
	Arithmetic Mean ±SD	993 (236.4)	1000 (262.3)	989 (302.0)		
	Vss/f [L] Arithmetic Mean ±SD					
	Parameter	Comparison	Ratio of LSM	90% CI (%)		
	AUC, [ng.h/mL]	Treatment A <sup>1</sup> vs. B <sup>2</sup>	99.2	(Lower, Upper) (94.1, 104.7)		
		Treatment A <sup>1</sup> vs. C <sup>2</sup>	98.8	(93.6, 104.2)		
		Treatment B <sup>2</sup> vs. C <sup>3</sup>	99.5	(94.3, 105.0)		
	AUCstat [ng.h/mL]	Treatment A <sup>1</sup> vs. B <sup>2</sup>	98.9	(94.0, 104.2)		
		Treatment A <sup>1</sup> yz. C <sup>3</sup>	98.1	(93.2, 103.3)		
	C <sub>mix</sub> [ng/mL]	Treatment B <sup>2</sup> vs. C <sup>3</sup> Treatment A <sup>1</sup> vs. B <sup>2</sup>	99.2	(94.2 , 104.4)		
		Trentment A <sup>1</sup> vs. C <sup>3</sup>	108.6	(100.9 , 116.8)		
		Treatment B <sup>3</sup> vs. C <sup>3</sup>	90.3	(90.8 , 105.7) (83.7 , 97.3)		
1. 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.					
2. 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					
pplicant (registration ertificate holder)	amlodipine appeared to be well tolerated by the healthy subjects in this study.  (signature)  Dr. Kai Schumacher  (full name)					

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	USA
has been conducted	
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 <sub>0-t</sub> , Auc <sub>0-Inf</sub> , C <sub>max</sub> , T <sub>max</sub> , kel and t <sub>1/2</sub>
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 Intransformed PK parameters AUC <sub>0-t</sub> , AUC <sub>0-Inf</sub> and C <sub>max</sub> for olmesartan and amlodipine.



<ol> <li>Demographic indices of studied population (sex, age, rac</li> </ol>		Tradi		Mule	(Nvda)		
radica population (sex, age, rac	Gender (Ma)		Male	(N - 13)	(N-15)	13 (46.4%	
tc.)	SHARKE (CAM)		Penule		15 (53.0%		
	Race (N%)		Caucusian Hispanic	1 (7.7%) 12 (92.3%)	6 15 (100.0%)	1 (3.6%)	
			Mom	306	27.9	27 (96.4% 29.2	
	Are (vr)	SD Madino		Age (yr) SE 9.42 Age (yr) Median 29.0		6.46	7.97
	1		Minimum	19	26.0 19	27.5 19	
			Manimum	171.00	NE	44	
			Mean SD		159.67 5.740	164.93 8.911	
	Height (cm)		Madina	8.103 172.00	159.00	164.00	
			Minimum Maximum	154.0	151.0	151.0	
		_	Meno	78.17	71.67	74.69	
	Weight day		SD	11.497	10.512	11.268	
	Weight (kg)		Medina	84.10 56.2	70.80 50.3	74.85	
	II.		Maximum	90.9	88.5	90.9	
			Mcan SD	26.59	28.04	27.37	
	BMI (kg/m²)		Median	26.46	3.254 29.70	2817	
			Minimum	23.7	21.2	21.2	
2 1100			Maximum	29.7	31.5	31.5	
O. Efficacy results	Otmesartan		Test'		Reference		
	AUCo. (ngh/mL)		(n = 26)		(a = 17)		
	Arithmetic Mean ±SD	44	54.0 ± 1315.07		5571.1 ± 1368.	27	
	Geometrie Mean (CV%)		399.7 (25.0%)		\$420.9 (24.5)		
	AUCour (ngh/mL)		564 . 1463 A.				
	Arithmetic Mean ±SD Geometric Mean (CV%)		49.2 ± 1323.20 433.6 (25.0%)		5622.8 ± 1320.		
	AUChe/AUChid				5470.5 (24.65	e)	
	Arithmetic Menn ±SO	0.1	9938 ± 0.00475		0.9916±0.009	89	
	Arithmetic Mean 45()		ISR3 ± 207.53		9389.107	4	
	Geometric Mean (CV%)		632.6 (26.2%)		835.7±197.9 810.9 (26.5%		
	Tana (h)						
	Median (Min – Max)	2.0	00 (1.02 - 4.00)		.000 (1.50 - 3.	03)	
	Arithmetic Mesn iSD	te	1.670 ± 2.7829		11.723 ± 4.304	60	
		Geome	iric LSM	Ratio (T/R)		90% CI	
	Parameters	Parameters Test Reference		of LSM	(L	wer, Upper	
	AUCs.(ng-h/mL)	(n = 26)	(n = 27)	(%)		(%)	
	[ VPC* (65.3/mc)						
		5374.2	5418.6	99.18		93.38 , 105.3)	
	AUCs inf (agrid/mL) Conta (mg/mL) 'C5-9663 Formulation G Oral Table 'Offsearten medesamil 40 mg (Ohn Senror: Table 14.2.4.5.	5407.5 833.3 t (elimesertae medieze	5468.3 810.3	98.89 102.85	(1)	93.38 , 105.3) 93.21 , 104.9) 94.81 , 111.6)	
	AUCs.inf (ng/h/mL)  C.max (ng/mL)  CS-863 Formulation G Oral Table  Olimerarius medesamit 40 mg (Ola	5407.5 833.3 t (elimesertae medieze	5469.3 810.3 810.3 mil 40 rog and amhodipine ber mbination with amhodipine ber Trest*	98.89 102.85	() oral tablet  Reference	93.21 , 104.9) 94.81 , 111.6)	
	AUCac (ag/h/mL)  C.mas (ag/mL)  C.8564 Formation G Oral Table Officeration mediation (40 mg (Ola Saurce: Table 14.2.4.5.  Ansinctiprine  AUC(pg/h/mL)	5407.5 833.3 t (alimesartan mediesan nece") eral tablet in co	5468.3 S10.3 S10.3 s10.4 rog and amindiples hay robination with amindiples ber Trest* (n - 26)	98.89 102.85 flate 10 mgj syfate 18 mg (Antzeal	(i) (ii) (iii) oral tablet  Reference (n = 27)	93.21 , 104.9) 94.81 , 111.6)	
	AUCs.int (agch/mL)  Cons. (ag/mL)  *CS-9663 Formulation G Oral Table  *Offsearten medicannik 40 mg (Ohn  Senroe: Tuble 14.2.1.5.  Australignine  AUCs., (pg.ls/mL)  Arithmetic Mean ±St)	5407.5 833.3 t (nimesartae mediesae occe*) eral rablet in co	5468.3 \$10.3 \$10.3 still 40 reg and ambedipine bear publication with ambedipine bear tress <sup>a</sup> (n = 26) 40.9 ± 98822.72	98.89 102.85 fate 10 mg sytate 18 mg (Antreal	(i) (i) (ii) (iii)	93.21 , 104.9) 94.81 , 111.6)	
	AUCs and (angla/mL)  Contact (angla/mL)  Contact (angla/mL)  Contact (angla/mL)  Contact (angla/mL)  Contact (angla/mL)  Analordispine  AUCs (pg/s/mL)  Arithmetic Mean 45D  Geometric Mean 45D  AUCs (angla/mL)  AUCs (angla/mL)  AUCs (angla/mL)	5407.5 833.3 t (nimesartae mediesae occe*) eral rablet in co	5468.3 S10.3 S10.3 s10.4 rog and amindiples hay robination with amindiples ber Trest* (n - 26)	98.89 102.85 fate 10 mg sytate 18 mg (Antreal	(i) (ii) (iii) oral tablet  Reference (n = 27)	93.21 , 104.9) 94.81 , 111.6)	
	AUCs.as (aght/mL)  Coss (ag/mL)  Coss (ag/mL)  Coss (ag/mL)  Cossessing the premission G Oral Table  Onteastrian medescands 40 mg (Olm Sources Table 14.2.1.5.  Austractic Hall.1.5.  Austractic Mann ASD Geometrie Mann (CV%)  AUCs.as (age/mid.1)  Artithenetic Mann ASD Geometrie Mann (CV%)	\$407.5 B33.3 Et (almosartan medutan nete*) aral tablet in co 4337 422	5468.3 \$10.3 \$10.3 \$10.3  Ill 40 reg and amindiplate key relation with amindiplate ber  Testa (n = 26) 40.9 ± 98822.72 166.6 (24.7%) 43.2 ± 138211.0	98.89 102.85 fate 10 mg) sytate 18 mg (Antreal	Referenses (n = 27) 23175.4 ± 1026 10104.7 (26.5	93.21 , 104.9) 94.81 , 111.6) 99.2.2 99.2	
	AUCs and (angla/mL)  Contact (angla/mL)  Contact (angla/mL)  Contact (angla/mL)  Contact (angla/mL)  Contact (angla/mL)  Analordispine  AUCs (pg/s/mL)  Arithmetic Mean 45D  Geometric Mean 45D  AUCs (angla/mL)  AUCs (angla/mL)  AUCs (angla/mL)	\$407.5 B33.3 Et (almosartan medutan nete*) aral tablet in co 4337 422	5468.3 \$10.3 \$10.3 still 40 reg and amindiples hay relies the with amindiples ber  Trest* (n = 26) 40.9 ± 98822.72 1466.6 (24.7%)	98.89 102.85 fate 10 mg) sytate 18 mg (Antreal	References (n = 27) 23175.4 ± 1030 210104.7 (26.5	93.21 , 104.9) 94.81 , 111.6) 99.2.2 99.2	
	AUC <sub>b-lot</sub> (agch/mL)  C <sub>oss</sub> (ng/mL)  CS-8643 Formulation G Oral Table Officestrian medication of Oral Table Officestrian medication of Oral Table Austinetic Nature AUC <sub>b-l</sub> (pg-b/mL) Arithmetic Mean ±8D Geormatric Mean ±8D Geormatric Mean ±8D Geormatric Mean ±8D Geormatric Mean ±8D Arithmetic Mean ±8D Arithmetic Mean ±8D	5407.5  833.3  1 (elimination mediation in telephone in t	5468.3 \$10.3 \$10.3 \$11.40 reg and amiddjene key inhination with amiddjene bes  Testa (n = 26) 40.9 ± 98822.72 1466.6 (24.7%) 43.2 ± 138211.0 682.2 (30.0%)	98.39 102.85 fate 10 mg) sytate 18 mg (Antocal	Referenses (n = 27) 23175.4 ± 1036 11790.5 ± 1415 181699.1 [31.4]	93.21 , 104.9) 94.81 , 111.6) 94.82 , 111.6)	
	AUC <sub>8-lot</sub> (ag/h/mL)  C <sub>600</sub> (ng/mL)  CS-8643 Formulation G Oral Table Officearrian medeanoid 40 mg (Olm Sources Table 14.2.1.5.  Austractiquime  AUC <sub>8-1</sub> (ogg-h/mL)  Arithmetic Moan ±8.D Geometric Moan ±8.D Geometric Moan (CV/4)  AUC <sub>8-1</sub> (ogg-h/mL)  Arithmetic Moan ±8.D Geometric Moan ±8.D Geometric Moan (CV/5)  AUC <sub>8-1</sub> AUC <sub>8-1</sub> (ogg-h/mL)  Arithmetic Moan ±8.D Range (Min - Mox)  Case (ogg-nl)  Case (ogg-nl)	5407.5  833.3  1 (elimesarian mediana receir) anal tablet in co  4337  422  5233  0.8  0	5468.3 \$10.3 \$10.3 \$10.3  If 40 reg and amiddjoine bey reliantian with amiddjoine bey Testin (n = 26) 40.9 ± 98822.72 146.6 (24.7%) 43.2 ± 138211.0 682.2 (30.0%) ides ± 0.06775 693 = 0.962	98.39 102.85 fate 10 mg) sytate 18 mg (Antocal	References (n = 27) 13175.4 ± 1030 11090.4 7 (26.5 11790.5 ± 1415 181609.1 [31.1	93.21 , 104.9) 94.81 , 111.6) 94.82 , 111.6)	
	AUC <sub>bat</sub> (ag/h/mL)  C <sub>stat</sub> (ng/mL)  CS-8643 Formaliston G Oral Table Of interaction mediation G Oral Table Of interaction mediation G Oral Table Anotheristic mediation of Oral Table Anotheristic mediation of Oral Table Anotheristic mediation of Oral Arithmetic Mean ±810 Geometric Mean ±810 Geometric Mean ±810 Geometric Mean ±810 Geometric Mean (CV%) AUC <sub>bat</sub> (AUC <sub>bat</sub> AUC <sub>bat</sub>	5407.5  833.3  1 (eliminaratus medicase etec*) anal tablet in co	5468.3  \$10.3  \$10.3  810.3  814 reg and amindiples hery minimation with amindiples hery minimation with amindiples between 269 (n - 26)  **Test** (n - 26)  **40.7 ± 98.822.72  146.6 (24.7%)  43.2 ± 138211.0  682.2 (32.0%)  443.3 ± 0.66775  6.93 - 0.962  15.8 ± 1561.42	98.89 102.85 fata 10 mg/ sytate 18 mg (Antxeal	(c) (c) (c) (d) (d) (d) (d) (d) (d) (d) (d) (d) (d	93.21 , 104.9) 94.81 , 111.6) 99.2.2 94.9 95.0.7 99.1 113.8	
	AUC_s.int (arg.la/mal.)  Coss.(arg/ml.)  Coss.(arg/ml.)  Coss.(arg/ml.)  Coss.(arg.ml.)  Coss.(arg.ml.)  Coss.(arg.ml.)  Ansinciprime  AUC_s.(pg.la/ml.)  Arithmetic Mean ±SD  Geometric Mean ±SD  Geometric Mean ±SD  Geometric Mean ±SD  Arithmetic Mean ±SD  Coss.(arg.ml.)  Arithmetic Mean ±SD  Coss.(arg.ml.)  Arithmetic Mean ±SD  Coss.(arg.ml.)  Coss.(arg.ml.)  Coss.(arg.ml.)  Coss.(arg.ml.)  Coss.(arg.ml.)  Coss.(arg.ml.)  Coss.(arg.ml.)  Coss.(arg.ml.)  Coss.(arg.ml.)	5407.5 833.3 1 (elimination mediation contest*) and tablet in contest*) and tablet in contest* 4337 422 5233 500 0.8 769	5468.3 \$10.3 \$10.3 \$11.40 reg and ambidipline beyindination with ambidipline beyindination with ambidipline beyindination with ambidipline beyond the second	98.89 102.85 fata 10 mg/ sytate 18 mg (Antxeal	(c) (d) (d) oral tablet  Reference (n = 27) (3175.4 ± 1030 (1040.7 (26.5 ± 1040.1 (19.5 ± 1415 (19.6 ± 19.6	93.21 , 104.9) 94.81 , 111.6) 992.2 993.2 993.2 993.2 993.2 993.2 993.2	
	AUC <sub>not</sub> (ag/h/mL)  C <sub>not</sub> (ng/mL)  CS-866 Formalistin G Oral Table Officestrian medication G Oral Table Officestrian medication G Oral Table Source: Table 14.2.1.5.  Anotheristin medication G Oral Table Source: Table 14.2.1.5.  Anotheristin Mean 48.0  Anotheristin Mean 48.0  Geometric Mean (CV44)  AUC <sub>not</sub> (pg-h/mL) Arithmetic Mean 48.0  Geometric Mean (CV44)  AUC <sub>not</sub> (AUC <sub>not</sub> Auctorial Arithmetic Mean 48.0  Range (Alia – Max)  Cons. (pg/mL) Arithmetic Mean 48.0  Geometric Mean  T <sub>not</sub> (b)  Median (Min – Max)	5407.5 833.3 1 (elimination mediation contest*) and tablet in contest*) and tablet in contest* 4337 422 5233 500 0.8 769	5468.3  \$10.3  \$10.3  810.3  814 reg and amindiples hery minimation with amindiples hery minimation with amindiples between 269 (n - 26)  **Test** (n - 26)  **40.7 ± 98.822.72  146.6 (24.7%)  43.2 ± 138211.0  682.2 (32.0%)  443.3 ± 0.66775  6.93 - 0.962  15.8 ± 1561.42	98.89 102.85 fate 10 mg/ sytate 16 mg (Antxeal	(c) (c) (c) (d) (d) (d) (d) (d) (d) (d) (d) (d) (d	93.21 , 104.9) 94.81 , 111.6) 99.2.2 94.9 95.0.7 95.0 113 8	
	AUC_s.int (arg.la/mal.)  Coss.(arg/ml.)  Coss.(arg/ml.)  Coss.(arg/ml.)  Coss.(arg.ml.)  Coss.(arg.ml.)  Coss.(arg.ml.)  Ansinciprime  AUC_s.(pg.la/ml.)  Arithmetic Mean ±SD  Geometric Mean ±SD  Geometric Mean ±SD  Geometric Mean ±SD  Arithmetic Mean ±SD  Coss.(arg.ml.)  Arithmetic Mean ±SD  Coss.(arg.ml.)  Arithmetic Mean ±SD  Coss.(arg.ml.)  Coss.(arg.ml.)  Coss.(arg.ml.)  Coss.(arg.ml.)  Coss.(arg.ml.)  Coss.(arg.ml.)  Coss.(arg.ml.)  Coss.(arg.ml.)  Coss.(arg.ml.)	5407.5  833.3  1 (elimesarian mediatas reter <sup>2</sup> ) anal tablet in conter <sup>2</sup> or al tablet in conter <sup>2</sup> or all tablet in conter <sup>2</sup> or al tablet in conte	5468.3 \$10.3 \$10.3 \$11.40 reg and ambidipline beyindination with ambidipline beyindination with ambidipline beyindination with ambidipline beyond the second	98.89 102.85 fate 10 mg/ sytate 16 mg (Antxeal	(c) paral table  Reference: (m = 27) (13175.4 ± 1036 (1016.47 (26.5 (1016.47 (26.5 (1016.47 (26.5 (1016.47 (26.5 (1016.47 (26.5 (1016.47 (26.5 (1016.47 (26.5 (1016.47 (26.5 (1016.47 (26.5 (1016.47 (26.5 (1016.47 (26.5 (1016.47 (1016.47 (26.5 (1016.47 (101	93.21 , 104.9) 94.81 , 111.6) 992.2 993.2 994.9 995.1 113 8	
	AUC <sub>s.int</sub> (ag/h/mL)  C <sub>sss.</sub> (ng/mL)  CS-8643 Formulation G Oral Table Officearrian medeanoid 40 mg (Olm Sources Table 14.2.1.5.  Austineligitime  AUC <sub>s.i.</sub> (pg/h/mL)  Arithmetic Moan ±8.D  Geometric Moan ±8.D  Geometric Moan (CV%)  AUC <sub>s.i.</sub> (pg-h/mL)  Arithmetic Moan ±8.D  Geometric Moan ±8.D  Geometric Moan ±8.D  Geometric Moan (CV%)  AUC <sub>s.i.</sub> (pg-h/mL)  Arithmetic Moan ±8.D  Geometric Moan (CV%)  AUC <sub>s.i.</sub> (pg-h/mL)  Arithmetic Moan ±8.D  Case (pg-mL)  Arithmetic Moan ±8.D  Geometric Moan  T <sub>max</sub> (h)  Median (Min – Max)  T(h, h)	5407.5  833.3  1 (elimesarian mediatas reter <sup>2</sup> ) anal tablet in conter <sup>2</sup> or al tablet in conter <sup>2</sup> or all tablet in conter <sup>2</sup> or al tablet in conte	5468.3 \$10.3 \$10.3 \$11.40 reg and armidiplate key reliabilistian with amiddiplate key reliabilistian with amiddiplate bed  Test* (n = 26) 40.9 ± 98822.72 1466.6 (24.7%) 43.2 ± 138211.0 682.2 (30.0%) 409 ± 0.06775 693 = 0.062 5.8 ± 1561.42 38.0 (21.3%) 3 (6.00 = 12.0)	98.89 102.85 fate 10 mg/ sytate 16 mg (Antxeal	(c)	93.21 , 104.9) 94.81 , 111.6) 992.2 993.2 994.9 995.1 113 8	
	AUC <sub>s.int</sub> (ag/h/mL)  C <sub>sss.</sub> (ng/mL)  CS-8643 Formulation G Oral Table Officearrian medeanoid 40 mg (Olm Sources Table 14.2.1.5.  Austineligitime  AUC <sub>s.i.</sub> (pg/h/mL)  Arithmetic Moan ±8.D  Geometric Moan ±8.D  Geometric Moan (CV%)  AUC <sub>s.i.</sub> (pg-h/mL)  Arithmetic Moan ±8.D  Geometric Moan ±8.D  Geometric Moan ±8.D  Geometric Moan (CV%)  AUC <sub>s.i.</sub> (pg-h/mL)  Arithmetic Moan ±8.D  Geometric Moan (CV%)  AUC <sub>s.i.</sub> (pg-h/mL)  Arithmetic Moan ±8.D  Case (pg-mL)  Arithmetic Moan ±8.D  Geometric Moan  T <sub>max</sub> (h)  Median (Min – Max)  T(h, h)	5407.5 833.3 11 (elimerarchia medican- cetes*) and tablet in co- cetes*) and tablet in co- 4337.4 422 5233.5 0.8 0.7 755 8.00	5468.3 \$10.3 \$10.3 \$11.40 reg and armidiplate key reliabilistian with amiddiplate key reliabilistian with amiddiplate bed  Test* (n = 26) 40.9 ± 98822.72 1466.6 (24.7%) 43.2 ± 138211.0 682.2 (30.0%) 409 ± 0.06775 693 = 0.062 5.8 ± 1561.42 38.0 (21.3%) 3 (6.00 = 12.0)	98.89 102.85 fate 10 mg/ sytate 18 mg (Antxeal	(c) (c) (c) (d) (d) (d) (d) (d) (d) (d) (d) (d) (d	93.21, 164.9) 94.81, 111.6) 992.2 993.1 13.8 997.9 10.0	
	AUC <sub>s.int</sub> (ag/h/mL)  C <sub>sss.</sub> (ng/mL)  CS-8643 Formulation G Oral Table Officearrian medeanoid 40 mg (Olm Sources Table 14.2.1.5.  Austineligitime  AUC <sub>s.i.</sub> (pg/h/mL)  Arithmetic Moan ±8.D  Geometric Moan ±8.D  Geometric Moan (CV%)  AUC <sub>s.i.</sub> (pg-h/mL)  Arithmetic Moan ±8.D  Geometric Moan ±8.D  Geometric Moan ±8.D  Geometric Moan (CV%)  AUC <sub>s.i.</sub> (pg-h/mL)  Arithmetic Moan ±8.D  Geometric Moan (CV%)  AUC <sub>s.i.</sub> (pg-h/mL)  Arithmetic Moan ±8.D  Case (pg-mL)  Arithmetic Moan ±8.D  Geometric Moan  T <sub>max</sub> (h)  Median (Min – Max)  T(h, h)	5407.5 833.3 11 (elimerarchia medican- cetes*) and tablet in co- cetes*) and tablet in co- 4337.4 422 5233.5 0.8 0.7 755 8.00	5468.3 \$10.3 \$10.3 \$10.3 \$10.3 \$10.3 \$10.9	98.89 102.85 fate 10 mg/ sytate 16 mg (Antxeal	(c)	93.21 , 104.9) 94.81 , 111.6) 97.2 98.9 97.2 98.9 97.9 98.9 97.9 98.9 97.9	
	AUC_sar (ag/sl/mL)  Casa (ag/sl/mL)  Casa (ag/sl/mL)  CS-8643 Formalisto G Oral Table Ofmeatries medesonit 40 mg (Olm Senree: Table 14.2.1.5.  Ansilnetic Mean ±8.0  Arithmetic Mean ±8.0  Geometric Mean ±8.0  Geometric Mean ±8.0  Geometric Mean ±8.0  Geometric Mean ±8.0  Arithmetic Mean ±8.0  Arithmetic Mean ±8.0  Casa (ag/sl/mL)  Arithmetic Mean ±8.0  Casa (ag/sl/mL)  Arithmetic Mean ±8.0  Geometric Mean ±8.0  Geometric Mean ±8.0  Arithmetic Mean ±8.0  Parameters	\$407.5  \$33.3  \$1 (eliminatura medicale etect*) eral tablet in co  4337  422  \$233  0.2  \$400  766  75  8.02	5468.3  \$10.3  \$10.3  ### 10 rog and amiddjoine boy  Testa* (n = 26)  ***********************************	98.89 102.85 fata 10 mg sytate 18 mg (Antxen) 42 51	(c)	93.21 , 104.9) 94.81 , 111.6) 97.2 98.9 97.2 98.9 97.9 98.9 97.9 98.9 97.9	
	AUCasa (aghl/mL)  Casa (aghl/mL)  Casa (aghl/mL)  CS-8643 Formatisina G Oral Table Otherstrian medeuscult 40 mg (Olin Sources Table 14.2.1.5.  Austractic Mean 450 Geometria Mean 450 AUCas (aghl/mL) Artitanestia Mean 450 Casa (aghl/mL) Artitanestia Mean 450 Geometria Mean Tasa (b) Median (Min – Max)  Tyl (b) Artitanestia Mean 450 Artitanestia Mean 450 Geometria Mean Tasa (b) Median (Min – Max)  Tyl (b) Artitanestia Mean 450 Artitanestia Mean	\$407.5  833.3  1 (elimeratria medican- teter) and tablet in co- teter) and tablet in co- 4337  422  5238  60  766  75.9  Support Control of the control of t	5468.3  \$10.3  \$10.3  \$10.3  \$10.3  \$10.3  \$10.9  \$10.3  \$10.9  \$10.3  \$10.9  \$10.3  \$10.9  \$10.3  \$	98.89 102.85 faita 10 mg systate 18 mg (Anticest  41  51  Ratio (T/R) of ISM (%) 103.38	(i)  Reference (in = 27) (3175.4 ± 1036 (10104.7 (26.5 ± 1036 (1059.1 (31.1 ± 0.066 0.652 - 0.94 (1059.1 (31.1 ± 0.066 0.94 (1059.1 (31.1 ± 0.066 0.94 (1059.1 (31.1 ± 0.066 0.94 (1059.1 (31.1 ± 0.066 0.94 (1059.1 (31.1 ± 0.066 0.94 (1059.1 (31.1 ± 0.066 0.94 (1059.1 (31.1 ± 0.066 0.94 (1059.1 (31.1 ± 0.066 0.94 (1059.1 (31.1 ± 0.066 0.94 (1059.1 (31.1 ± 0.066 0.94 (1059.1 (31.1 ± 0.066 0.94 (1059.1 (31.1 ± 0.066 0.94 (1059.1 (31.1 ± 0.066 0.94 (1059.1 (31.1 ± 0.066 0.94 (1059.1 (31.1 ± 0.066 0.94 (105	93.21, 104.9) 94.81, 111.6) 99.2 96.2 96.3 113 8 997 101 7 90% C1 wwer, Upper	
	AUCac (ag/h/mL)  Coss (ag/mL)  Coss (ag/mL)  Coss (ag/mL)  Coss (ag/mL)  Coss (ag/mL)  Coss (ag/mL)  Ansimelisme  AUCc (ag/h/mL)  Arithmetic Mean ±8D  Geometric Mean ±8D  Coss (ag/mL)  Arithmetic Mean ±8D  Coss (ag/mL)  Arithmetic Mean ±8D	5407.5  833.3  1 (elimeration mediana reter*) anal tablet in conterts and attacked in content attacke	5468.3 \$10.3 \$10.3 \$10.3 \$10.3 \$10.3 \$10.3 \$10.9 \$10.3	98.89 102.85 fata 10 mg sytate 18 mg (Antxeal  41  51  Ratte (T/R) e (1.5M) (%) 103.38	(() () () () () () () () () () () () ()	93.21, 104.9) 94.81, 111.6) 97.2.2 98.5 97.26 98.7 99.7 99.7 99.7 100.1, 106.8) 100.8, 109.0)	
	AUCac (ag/h/mL)  Coss. (ag/mL)  Coss. (ag/mL)  Coss. (ag/mL)  Coss. (ag/mL)  Coss. (ag/mL)  Anstruction me de tossile 46 mg (Ohr Sources Trible 14.2.1.5.  Anstruction in the tossile 45 mg (Ohr Sources Trible 14.2.1.5.  Anstruction Mean 450 Geometric Mean 450 Geometric Mean 450 Geometric Mean (CV%)  AUCac (ag/mL)  Arithmetic Mean 450 Range (AVIn - Mean)  Arithmetic Mean 450 Geometric Mean  Tana, (b)  Median (Min - Max)  TV, (b)  Arithmetic Mean 450  Arithmetic Mean  Tana, (c)  Arithmetic Mean  Arithmetic Mean  Arithmetic Mean  Arithmetic Mean  Arithmetic Mean  AUCac (b)  Arithmetic Mean	5407.5  833.3  1 (elimeration medicates coefees) and tablet in coefees  4337  422  5233  0.2  0  Geome Test' (n = 26)  424784.8  505286.7  7642.9	5468.3  \$10.3  \$10.3  \$10.3  \$10 vag and smiddplate key reliable they re	98.89 102.85 fata 10 mg sytate 18 mg (Antxeal  41  51  Ratio (T/R) of 1.5M (%) 103.38 104.78 103.93	(c) (c) (c) (d) (d) (d) (d) (d) (d) (d) (d) (d) (d	93.21, 104.9) 94.81, 111.6) 94.81, 111.6) 97.22 98.31 99.31	
	AUC (ag/h/mL)  Com. (ag/mL)  Com. (ag/mL)  Com. (ag/mL)  Com. (ag/mL)  Com. (ag/mL)  Austinetia Formatiston G Oral Table  Ofmeastrian medeanomit 40 mg (Chin Source: Table 14.2.1.5.  Austinetia Moan ±8.10 Geometrie Moan (CV%)  AUC (ag/ml.)  Arithmetia Mean ±8.10 Geometrie Moan ±8.10 Range (Min - Mox)  Com. (ag/ml.)  Arithmetia Moan ±8.10 Geometrie Moan ±8.10 Geometrie Moan ±8.10 Geometrie Moan ±8.10 Geometrie Moan ±8.10 Arithmetia Moan ±8.10  Tom. (h) Median (Min - Max.)  TV (h)  Arithmetic Moan ±8.10  Funantie Moan ±8.10  Arithmetic Moan ±8.10  Tom. (h)  Median (Min - Max.)  TV (sc.)  AuC (pg/mL)  AUC (pg/mL)  Com. (pg/mL)  Com. (pg/mL)  Com. (pg/mL)  Com. (pg/mL)  Com. (pg/mL)  Com. (pg/mL)	5407.5  833.3  1 (elimeration medicates coefees) and tablet in coefees  4337  422  5233  0.2  0  Geome Test' (n = 26)  424784.8  505286.7  7642.9	5468.3  \$10.3  \$10.3  \$10.3  \$10 vag and smiddplate key reliable they re	98.89 102.85 fata 10 mg sytate 18 mg (Antxeal  41  51  Ratio (T/R) of 1.5M (%) 103.38 104.78 103.93	(c) (c) (c) (d) (d) (d) (d) (d) (d) (d) (d) (d) (d	992.2 (104.9) 94.81 (111.6) 94.81 (111.6) 94.81 (111.6) 97.25 (113.8) 97.7 98% C1 (100.1, 106.8) 100.8 (109.0) 100.1, 106.8 (109.0) 100.8 (109.0)	
Safaty regults	AUC (ag/h/mL)  Com. (ag/mL)  Com. (ag/mL)  Com. (ag/mL)  Com. (ag/mL)  Com. (ag/mL)  Austinetic Normalisten G Oral Table  Ofmeastrien medeanomit 40 mg (Chin Source: Table 14.2.1.5.  Austinetic Normalisten (Chin Autitametic Normalisten (CV/d)  AUC	5407.5  833.3  1 (almassartan mediatan eter') aral tablet in conter') aral tablet in conter') aral tablet in conter') aral tablet in conter') aral tablet in conter' (all tablet in conter') aral tablet in conter'	5468.3  \$10.3  \$	98.89 102.85 fata 10 mg sytate 16 mg (Antscal  41  51  Ratio (T/R) of LSM (%) 103.93 104.78 103.93 105.93 1	(i)  Reference (in = 27)  (in = 2	93.21, 104.9) 94.81, 111.6) 94.81, 111.6) 99.2 96.2 96.3 97.3 98.8 99.7 99.7 99.7 100.1, 106.8) 100.1, 106.8) 109.8, 109.9 109.8, 109.9	
. Safety results	AUCac (ag/h/mL)  Cons. (ag/mL)  Cons. (ag/mL)  Cons. (ag/mL)  Cons. (ag/mL)  Cons. (ag/mL)  Antimeting an expectation of Oral Table  Otherserian medeanomic 40 mg (Ohn Sources Table 14.2.1.5.  Antimetic Mean 48.D Geometric Mean 48.D Arithmetic Mean 48.D Arithmetic Mean 48.D Cons. (ag/mL) Arithmetic Mean 48.D Arithmetic Mean 48.D Geometric Mean  Tons. (b) Median (Min - Max)  TV (b) Arithmetic Mean 48.D  Parameters  AUC(pg/m/mL)  Cons. (pg/mL)	\$407.5  833.3  1 (elimination mediates reter*) anal tablet in contests of a state of tablet in contests of tab	5468.3  \$10.3  \$10.3  \$10.3  \$10.3  \$10.3  \$10.3  \$10.3  \$10.9  \$10.3  \$10.9  \$10.3  \$10.9  \$10.3  \$10.9  \$10.3  \$	98.89 102.85 fata 10 mg) systate 18 mg (Anticest  42  51  Ratto (T/R) of 1.8M (%6) 103.38 104.78 103.93 size 10 mg) (Anticest  PTC gnan	(() () () () () () () () () () () () ()	93.21, 104.9) 94.81, 111.6) 99.2.2 99.2 99.3 10.6) 97 99% C1 ower, Upper (%) 100.1, 106.8, 109.0) 99.87, 108.2)	
. Safety results	AUCac (ag/h/mL)  Cons. (ag/mL)  Cons. (ag/mL)  Cons. (ag/mL)  Cons. (ag/mL)  Cons. (ag/mL)  Antimeting an expectation of Oral Table  Otherserian medeanomic 40 mg (Ohn Sources Table 14.2.1.5.  Antimetic Mean 48.D Geometric Mean 48.D Arithmetic Mean 48.D Arithmetic Mean 48.D Cons. (ag/mL) Arithmetic Mean 48.D Arithmetic Mean 48.D Geometric Mean  Tons. (b) Median (Min - Max)  TV (b) Arithmetic Mean 48.D  Parameters  AUC(pg/m/mL)  Cons. (pg/mL)	\$407.5  833.3  1 (elimination mediates reter*) anal tablet in contests of a state of tablet in contests of tab	5468.3  \$10.3  \$10.3  \$10.3  \$10.3  \$10.3  \$10.3  \$10.3  \$10.9  \$10.3  \$10.9  \$10.3  \$10.9  \$10.3  \$10.9  \$10.3  \$	98.89 102.85 fata 10 mg) systate 18 mg (Anticest  42  51  Ratto (T/R) of 1.8M (%6) 103.38 104.78 103.93 size 10 mg) (Anticest  PTC gnan	(() () () () () () () () () () () () ()	93.21, 104.9) 94.81, 111.6) 94.81, 111.6) 97.2.2 98.9 99.9 10.0 99.9 10.0 10.1, 106.8, 109.0) 99.87, 108.2)	
. Safety results	AUC (ag/h/mL)  Com (ag/mL)  Com (ag/mL)  Com (ag/mL)  Com (ag/mL)  Com (ag/mL)  Anstandispiane  AUC (ag/h/mL)  Arithmetic Mean ±8D  Geometric Mean ±8D  Arithmetic Mean ±8D  Geometric Mean ±8D  Arithmetic Mean ±8D  Geometric Mean  Tan (b)  Median (Min – Max)  TV (8)  Arithmetic Mean ±8D  Com (b)  Arithmetic Mean  Tom (b)  Median (Min – Max)  TV (8)  Arithmetic Mean ±8D  Com (b)  Arithmetic Mean  SD  Com (c)  Com	\$407.5  833.3  (tolersartan medican teter) and tablet in content to the state of th	5468.3  \$10.3  \$10.3  \$10.3  \$10.3  \$10.3  \$10.9  \$10.3  \$10.9  \$10.3  \$10.9  \$10.3  \$10.9  \$10.3  \$10.9  \$10.3  \$	98.89 102.85 faita 10 mg) sytate 18 mg (Antxeal  41  51  Ratio (T/R) of 1.5Mt (%) 103.38 104.78 105.93 rata 18 mg (Antxeal  pregnan n that wa	(c) (c) (d) (d) (d) (e) (e) (e) (e) (e) (e) (e) (e) (e) (e	992.2 (104.9) (104.81 , 111.6) (104.81 , 111.6) (104.81 , 111.6) (104.81 , 111.6) (104.81 , 1	
. Safety results	AUC (ag/h/mL) C (ag/h/mL) C (ag/mL) Antidemetic Mean (CVM) AUC (ag/mL) Arithmetic Mean ±SD Geometric Mean (CVM) AUC (ag/mL) Arithmetic Mean ±SD Geometric Mean (CVM) AUC (ag/mL) Arithmetic Mean ±SD Geometric Mean ±SD Geometric Mean Arithmetic Mean ±SD Geometric Mean Touch Median (Min - Max) TV, (b) Arithmetic Mean ±SD Arithmetic Mean AUC (ag/mL) C (ag/mL)	\$407.5  \$33.3  \$1 (eliminatura medican receter*) anal tablet in contect*) anal tablet in contect*) anal tablet in contect*)  4337-422  \$233-502  0.8  609-75  8.00  540  Geome Test* (n = 26) 424784.8 505286.7  7642.9 (columnatura medicana rece*) anal tablet in contect* as withdr	5468.3  \$10.3  \$10.3  \$10.3  \$10.3  \$10.3  \$10.40  \$10.3  \$10.3  \$10.40  \$10.3	P&89 102.85 faita 10 mig) systate 10 mg (Anticest  41  51  Ratio (T/RR  of LSM  (%) 103.38 104.78 104.78 104.78 101.93 104.78 105.93 105.93 10	(() () () () () () () () () () () () ()	93.21, 104.9) 94.81, 111.6) 94.81, 111.6) 94.81, 111.6) 94.81, 111.6) 95.2 96.2 96.3 97.9 98.4 C1 98.4 99.7 98.4 C1 98.4 99.7 100.1, 106.8, 109.0) 99.87, 108.2) 1 later ured a	
. Safety results	AUC (ag/h/mL) C (ag/h/mL) C (ag/mL) Antidemetic Mean (CVM) AUC (ag/mL) Arithmetic Mean ±SD Geometric Mean (CVM) AUC (ag/mL) Arithmetic Mean ±SD Geometric Mean (CVM) AUC (ag/mL) Arithmetic Mean ±SD Geometric Mean ±SD Geometric Mean Arithmetic Mean ±SD Geometric Mean Touch Median (Min - Max) TV, (b) Arithmetic Mean ±SD Arithmetic Mean AUC (ag/mL) C (ag/mL)	\$407.5  \$33.3  \$1 (eliminatura medican receter*) anal tablet in contect*) anal tablet in contect*) anal tablet in contect*)  4337-422  \$233-502  0.8  609-75  8.00  540  Geome Test* (n = 26) 424784.8 505286.7  7642.9 (columnatura medicana rece*) anal tablet in contect* as withdr	5468.3  \$10.3  \$10.3  \$10.3  \$10.3  \$10.3  \$10.40  \$10.3  \$10.3  \$10.40  \$10.3	P&89 102.85 faita 10 mig) systate 10 mg (Anticest  41  51  Ratio (T/RR  of LSM  (%) 103.38 104.78 104.78 104.78 101.93 104.78 105.93 105.93 10	(() () () () () () () () () () () () ()	93.21, 104.9) 94.81, 111.6) 94.81, 111.6) 94.81, 111.6) 94.81, 111.6) 95.2 96.2 96.3 97.9 98.4 C1 98.4 99.7 98.4 C1 98.4 99.7 100.1, 106.8, 109.0) 99.87, 108.2) 1 later ured a	
. Safety results	AUCac (ag/h/mL)  Come (ag/h/mL)  Come (ag/mL)  Come (ag/mL)  Come (ag/mL)  Antilometic beautiful on gettle sentence: Table 14.2.1.5.  Antilometic beautiful on (CV/h)  AUCac (pg/h/mL)  Arithmetic beautiful on (CV/h)  AUCac (pg/h/mL)  Arithmetic beautiful on Aux)  Come (pg/mL)  Arithmetic beautiful on Aux)  Come (pg/mL)  Arithmetic beautiful on Aux)  Come (pg/mL)  Arithmetic beautiful on Aux)  Tome (h)  Median (Min - Max)  Tome (h)  Arithmetic beautiful on (Aux)  Tome (h)  Aucac (pg/mL)  AUCac (pg/mL)  AUCac (pg/mL)  Come (pg/mL)  Come (pg/mL)  Come Subject with the come of the second of the (Aux)  Come (pg/mL)  Come Subject with the come of the (Aux)  Come Subject with the come of the (Aux)  Auxac (pg/mL)  Come Subject with the properties of the (pg/mL)  Come Subject with the properties of the (pg/mL)  Come Subject with the (pg/mL)  Auxac	\$307.5  \$33.3  \$1 (eliminaria francisca medicata reciter) anal tablet in co  4337.422  \$233.503  0.8  6  7667.75  8.00  54  Test* (n = 26) 424784.8 505286.7  7642.9 (columerarian medicata medi	5468.3  \$10.3  \$	P8.89 102.85 fata 10 mg) systate 16 mg (Anticeal  Attack (TAR) (103.38 104.78 103.38 104.78 103.93 into 10 mg) pregnan in that was d in 11 s s reportin	(c) (c) (c) (d) (d) (d) (d) (d) (d) (d) (d) (d) (d	93.21, 104.9) 94.81, 111.6) 99.2.2 99.2 99.3 99.3 10.0 99.3 10.0 99.3 10.0 10.1, 10.0 10.0 10.1, 10.0 10.0 10.1 10.1 10.1 10.1 10.1 10.1	
. Safety results	AUCac (ag/h/mL)  Come (ag/h/mL)  Come (ag/mL)  Come (ag/mL)  Come (ag/h/mL)  Ansinetispine  AUCc (ag/h/mL)  Arithmetic Mean ±8D  Geometric Mean ±8D  Arithmetic Mean ±8D  Geometric Mean ±8D  Arithmetic Mean ±8D  Geometric Mean  Toma (h)  Median (Min - Max)  TV (h)  Arithmetic Mean ±8D  Parameters  AUC(pg/mL)  Come (pg/mL)  Come (pg/mL)  Come (pg/mL)  Come (pg/mL)  Come (pg/mL)  One subject with experienced at SAE. A total of (39.3%). The froughly equal	Geometria medican reference of a rather in co	5468.3  \$10.3  \$	Ratte (T/R) et.sm (%) 103.38 104.78 103.93 ate 50 mg) prize 10 mg (Antsent) pregnan n that wa d in 11 s s reportir with 6 su	( ( ( ( ) ) oral table   Reference (n = 27)	93.21, 104.9) 94.81, 111.6) 97.2.2 97.9 98.7 99.7 10.0 10.1, 106.8) 100.8, 109.0) 99.87, 108.2) 11 later ured a	
. Safety results	AUCac (ag/h/mL)  Come (ag/h/mL)  Come (ag/mL)  Come (ag/mL)  Come (ag/h/mL)  Ansinetispine  AUCc (ag/h/mL)  Arithmetic Mean ±8D  Geometric Mean ±8D  Arithmetic Mean ±8D  Geometric Mean ±8D  Arithmetic Mean ±8D  Geometric Mean  Toma (h)  Median (Min - Max)  TV (h)  Arithmetic Mean ±8D  Parameters  AUC(pg/mL)  Come (pg/mL)  Come (pg/mL)  Come (pg/mL)  Come (pg/mL)  Come (pg/mL)  One subject with experienced at SAE. A total of (39.3%). The froughly equal	Geometria medican reference of a rather in co	5468.3  \$10.3  \$	Ratte (T/R) et.sm (%) 103.38 104.78 103.93 ate 50 mg) prize 10 mg (Antsent) pregnan n that wa d in 11 s s reportir with 6 su	( ( ( ( ) ) oral table   Reference (n = 27)	93.21, 104.9) 94.81, 111.6) 97.2.2 97.9 98.7 99.7 10.0 10.1, 106.8) 100.8, 109.0) 99.87, 108.2) 11 later ured a	
. Safety results	Austraction and the second state of the second seco	4337 4337 4337 4337 422 5233 503 0.2 0 Geome Test* (n = 26) 424784.3 50328.7 7642.9 (collegation and collegation and collegati	5468.3  \$10.3  \$10.3  \$10.3  \$10.3  \$10.4  \$10.3  \$10.3  \$10.4  \$10.3  \$	Ratio (T/R) of the ling (Anticell  102.85 faits 10 mig) of the ling (Anticell  103.38 104.78 104.78 104.78 pregnan n that was d in 11 s s reportin with 6 su CS-8663	References (n = 27) 23175.4 ± 1036 21070.47 (26.4 ± 1036 21070.5 ± 1415 211790	903.21, 164.9) 94.81, 111.6) 92.22 94.9 95.1 13 14 997 95.1 10.1 10.1, 106.8) 100.8, 109.9) 99.87, 108.2) 11 later ured a S S was	
. Safety results	Austraction and the second state of the second seco	4337 4337 4337 4337 422 5233 503 0.2 0 Geome Test* (n = 26) 424784.3 50328.7 7642.9 (colorosarias medicano tect*) oral tablet is co	5468.3  \$10.3  \$10.3  \$10.3  \$10.3  \$10.4  \$10.3  \$10.3  \$10.4  \$10.3  \$	Ratio (T/R) of the ling (Anticell  102.85 faits 10 mig) of the ling (Anticell  103.38 104.78 104.78 104.78 pregnan n that was d in 11 s s reportin with 6 su CS-8663	References (n = 27) 23175.4 ± 1036 21070.47 (26.4 ± 1036 21070.5 ± 1415 211790	903.21, 164.9) 94.81, 111.6) 92.22 94.9 95.1 13 14 997 95.1 10.1 10.1, 106.8) 100.8, 109.9) 99.87, 108.2) 11 later ured a S S was	
. Safety results	AUCac (ag/h/mL) Cac (ag/h/mL) Cac (ag/mL) Antihmetic Noran stato Geometric Mona stato Time (a) Median (Min - Max) TV(s) Arithmetic Mona stato Conce (ag/mL) Conce (ag/mL) AUCac (ag/mL) AUCac (ag/mL) Conce (ag/m	4337 4337 4337 4337 422 5233 503 0.2 0 Geome Test* (n = 26) 424784.3 50328.7 7642.9 (colorosarias medicano tect*) oral tablet is co	5468.3  \$10.3  \$10.3  \$10.3  \$10.3  \$10.4  \$10.3  \$10.3  \$10.4  \$10.3  \$	Ratio (T/R) of the ling (Anticell  102.85 faits 10 mig) of the ling (Anticell  103.38 104.78 104.78 104.78 pregnan n that was d in 11 s s reportin with 6 su CS-8663	References (n = 27) 23175.4 ± 1036 21070.47 (26.4 ± 1036 21070.5 ± 1415 211790	903.21, 164.9) 94.81, 111.6) 92.22 94.9 95.1 13 14 997 95.1 10.1 10.1, 106.8) 100.8, 109.9) 99.87, 108.2) 11 later ured a S S was	
	Australians of the Australia Austral	Geometra medican referency oral tablet in co	5468.3  \$10.3  \$10.3  If 40 reg and smiddly late bey reliable steen with an ideligate bey reliable steen	Ratte (T/R) et 1.5 mg (Antxent)  Ratte (T/R) et 1.5 mg (Antxent)  42  43  44  45  103.93  104.78  103.93  104.78  pregnan  n that was d in 11 s s reportir with 6 su CS-8663  40 mg an	Reference (n = 27) (1 - 20) (2 - 20) (3 - 21) (3 - 21) (3 - 21) (3 - 21) (4 - 20) (4 - 20) (5 - 20) (5 - 20) (6 - 20) (6 - 20) (7 - 20) (7 - 20) (8 - 20) (9	992.2 (104.9) (104.8) (111.6)	
	AUCac (ag/h/mL) Cac (ag/h/mL) Cac (ag/mL) Antihmetic Noran stato Geometric Mona stato Time (a) Median (Min - Max) TV(s) Arithmetic Mona stato Conce (ag/mL) Conce (ag/mL) AUCac (ag/mL) AUCac (ag/mL) Conce (ag/m	Geometra medican referency oral tablet in co	5468.3  \$10.3  \$10.3  If 40 reg and smiddly late bey reliable steen with an ideligate bey reliable steen	Ratte (T/R) et 1.5 mg (Antxent)  Ratte (T/R) et 1.5 mg (Antxent)  42  43  44  45  103.93  104.78  103.93  104.78  pregnan  n that was d in 11 s s reportir with 6 su CS-8663  40 mg an	Reference (n = 27) (1 - 20) (2 - 20) (3 - 21) (3 - 21) (3 - 21) (3 - 21) (4 - 20) (4 - 20) (5 - 20) (5 - 20) (6 - 20) (6 - 20) (7 - 20) (7 - 20) (8 - 20) (9	992.2 (104.9) (104.8) (111.6)	
. Safety results	Australians of the Australia Austral	Geome Test" (n = 26) 42784.8 50326.7 Geome Test" (n = 26) 424784.8 50326.7 7642.9 (columeratian medicano tee") eral tablet in control tabl	5468.3  \$10.3  \$10.3  \$10.3  \$10.40 reg and smoldplate bey rehistation with an idediplate bey rehistation with an idediplate bey rehistation with an idediplate bey rehistation of subjects treatments of subjects treatments of the receiving Colmetec® of the receiving Colmetec® receiving Colmetec® retains of old manual columns of the receiving Colmetec® receiving Colmetec® retains of old manual columns of old matter a receiving Colmetec® receiving Colmetec® receiving Colmetec® retains of old matter a receiving Colmetec® rec	Ratio (T/R) 102.85 fata 10 mg) systet 10 mg (Anticest  41  41  41  41  41  41  41  41  41  4	Reference (n = 27) 23175.4 ± 1036 21076.4 ± 1036 21076.4 ± 1036 21076.3 ± 1419 21179.5 ± 1419 21179.5 ± 1419 2131.3 (24.3 ± 1036 2131.3 (24.3 ± 10	992.2 (104.9) 94.81, 111.6) 94.81, 111.6) 94.81, 111.6) 97.2.2 (10.9) 97.7 (10.9) 97.7 (10.9) 97.7 (10.9) 97.7 (10.8) 100.8, 100.9) 97.87, 108.2) 1 later ured a s s s was s and £ tacal®	

rmulation G) is bioequivalent to the co-administration Colmetec® 40 mg and Antacal® 10 mg tablets.
ngle, oral doses of CS-8663 oral tablets appeared to be fe and well tolerated by the healthy male and female bjects in this study.
gnature)  Or. Kai Schumacher  all name)



Name of medicinal product	ATTENTO ® PLUS 40/10/25 mg
(registration certificate №, if available	
)	
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 <sub>0-t</sub> , AUC <sub>0-Inf</sub> , C <sub>max</sub> , T <sub>max</sub> , kel, t <sub>1/2</sub>
17. Criteria for evaluation safety	Adverse events, clinical laboratory measurements,

	vital s ECGs	signs s.	, phys	sical o	exam	inatio	ns an	d 12	-lead
18. Statistical methods	90% CIs for the difference between treatment								
	LSMs were derived from the Analysis of Varian (ANOVA) on the ln transformed PK parameters AUC <sub>0-t</sub> , AUC <sub>0-inf</sub> and C <sub>max</sub> for olmesartan and								
	amloc	).t, A lipin	$UC_{0-1}$ e in ea	<sub>nf</sub> and ach c	C <sub>max</sub> ohort	for o	lmes	artan	and
9. Demographic indices of studied	Tir	ılı	Males	Cohort 1 Females	Overall	Malex	Cohort 2 Families	Overall	Study Overali (N=60)
oopulation (sex, age, race, etc.)	Gender	Male Pemale	(N=23)	(N=7)	(N-de) 23 (76.7%) 7 (23.3%)	(Ni-bis	(Ned)	20 (86.7% 4 (13.3%)	49 (81.7%)
	Race	Black Concasino	15 (65.294) 4 (17.4%)	2 (28.6%) 2 (28.6%)	17 (56.7%) 6 (20.0%)	19 (73.1%) 4 (15.4%)	1 (75.0%)	22 (73.3%)	
		Hispania Other	4 (17.4%)	3 (42.0%)	7(23.3%)	2 (7.7%) 1 (3.8%)	1 (25.0%)	2 (6.7%)	9 (15.0%) 2 (J.3%)
	Age (yr)	Mean SD Medien	32.0 5.64 32	32.6 9.38 35	6.22	30.7 7.67	27.0 6.68	30.2 7.55	31.2 6.93
	April 10	Minimum	23	23	32 23 43	29 21 45	28 19 33	29 19 45	29.5 19 45
		Mean SD	175.43 7.835	162.57	172.43 9.085	177.00	162.75 6.23H	125.2	173.77 8.796
	Height (cm)	Median Minimum	176 156	163	173	179.5	162 256	176.3	175 154
		Maximum Mean	79.18	76.59	193 78.57	1EE	171 65.9%	2024	192 79.41
	Weight (kg)	Molim Molim	11.832	12,919 RU.N	11.915	11.901 £3.1	66.25	12.953	12.36E 79.5
		Minimum Meximum Mean	59.5 103.1 25.72	50.5 107 21.96	50.5 143.1 26.43	61 101.6 26.27	99.2	101.6	50.5 103.1
	PMI (kg/m²)	SD Median	3,475	3.674	3.727	3.373	24.X3 3.907 2) E	3.411 25.55	3.548
		Maximum Maximum	19.4 31.7	21.4 31.7	19.4 31.7	19.8 31.5	21.3	19.8	23.95 19.4 31.7
0. Efficacy results	Olymenscia			Tresis	ment A	Cabort	-	ren Intend	
	AUCoctugh	mL)		(= -	-30)			(n=30)	
	Arithmetic Geometric	Menn ±SD Menn (CV%)			£ 407.38 (23.9%)			13K.6 ± 391.0 606.3 (23.0)	
	AUCear (age Arithmetic Geometric				± 403,11 (23,1%)			78.3 ± 403.6	
	AUC <sub>64</sub> / AUC Arithmetic	164		0.9A27 ±	- Address - Addr			\$35 ± 0.000	
	Constitution (Constitution)			347.5 : 338.0 (			3	H16.0 ± 10.55	1
	Total (b) Median (M	-			20 - 4.02)			95.7 (27.3% 00 (1.68 - 4.	
	T%(h) Arithmetic			14.326				A39 ± 5.601	
		****		11.00		-			
	Olmesartan	-	Geomei Treatment A	Treatme		of LSM	95% C (Lower, E		Intra-Subject
	AUCse(ng/h/s	47	(u = 30) 1824.7	(n = 3)		(%) 107,57	(%)	(41)	CV (%)
	AUCsur(ugh/	_	1857.1	1729.4	-	107.39	(99.42 , 11	-	17.5
	Cuta (ng/mL)		338.0	295.7		114.30	(106.6 , 12	12.5)	15.9
	Olmesarian			Tresto		Colori 2		Talmen! D	
	AUC, tagh/s Arithmetic h	al.)		(n ==	29)			(u = 29)	
	Germenic h AUCsur (ng-h Arithmesic )	tenn (CV%) tell.)		5760.8 (	29.2%)		52	211 (260%)	
	Geometric M AUC+ / AI/C, Arithmetic M	less (CV%)	NAME OF THE OWNER, OWNE	5943.1 (2	18.2%)*		53.	1.5 ± 1327.7 21.7 (26.3%) 109 ± 0.0164	
	C <sub>mat.</sub> (ag/ml.) Arithmetic h	fean àSD		918.7±	240.44		25	9.1 ± 182.23	
	Geometric A Time (h) Median (Min	3500.00		2.000 (1.0				7/1/02 21	
	TYS (h) Arithmetic h			15.630±	and the second			7 (1,00 - 3,1 273 ± 8,129	
			Comme	tric LSM	l p	d_ (P)P	99% CI		
	Olmesartan		Trestment C (n = 29)	Treatme (a = 2	ut D 0	tio (C/D) of LSM (%)	(Lower, Up.		latru-Subject CV (%)
	AUCs (ng h/m	_	5790.3	5164.	1	112.11	(103.3 , 121		18.1
	Cons (ng/mL)	nL)	911.9	5265.°	-	109.73	(104.7 , 123	_	17.4
		C-1		1 0,1,0		111111	giwi.p, tla	100	



	Aniodipine		Trestment A	Oskor	Trestas			
	AUC., (pg h/ml.) Arithmetic Mans ±5		(n - 30) 152301.8 ± 42413		149952 R ±			
	AUC_nist (ng le/ml_2 Arithmetic Mean ±SD 168328.2 ± 54018.97 Geometric Mean (CV%) 160188.7 (33.8%)				144154.0 (			
				165675.9 ± 56421.90 157724.4 (\$2.8%)				
	AUCo+/ AUCo+ot  Arithmetic Mean ±SD				0.9150 ± 0.04209			
	Arithmetic Mean &Si Gennesrie Mean	)	3168.7 ± 806.56 3074.2 (25.3 %)		21.88.0 £ 764.42			
	T <sub>stee</sub> (h) Median (Min - Max)		8.017 (6.00 - 12.1	1	3104 N (2 8.000 (6.00			
	Til (h) Arithmetic Mean ±Si	,	40.74 ± 9.692		49.46±5			
	THE STATE OF THE S		- AM. 1 4 A.		111111111			
		Green	setric LSM	Ratio (A/B)	90% CI			
	Amladipine	Treatment A (n = 30)	Trestment B (n = 30)	of LSM (%)	(Lower, Uppex)	Intra-Subject CV (%)		
	AUCas(pg-h/mL)	146500.5 160308.7	144154.0	101.63	(99.13 , 104.2) (99.04 , 104.3)	5.7		
	Cup (pg/mL)	3074.2	3104.8	99.91	(95.65 , 102.5)	7.9		
	Antindiplace		Treatment C	Color				
	AUC., (pg h/mt.)		(n = 29)		Treatme (n = 2			
	Arithmetic Mean aSD Geometric Mean (CV	4)	318909.8 ± 79462.1 309233.5 (26.1%)	6	309796.6±6			
	AUCook (pg h/mL) Arithmetic Mean #SD		350212.2 ± 91655.2	6	341976.5±	14607.54		
	Gestoctric Mean (CV AUCon/AUCon Arithmetic Mean (CV		338307.8 (27.8%)		331201.5 (			
	Arithmetic Mean ±SD C <sub>nds</sub> (pg/ml.) Arithmetic Mean ±SD	8	0.9147 ± 0.01393		0.9117 ± 0			
	Geometric Mean T <sub>stet</sub> (h)		6643.1 (24.656)		6238,3 ± 1 6084,9 (2)			
	Median (Min Max)		6.100 (6.00 - 12.0)		7.983 (5.98	- (20)		
	Arithmetic Meun ±SD		40.24 ± 7.534		49.79 ± 7	.114		
	Amledipine	Treatment C	tric LSM Treatment D	Ratin (C/D) of LSM	98% CI (Lower, Upper)	letra-Subject		
	AUCas(pg h/mL)	(n=29) 307935.3	(n = 19) 303057.1	(%) 101.61	(%)	CV (%)		
	AUC sur (pg h/mL)	336543.6	332572.6	101.19	(97.25 , £06.2) (96.5% , £06.0)	9.7		
01.00	Cass (pg/mL)	6625.3	6118.6	108.28	(103.2 , 113.6)	10.5		
21. Safety results	No seriou	s or se	vere TEA	AEs oc	curred in	the study		
	Most TEA	Es we	re mild,	and no	modera	te TEAEs		
	were relat							
	was with							
	lower jaw	/naroti	tic) and	noder	to cocine	onbilia.		
	these TEA	Farm	us) and i		ne cosme	эршпа;		
	treatment.	No II	LAE was	COnch	dered det			
		tolotod		COHSI	acrea de	finitely of		
22. Conclusion (summary)			to the st	udy tre	atments.			
(Summary)	The lower		to the st	udy tre	atments.			
		streng	to the st	udy tre -8663	eatments. oral tabl	et (fixed		
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	dose comband amloc	streng sination lipine l inister	to the st th of CS n of olm pesylate ed Olme	-8663 esartar 5 mg) tec® 1	eatments. oral table medoxo was bioe	et (fixed omil 10 m		
	dose comi and amloo to co-adm 5 mg unde	streng pination lipine l inistere er fastin	to the st th of CS n of olm pesylate ed Olme ng condi	-8663 esartar 5 mg) tec® 1 tions.	eatments, oral tabl n medoxo was bioe 0 mg and	et (fixed omil 10 m quivalent d Antacal		
	dose comi and amloo to co-adm 5 mg unde	strengoination dipine di inistere er fastin	to the st th of CS n of olm besylate ed Olme ng condi	udy tre -8663 esartar 5 mg) tec® 1 tions.	oral table a medoxo was bioe 0 mg and	et (fixed omil 10 m equivalent d Antacal		
	dose cominand amlood to co-admin 5 mg under The higher dose cominant to the community of th	streng oination lipine l inistere er fastin r streng	to the st th of CS n of olm besylate ed Olme ng condi gth of CS n of olm	udy tre -8663 esartar 5 mg) tec® 1 tions. 5-8663 esartar	oral table	et (fixed omil 10 m equivalent d Antacal let (fixed omil 40 m		
	dose comi and amloo to co-adm 5 mg undo The highe dose comi and amloo	strengoination lipine linistere er fastion r strengoination lipine l	to the st th of CS n of olm besylate ed Olmer ng condi- gth of CS n of olm- besylate	udy tre -8663 esartar 5 mg) tec® 1 tions. 6-8663 esartan 10 mg)	oral table	et (fixed omil 10 m quivalent d Antacal let (fixed omil 40 m equivaler		
	dose cominand amlood to co-admin 5 mg under The higher dose cominant to the community of th	strengoination lipine linistere er fastion r strengoination lipine l	to the st th of CS n of olm besylate ed Olmer ng condi- gth of CS n of olm- besylate	udy tre -8663 esartar 5 mg) tec® 1 tions. 6-8663 esartan 10 mg)	oral table	et (fixed omil 10 m quivalent d Antacal let (fixed omil 40 m equivaler		
	dose comi and amloo to co-adm 5 mg undo The highe dose comi and amloo to co-adm	strengoination lipine linistere er fastion r strengoination lipine linistere	to the st th of CS n of olm besylate ed Olmeng condi- gth of CS n of olm- besylate ed Olmen	udy tre -8663 esartar 5 mg) tec® 1 tions. 6-8663 esartar 10 mg) tec® 4	oral table	et (fixed omil 10 m quivalent d Antacal let (fixed omil 40 m equivaler		
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Applicant (registration certificate holder	dose comi and amloo to co-adm 5 mg unde The highe dose comi and amloo to co-adm 10 mg und	r strenge bination lipine linister fastion r strenge bination lipine linister fastion lipine linister fast	to the st th of CS n of olm besylate ed Olme ogth of CS n of olm besylate ed Olme oesylate ed Olme oesylate	udy tre -8663 esartar 5 mg) tec® 1 tions. 6-8663 esartar 10 mg) tec® 4	oral table	et (fixed omil 10 m quivalent d Antacal let (fixed omil 40 m equivaler		



1. Name of medicinal product (registration certificate №, if available)	ATTENTO ® PLUS 40/10/25 mg 19
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

12. Main inclusion criteria	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.  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	<ul> <li>OM 40 mg + AML 10 mg</li> <li>OM 40 mg + HCT 25 mg,</li> <li>AML 10 mg + HCT 25 mg</li> </ul>
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, <20/80 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.)	OM460			
20. Efficacy results	Mean (SD)   33.1 (7.27)   33.1 (7.25)   33.0 (7.05)   33.2 (6.99)			





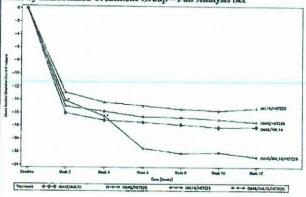


Table S2. Number (%) of Subjects Reaching Blood Pressure Treatment Goal at Week 12 with LOCF – Full Analysis Set

	OM40/ AML10 (N = 624)	OM40/ HCTZ25 (N = 627)	AML10/ HCTZ25 (N = 593)	OM40/ AML10/ HCT225 (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/HCT225 [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)	AMLII/ HCTZ25 (N=95)	OM40/ AMLtu/ HCT225 (N = 117)		
96	101	83	100		
E8.6 (10.41)	88.7 (10.22)	88.6 (10.07)	87.2 (9.38)		
-13.9 (8.09)	-14.5 (8.73)	-10,7 (7.46)	-IR.0 (E.11)		
-13.8 (0.69)	-14.3 (0.68)		-18.5 (0.68)		
<0.0001	1000,00	<0.0001	<0.0001		
	Between treatmen	et comparisons [4			
LS Me	LS Mean (SE)		P-value		
		<0.0001			
		<0.0001			
-8.0 (	1.011	<0.0001			
96	101	83	100		
			140		
149.7 (13.91)	[47.3 (13.63)	147.0 (12.13)	147.4 (13.58)		
		(1-2-10-)			
-23.5 (11.80)	-23.9 (13.10)	-18.5 (10.67)	-30.3 (13.85)		
-22.6 (1.09)	-24.2 (1.05)		-30.5 (1.07)		
<0.0001	<0.0001	<0.0001	1000.0>		
		LS Mean (SE)			
		<0.0001			
		<0.0001			
		<0.0001			
	AMI.10 (N = 112)  96  88.6 (10.41)  -13.9 (8.09) -13.8 (0.69) -13.8 (0	AML10 (N = 112) (N = 112) (N = 112) (N = 112) (N = 110)  88.6 (10.41) 88.7 (10.22)  -13.9 (8.99) -14.5 (8.73) -13.6 (8.9) -13.6 (8.9) -14.6 (9.9) -14.6 (9.9) -14.6 (9.9) -14.7 (0.97) -4.2 (0.96) -8.0 (1.01)  96 101  149.7 (13.91) 147.3 (13.63) -23.5 (11.80) -23.5 (11.80) -23.5 (11.80) -23.6 (1.91)  -23.6 (1.91)  -23.6 (1.91)	AML10   HCT225   HCT235   (N = 112)   (N = 116)   (N = 55)    96   101   83    88.6 (10.41)   88.7 (10.22)   88.6 (10.67)    -13.9 (8.09)   -14.5 (8.73)   -10.7 (7.46)    -13.8 (0.69)   -14.3 (0.63)   -10.5 (0.75)    -4.0.001   -0.0001   -0.0001    Between treatment comparisans (€ LS Mean (SE)   F-v    -4.7 (0.97)   <0.1    -8.0 (1.01)   <0.001   -10.5 (0.75)    -1.1 (1.0.7 (1		

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) efter Extremen hor (signature) Dr. Kai Schumacher (full name)



1. Name of medicinal product (registration certificate №, if available )	ATTENTO ® PLUS 40/10/25 mg 24			
2. Applicant	Menarini International Operations Luxembourg S.A., Luxembourg  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)			
3. Manufacturer				
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	<ul> <li>Period III (open-label extension period):</li> <li>To gain long-term efficacy and safety experience with the co-administration of OM + AML (plus the addition of HCT, if needed).</li> <li>To evaluate the number (%) of patients achieving BP control (defined as BP &lt; 140/90 mmHg, &lt; 130/80 in diabetic patients).</li> </ul>			
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	<ul> <li>OM 40 mg + AML 10 mg</li> <li>OM 40 mg + AML) 10 mg + hydrochlorothiazide (HCT) 12.5 mg</li> <li>OM 40 mg + AML 10 mg + HCT 25 mg</li> </ul>
15. Concomitant therapy	Standard antihypertensive therapy was allowed at study start and discontinued during the washout period.
16. Criteria for evaluation efficacy	<ul> <li>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.</li> <li>Number (%) of patients achieving BP control (defined as BP &lt; 140/90 mmHg, &lt; 130/80 in diabetic patients).</li> </ul>
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 Patients Entering Period III (N - 1684) Baseline Characteristic population (sex, age, race, etc.) Age (years) N Mean (SD) Age Group (n, %)<sup>2</sup> <65 years ≥65 years and <75 years 54.1 (10.98) (353 (80.3) 277 (16.4) ≥75 years Gender (n, %)² 54 (3,2) Gende 927 (55.8) Female Ethnicity (n, %) 757 (45.0) Hispanie or Latino Not Hispanie or Latino Ruce (n. %)\* Caracasian Black 214 (12.7) 1205 (71.6) 413 (24.5) Asian 33 (2.0) 10 (0.6) American Indian/Alaskan Native Native Hawaiian/Pacific Islander Weight (kg) N Mean (SD) 1683 95.1 (21.77) Normal (SD)
Body muss index (kg/m²) 4
N 170.2 (10.40) Mean (SD) 33.4 (7.08) Table 7: Seated Diastelle Blood Pressure (mmHg) by Week and Dosing 20. Efficacy results Regimen - All Patients Entering Period III OM40/ AML5 AMILIO/ Week Exectine HCTZ125 HCTZ25 Other4 1683 101.5 ± 4.97 1640 N Mam ± 5D 92.8 ± 8.07 75.3 ± 3.61 3 (100.0) 792 (48.3) 2(18.2) 82.1 ± 7.69 87.0 ± 8.26 92.6 ± 7.88 82.5 ± 7.55 n (%) to BF go Week 18 643 (72.9) 247 (35.6) 1 (3.1) 435 30 85.0 ± 7.39 7 (23.3) 101 Mezer L SD #3.7±7,95 247 (56.8) 85.8 ± 8.67 145 (37.1) n (%) to BP go Week 26 526 (75.5) 232 Mean J. SD 85.0 ± 7.15 15 (48.4) 30.9 ± 7.71 82.4 ± 7.61 n (%) to BP goal Week 34 N 271 (69.3) 450 (79.R) 167 (54.2) 360 279 479 316 Mean ± SD n (%) to BP goal Week 42 N 80.1 ± 7.62 412 (86.0) 81.7 ± 7.30 268 (74.4) 81.5 ± 7.65 81.8 ± 8.12 192 (68.8) 131 (41.5) 23 (62.2) 431 335 258 155 79.2 ± 7.01 387 (89.8) 80.5 ± 7.67 268 (80.0) 80.1 ± 7.52 199 (77.1) R2.5 ± 8.42 185 (\$2.1) \$0.9 ± 6.93 35 (74.5) n (%) to BP go Week \$2 412 248 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 so Week 52/ET N Mean ± SD 355 (86.2) 244 (78,2) 171 (69.0) 180 (48.4) 40 (71.4) 63 79.4 ± 9.90 n (%) to BP goal<sup>2</sup> Week 54/Follow-up 420 (88,0) 267 (70.6) 191 (66.6) 194 (46.3) 43 (68.3) 247 Mean & SD n (%) to BP goal 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

	<ul> <li>SeSBP of 127 mmHg. 80.0% of these patients reached their BP goal</li> <li>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.</li> <li>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.</li> <li>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.</li> </ul>
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)



1. Name of medicinal product	ATTENTO ® PLUS 40/10/25 mg 28			
(registration certificate №, if available )  2. Applicant	Managini Intermeticanal Operations I would be a C. A.			
	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 openlabel 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			
	<b>Period III</b> : 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			

13. Investigational medicinal product, mode of administration and strength	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.  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	+ AML 10 mg + HCT 25 mg Standard antihypertensive therapy was allowed
Land and the same	at study start and discontinued during the washout period.
16. Criteria for evaluation efficacy	<ul> <li>Mean SeDBP at weeks 28, 34, 43 and 52</li> <li>Mean SeSBP at weeks 28, 34, 43 and 52</li> <li>Mean changes in SeDBP and SeSBP during period IV with titration from one dose regimen to the next.</li> <li>Number (%) of patients achieving BP goal (140/90 mmHg; 130/80 mmHg in diabetic patients)</li> <li>Number (%) of patients reaching BP thresholds (&lt;120/80 mmHg, &lt;130/80 mmHg, &lt;130/85 mmHg and 140/90 mmHg) during Period IV</li> </ul>
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

	Deriod IV Dogo	intiro	totictica		
	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 O	M 40 m	g + AN	II. 10 n	o from
	OM 40 mg + AN	/IL 10 n	ng to Ol	M 40 m	σ+
	AML 10 mg + H	ICT 12.	5 mg ar	d from	OM 40
	mg + AML 10 n				
	mg + AML 10 n				
19. Demographic indices of studied					Who Entered
population (sex, age, race, etc.)	Churacteristic				od IV : 692)
	Gender n (%) Male			430	(62.1)
	Female Ethnic origin n (%)			262 (37.9)	
	Caucasian Other			690 (99.7) 2 (0.3)	
	Age (years)			6	92
	Mean (SD) Age group n (%)			55.7	(9.52)
	<65 years ≥65 years				(79.0) (21.0)
	≥65 years to <75 years ≥75 years			137	(19.8)
	Weight (kg)				92
	Mean (SD) Height (cm)				13.64)
	n Mean (SD)				92
	Body mass index (kg/m²)				(8.83)
20. 700	Mean (SD)				(3.86)
20. Efficacy results	Time Point Statistic	OM40/ AMLS	OM40/ AML10	AML10/	OM44/ AME10/
	Week 8 (haseling) N entering Period IV	692	Autilia	HCTZ12.5	RCT225
	Sitting DBP mean (SD) Sitting SBP mean (SD)	97.0 (5.11) 154.5 (10.89)			
	Weak 28 N	665	20		
	Sitting DBP mean (SD) Sitting SBP mean (SD) n (%) to BP gool [1]	84.1 (7.63) 133.4 (12.68) 468 (70.4)	89.7 (7.44) 141.8 (14.45) 9 (45.0)		
	Week 34 N	546	114	L3	4
	Sitting DBP mean (SD) Sitting SBP mean (SD) n (%) to BP gool [1]	83.6 (7,04) 132.3 (10.68)		89.6 (8.00) 143.1 (10.82)	86.3 (4.91) 140.8 (10.64)
	Week 43	403 (73.8)	38 (33.3)	5 (38.5)	1 (25.0)
	Sitting DBP mean (SD) Sitting SBP mean (SD)	82.9 (6.08) 131.3 (10.55)	86.0 (6.42)	87.8 (6.57) 140.9 (10.62)	89.7 (R.66) 144.3 (13.29)
	o (%) to BP goal [1] Week 52 [2]	364 (77.9)	76 (56.3)	23 (34.8)	2 (40.0)
	Sitting DBP mean (SD) Sitting SBP mean (SD)	83.2 (6.47)	142 85.3 (6.63) 134.8 (9.79)	68 87.3 (5.99)	27 89.7 (5.42)
	a (%) to BP goal [1] Week 52/ET	131.6 (10.18) 321 (74.5)	84 (59.2)	138.3 (10.52) 32 (47.1)	9 (33.3)
	N Sitting DBP mean (SD)	452 83.1 (6.56)	144 85.4 (6.82)	68 87.3 (5.99)	27 89.7 (5.42)
	Sitting SBP mean (SD) n (%) to BP goal [1]	336 (74.3)	85 (59.0)	138.3 (10.52) 32 (47.1)	9 (33.3)
	• Of the 69				
	mg + AML 5 mg, 537 (77.7%) reached				
	the <140/90 mmHg threshold, 361 (52.2%) reached the <130/85mmHg				
	threshold				
	<130/80				
	1				
	(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%			-	
	threshold				
	<130/80 1	0.7			

	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)



1. Name of medicinal	ATTENTO ® PLUS 40/10/25 mg
product (registration	
certificate №, if available)	
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
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 <sub>0-t</sub> , AUC <sub>0-Inf</sub> , AUC%extr, C <sub>max</sub> , T <sub>max</sub> , Lambda Z, t <sub>1/2</sub> 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 Intransformed AUC <sub>0-t</sub> , AUC <sub>0-Inf</sub> and C <sub>max</sub> for OM, AML and HCT. The ANOVA model included sequence, treatment and period as fixed effects.

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19. Demographic indices of		**	Trait	***	Overall	
studied population (sex, age,	Frant			(n = 36)		
race, etc.)	Gender		Male	MASAR SOCIETY OF THE STATE OF T	28 (77.8%)	
	(N%)		Female		8 (22.2%)	
	Ethnicity (N%)		Hispanic or La Not Hispanic or		11 (30.6%) 25 (69.4%)	
	1000	Arr	erican Indian/Ala		2 (5.6%)	
	Race			skar Native	1 (2.8%)	
	(N%)		Asian Black or African A	merican	26 (72.2%)	
			White		7 (19.4%)	
	Age		Mean ± SI	)	30.5 ± 7.66	
	(yr)	INTERNAL IV			30.5 (19 -45)	
	Height		Mean ± SI	*	176.5 ± 9.85	
	(cm)		Median (Min -		177.0 (156 – 193)	
	Weight		Mean ± SI		80.83 ± 12.559	
	(kg)		Median (Min -		79.25 (53.6 – 107.6)	
	BMI		Mean ± St		25.86 ± 2.829	
	(kg/m²)		Median (Min -	Max)	26.43 (19.4 – 31.0)	
20. Efficacy results	Olmes	artan	Treatm N=:		Treatment B N = 35	
	AUC <sub>o4</sub> (r					
		Mean ±SD	6134.4 ± 1		6399.5 ± 1816.81	
	AUCair (	Mean (CV%)	5938.7 (2	3.0%]	6068.9 (38,3%)	
	Arithmetic	Mean ±SD	6249.8 ± 1678.98		6501.9 ± 1837.56	
	Geometric Mean (CV%)		6055.8 (25.5%)		6189.9 (35.8%)	
	C <sub>max</sub> (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 <sub>max</sub> (h) Median (Min, Max)		1 002 (1 00 4 00)		1 083 (1 00 2 00)	
	t <sub>sc</sub> (h)		1.983 (1.00, 4.00)		1.983 (1.00, 3.00)	
	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	
			0.001	1000	V.750 - 3.0-137	
	Geometric		c LSMEANS Ratio of		T	
	PK Parameter	Treatment A (Test)	Treatment B (Reference)	LSMEANS (%) (A/B)	90% C.I. for Ratio (%)	
	AUC <sub>0-inf</sub>	5989	6184	96.84	(89.14, 105.20)	
	AUC <sub>0-4</sub>	5876	6068	96.83	(88.49, 105.96)	
	C <sub>max</sub>	866.2	954.1	90.79	(83.24, 99.01)	
	r <del>-</del>					
	Amledipine		Treatment A N = 33*		Treatment C N = 34	
	AUC <sub>B-1</sub> (ng.h/m Arithmetic Mea Geometric Mea	an ±SD	339.1 ± 8 327.7 (27		334.7 ± 95.38 321.3 (30.1%)	
	AUC <sub>t-lef</sub> (ng.h/mL) Arithmetic Mean ±SD Geometric Mean (CV%)		381.9 ±112.01 365.8 (31.0%)		378.3 ± 126.45 358.6 (34.2%)	
	C <sub>max</sub> (ng/mL)					
	Arithmetic Mea Geometric Mea		7.456 ±1.9622		7.013 ± 2.0320	
	T <sub>max</sub> (h)		7.224 (25.7%)		6.747 (28.7%)	
	Median (Min, )	100,000	7.017 (5.98, 12.0)		7.000 (5.97, 12.0)	
	CL/F (L/h)	m #5D	45.18±1	2.802	44.11 ± 12.909	
	Arithmetic Mea	nn ±SD	28.63 ± 9	0.356	29.43 ± 10.022	
		Geometric	LSMEANS		774.00	
	PK Parameter	Treatment A	Treatment C	Ratio of LSMEANS (%)	90% C.I. for Ratio	
		(Test)	(Reference)	(A/C)	(%)	
	AUCoint	365.6	361.8	101.05	(95.89, 106.49)	
	AUC <sub>0.1</sub>	328.4	324.6	101.19	(96.71, 105.87)	
	Cmax	7.186	6.768	106.18	(101.97, 110.56)	



	Hydrockie	orothiazide		nent A = 34	Treatment B N=35
	AUCot (ng.h/ml.) Arithmetic Mean ±SD Geometric Mean (CV%) AUCot (ng.h/ml.) Arithmetic Mean ±SD Geometric Mean (CV%)			± 224.90 (21.6%)	1052.7 ± 231.13 1021.8 (27.4%)
				± 224.78 (21.0%)	1079.8 ± 229.12 1050.9 (25.8%)
	Comx (ng/mL) Arithmetic Mc Geometric Mc Tmax (h)			= 53.714 (31.8%)	164.78 ± 57.837 155.34 (37.0%)
	Modian (Min.	Max)	1.5000 (0.	983, 4.00)	1.5000 (0.983, 4.00)
	Arithmetic Me CL/F (L/h) Arithmetic Me		10.800 ±		10.866 ± 2.0647 24.70 ± 8.513
		Geometric	LSMEANS	Ratio of	T
	PK Parameter	Treatment A (Test)	Treatment B (Reference)	LSMEANS (%) (A/B)	90% C.I. for Ratio (%)
	AUC <sub>0-inf</sub>	1051	1050	100.06	(95.01, 105.39)
	AUC <sub>04</sub>	1025	1021	100.33	(94.93, 106.05)
21. Safety results	Cmax	154.9	155.1	99.89	(91.97, 108.48) during the study.
22. Conclusion (summary)	A, B, and The pharm				
	combinati administra affected b PK of hyd	on (Benication of a y the fixed drochlorou HCT®) ar	car HCT® mlodipine ed dose co thiazide in	are not a e. The PK ombination the fixed	the fixed dose affected by the co- of amlodipine are not (Benicar HCT®). The dose combination e co-administration of
	combinati administra affected b PK of hyd (Benicar I amlodipin The conce olmesarta	on (Benication of a sy the fixed rochlorof HCT®) and the comitant account medox and well to	car HCT@ mlodipine ed dose co thiazide in re not affe dministrate omil 40 m	e. The PK of the fixed the fixed by the cion of aml g and hydrones.	of amlodipine are not (Benicar HCT®). The dose combination



1. Name of medicinal	ATTENTO ® PLUS 40/10/25 mg
product (registration	ATTENTO @ FLOS 40/10/23 mg
certificate №, if available	
)	
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
	Medicinal product with fixed combination
product, which has been	
or will be registered	
5. Title of clinical trial,	866-126
code number of clinical	
trial	A randomized, open-label, three-way crossover bioequivalence study of
	CS-866 tablets plus hydrochlorothiazide capsules or tablets and CS-
6. Phase of clinical trial	866/hydrochlorothiazide combination tablets in healthy adult volunteers. Phase I
	10 Aug 2001 to 28 Aug 2001
8. Countries, where clinical trial has been	USA
conducted	
9. Number of trial	planned: 33
subjects	actual:30(completed)
10. Objective and	To determine the bioequivalence of the clinical trial supply of CS-866
secondary endpoints of	tablets and hydrochlorothiazide (HCT) capsules or tablets administered
clinical trial	orally in combination versus oral administration of the market-image
Continues on Color Veril, Color Coul)	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	Volunteers for the study were healthy male and non-pregnant female
criteria	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	20 mg CS-866/12.5 mg HCT market image combination tablet, single-
	dose, p.o. (formulation C)
of administration and	dose, p.o. (formulation C)
strength	
14. Reference product,	20 mg CS-866 investigational tablet + 12.5 mg HCT capsule, single-
dose, mode of	dose, p.o. (formulation A)
administration and	
strength	20 mg CS-866 investigational tablet + 12.5 mg NCT tablet, single-dose,
	p.o. (formulation B)
15. Concomitant therapy	None

16. Criteria for	AUC <sub>0-Int</sub>	, AUC <sub>0</sub>	-lacs Cmax	, k <sub>el</sub> a	nd tur	for th	ne CS	-866 me	tabolite RNH
evaluation efficacy	6270 and	HCT	iqe) - ilia	.,	1/2	101 61	10 00	ooo me	abonic Kivi
17. Criteria for	Physical examinations, vital signs, clinical adverse events and								
evaluation safety	hematology, blood chemistry and urinalysis test results.								
	Ln-transformed AUC <sub>0-lqc</sub> , AUC <sub>0-lnf</sub> and C <sub>max</sub> 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				ALL 6	UBJECTS	_			
indices of studied	N (%)			33	(100%)				
population (sex, age, race, etc.)	GENDER N (* MALE FEMALE	b)		17	(52%) (48%)				
	RAGE N (%) CAUCASIAN BLACK ASIAN HISPANIC OTHER	•		12 14 1 5	(36%) (42%) (3%) (15%) (3%)				
	PRAME SIZE SMALL MEDIUM LARGE	и (*)		2 26 5	(6%) (79%) (16%)				
	AGE (Yr) MEAN (SD) RANGE				( 7.87) - 44.0				
	HEIGHT (in MEAN (SO RANGE	*)			( 4.07) - 73.0	ı			
	WEIGHT (1b MEAN (8b RANGE	•)			(25.96) -212.0	-			
	and the in HCT cap were biod 1.04, 1.04 between contained Similarly for AUC and B, and	nvestiga sule (fo equivale 4 and 1. formula I within f, RNH- lqc, AU d the 90 or bioeq	ntional Crmulation of the stand	S-866 on A: ratio julicon A: and A dard in Cmax, or all ice. Ple	of tablet US) or point e point e to the S to the S bounds int estin respect 3 ratios	table stimate table stimate table stimate table stivel	ombiret (for ates for ates for and (CI for bioeq s were by between summ	nation we mulation or RNH- C <sub>max</sub> , restrall 3 radivalence 1.07, 1 ween for tained we mary PK	rmulation C) ith marketed n B; Europe) 6270 were spectively, tios were se.  .07 and 1.08 rmulations C yell within the for RNH-
	-	FORMRATION A.	FORMULATION B	FERMEATIE (Rr30)	N C COMPA		FORM C TO FOR		FORM C TO FORM B
	PANAMETER	MENN (200)	NEAN (SID)	NEAN (80	6311	HATE (10)	SON CI (H-GC)	AATIO POINT ESTIMATE (N=30)	GON-VAIRON BOA CI (M-30)
	ANC O-Boc (rojet) the ANC O-bot (rojet) thr Ceax (rojet) Teax (hr) t #/2 (hr)	3463,56 (720.68) 3561,43 (843.38) 559.67 (123.23) 2.03* 21.44 (17.60)	0372.77 (781.04) 8459.21 (806.15) 869.67 (718.09) 1.50* 21.50 (10.47)	3602.66 (91 3654.51 (87 600.60 (136 2.00* 20.44 (18.2	(2.05) 1,0 (.41) 1,0	04 04 09	0.90 - £, 0.90 - £, 1.02 - 1.	10 1,07	1.01 - 1.13 1.01 - 1.12 1.01 - 1.15
	Bioequive estimates those obs below:	and 909	% CI of	the ra	tios be	twee	n for	nulation	point ns similar to PK for HCT



	FABLE 7.2.3.2 SUMMART OF PLASMA PHASMAGENITICS PARAMETERS FOR INTRODUCTIONATIVE (HEIZ)  FORE C TO FORM A  FORE C TO FORM A								
	PARAMETER	FORMULATION A (N+30) MERH (SD)	FORMULATION IN (IN-80) NEAH (SD)	FORMULATION C (N-30) NEAH (SD)	COMPARISON A COMPARISON RATIO POINT ENTERATE (N-30)	FORM G TO FORM COMPARESON 90% GI (N*30)	A COMPANISON A COMPANISON RATIO POINT ENTINATE (BECA)	FORM C TO FERM M COMPARISON SON CI (NedD)	
	AUC O-Ige (ogfst)*he AUC D-inf (ngfst)*he Csax (ngfst) Teix (he) t 1/2 (he)	\$07.32 (156.53) \$88.09 (140.16) \$0.54 (29.50) 2.09* 11.29 (7.22)	494.62 (197.85) 648.80 (124.78) 98.84 (27.84) 1.50* 16.58 (2.42)	\$22.00 (121.08) 584.55 (117.56) 94.50 (31.91) 1.80* 11.02 (2.86)	1.04 1.06 1.08	8.98 - 1.10 0.89 - 1.10 0.68 - 1.15	1.00	1.01 - 1.15 1.02 - 1.14 0.98 - 1.15	
21. Safety results	10 TEAEs CS-866+1 6 (19.4%) tablet (for who recei Headache overall. O receiving No serious	2.5 mg subject mulatio ved the dizzing ne subject formula	HCT (f is who ren B) and market ess and sect who ation B v	ormulaticeceived of 17 TE. image con ausea very experiences with	ion A), 2 20 mg ( AEs wer ombinat were the need 14 adrawn c	23 TEA CS-866+ re reportion table most coof the 2	Es were 1 -12.5 mg ted by 12 et (formu ommon T 3 TEAE	subjects lation C) EAEs after	
22. Conclusion (summary)	The study formulation supplies under European tablets). The page of the standard by the standa	on of CS sed in U clinical he 90% Infand C	S-866/H JS clinic studies CI surr max for	CT was cal studi (CS-866 ounding RNH-62	bioequies (CS-8) investigation in the ration of the ration	valent to 366 + H gationa o point for HC	o the clin CT capsultablets of estimates	ical ales) and + HCT s for AUC	
Applicant (registration certificate holder)	(signature Dr. Kai S (full name	Schuma	leca &	1/7	uml	•			



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
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 <sub>0-Inf</sub> , AUC <sub>0-Iqc</sub> , C <sub>max</sub> , T <sub>max</sub> , k <sub>el</sub> , t <sub>1/2</sub> 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 <sub>0-lqc</sub> , AUC <sub>0-lnf</sub> and C <sub>max</sub> were analyzed by ANOVA. The treatment differences a their corresponding 90%CIs were obtained from tanalyses and were exponentiated to obtain treatment bioequivalence ratios and their corresponding 90%CIs.						and the ent	
19. Demographic indices of studied	200			ALL SUBJECT	TS			
population (sex, age, race, etc.)	TOTAL N (%)			42 (100%)	,			
	GENDER N (4) MALE FEMALE			27 (64%) 15 (36%)	1			
	RACE N (%) CAUCA STAN BLACK ASIAN HISPANIC GTHEN			2 (56) 3 (56) 3 (56) 3 (76)				
	PRAME BIZE N (%	·>						
	WEDIUM LARGE AGE (9T)			4 (10%) ac (7%) 8 (19%)				
	MEAN (SO) MANUE HEIGHT (SII)			28.4 (7.50 19.6 - 44.0				
	WEIGHT (15) WEAN (SD)			66.1 (4-1 60.0 - 76.	đ			
	MANGE 156.1 (25.87)							
20. Efficacy results			RNH-6270 PK Parameter Treatment A Treat		ment B Treatment C		T	
ist Efficiely Testing	Parameter	(n=40 Mean ( Geomean ( Medi	) <sup>(</sup> 5D) %CV)	(n=40) <sup>1</sup> Mean (SI Geomean (*/ Median	o)	(n=40) <sup>1</sup> Mean (SD) Geomean (%CV) Median		
	AUCs.tec (ng.te/mL)	6632.70 (1704.33) 6406.51 (28.04)		6601.34 (2056.43) 6312.44 (30.75)		6362.25 (1525.58) 6188.29 (24.21)	1	
	AUC <sub>b-r</sub> (ng.lv/mL)	6758.62 (10 6539.03 (2	6628.59 6758.62 (1698.51) 6539.03 (27.22) 6694.36		0.74)	6137.50 6569.04 (1587.33) 6384.67 (24.62) 6342.09		
	(ng/nal.)	1010.07 (	1048.08 (289.24) 1010.07 (28.89)		1.47) .67)	1070.66 (269.76) 1038.95 (25.12)		
	Comp/AUCoun(1/lt)	989.3 0.16 (0.	03)	977.20 0.16 (0.03	1)	985.31 0.17 (0.03)		
	T <sub>max</sub> , (hrs) T <sub>1/2</sub> (hrs)	19.31 (1:	1.97)	2.00° 19.03 (13.39)		1.50* 21.44 (21.02)		
		13.4		13.87		14,30	l	
	Parameter AUC <sub>t-loc</sub>		Treatment C vs. Treatment A Ratio Point Estimate (90% CI) <sup>4</sup> 0.97 (0.90, 1.04)		Treatment C vs. Treatment B Rutin Point Estimate (90% CI) <sup>1</sup> 0.97 (0.91, 1.05)			
	AUC <sub>prets</sub>		0.98 (0.91, 1.05) 1.03 (0.96, 1.11)		0.99 (0.92, 1.06)			
	C <sub>max</sub> /AUC <sub>5-ca</sub>		DESCRIPTION OF PERSONS ASSESSMENT	26, 1.11) 1.03 (0.96, 1.11) 10, 1.11) 1.04 (0.98, 1.10)				
			HATT DE	Parameters				
	Parameter	(n-4 Mean Geomean	Treatment A Treatment (m=40) <sup>3</sup> (n=40) Mean (SD) Mean (Geomean (%CV) Geomean		)) <sup>1</sup> SD)	Treatment C (n=40) <sup>4</sup> Mean (SD) Geomean (%CV)	tinkd <sub>e</sub> ,	
	AUC <sub>D.tep</sub> (ng.h/mL)	493.41 ( 483.51 (	20.74)	489.24 (12 475.07 (2	21.77) 4.86)	Median 472.11 (108.48) 460.60 (22.71)	-	
	AUC, (ng.ls/mL)	(ng.ls/mL) 533.54 (18.11)		471.22 542.54 (120.95) 530.08 (21.92)		456.24 521.79 (104.98) 512.02 (19.74)	_	
	C <sub>min</sub> (ng/mL)	531.93 80.39 (21.71) 77.67 (27.64) 78.29		524.44 79.98 (29.71) 74.76 (33.09) 71.46		78.18 (22.12) 75.24 (28.63)	-	
	C <sub>mas</sub> /AUC <sub>e-r</sub> (1/b) T <sub>mas</sub> (hrs)	0.15 (0	1.03)	0.14 (0.	03)	76.01 0.15 (0.03) 1.50*		
	T <sub>1/2</sub> (hrs)	9.63 (1	.83)	10.07	.72)	10.01 (1.96) 9.98		
	Parameter		Point Est	s. Treatment A mate (90% CI) <sup>1</sup>	Ratio Po	uent C vs. Treatment B dut Estimate (90% CI) <sup>1</sup>		
	AUC <sub>0-lot</sub>		0.95 (0.90, 1.00) 0.96 (0.92, 1.00)			0.97 (0.92, 1.02)		
	Cmex		0.96 (0.92, 1.00)			0.96 (0.92, 1.01) 1.01 (0.93, 1.08)		
	CHEKANC®-0		1.01 (9.95, 1.07)			1.04 (0.99, 1.10)		



01 0 0 1	
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 marketimage 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



1. Name of medicinal product	ATTENTO ® DI LIC 40/10/25
(registration certificate №, if	ATTENTO ® PLUS 40/10/25 mg
available)	
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 <sub>0-t</sub> , AUC, <sub>0-Inf</sub> , AUC%extr, C <sub>max</sub> , T <sub>max</sub> , Lambda Z, t <sub>1/2</sub> 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 Intransformed AUC <sub>0-t</sub> , AUC <sub>0-Inf</sub> and C <sub>max</sub> . The ANOVA model included sequence, treatment and period as fixed effects

9. Demographic indices of	11		Trait	7		
tudied population (sex, age,		(n = 36)				
ace, etc.)	Gender Male (N%) Female			ale	30 (83.3%) 6 (16.7%))	
,)	Ethnicity Hispanic or Lut (N%) Not Hispanic or L			B (22.2%)		
	Race Asian		325	28 (77.8%) 1 (2.8%)		
			Wh	ite	27 (75.0%) 8 (22.2%)	
	Age (yr)		Mean (M		31.1 ± 7.75 30.5 (19 - 45)	
	Height (cm)		Mean	± SD	173.5 ± 8.47	
	Weight		Median (M Mean		173.5 (156 - 188) 78.4 ± 12.578	
	(kg)		Median (M		76.5 (54.0 - 104.8)	
	(kg/m²)		Median (M		26.03 ± 3.628 26.22 (19.0 - 31.9)	
0. Efficacy results		sartan		stment A	Treatment B	
		ng.h/ml.)	N	=33*	N=30	
	Arithmetic	Mean (CV%)		2 ± 1709.89 8 (26.8%)	6776.1 ± 1503.53	
	AUC	(ng.h/ntL)			6617.3 (22.5%)	
		Mean (CV%)		1 ± 1748.65 2 (26,3%)	6879.1 ± 1506.23	
	C <sub>max</sub> (	ng/mL)			6721.5 (22.3%)	
		Mean (CV%)		1 ± 304.01 6 (29.6%)	1055.1 ± 306.40 1013.6 (29.6%)	
		x (b)			No. of the last of	
	t <sub>x</sub>	Min, Max) (h)	1,9830 (	(0.983, 3.98)	2.000 (1.00, 4.00)	
	Arithmetic	Moan ±SD	15,83	5 ± 6,1931	15.560 ± 6.1679	
		Mean ±SD	6.001	±1,6977	6.093 ± 1.3700	
	Parwas Pekter 11 4	11100111111				
		Geometric	e LSMEANS			
			1	Ratie of		
	PK Parameter	Treatment A (Test)	(Reference)	LSMEANS (%) (A/B)	90% C.J. for Ratio (%)	
	AUCainf	6912	6537	105.74	(99.15, 112.77)	
	AUC	6763	6395	105.76	(99.01, 112.97)	
	Cmex	1020	975.8	104.56	(96.84, 112.90)	
	Amladipine		Treatment A N = 33		Treatment B N = 30	
	AUChe (ng.h/ml. Arithmetic Mear	±SD	359.4 ± 127.09		364.7 ± 110.24	
	Geometric Mean	(CV%)		(37.0%)	347.2 (33.9%)	
	Arithmetic Mese	±SD		± 170.89	416.0 ± 139.30	
	Cometrie Mean			(42.0%)	392.1 (37.2%)	
	Arithmetic Mean Geometric Mean			± 2.0067 (29.1%)	7.782 ± 2.4615 7.426 (31.9%)	
	T <sub>max</sub> (h) Median (Min. M	ov)		5.98, 16.0)	A CALL COMPANY AND	
	t <sub>k</sub> (h) Arithmetic Mean				7.983 (5.98, 12.0)	
	CL/F (L/b)		44.36 ± 10.765		46.36±11.213	
	Arithmetic Mean	±SD	28.51	± 11.213	27.23 ± 10.559	
		١		r.		
		Geometric	LSMEANS	Ratio of	VIII VIII VIII VIII VIII VIII VIII VII	
	PK Parameter	Treatment A	Treatment B	LSMEANS (%)	90% C.I. for Ratio	
	AUC <sub>0.ur</sub>	(Test) 383.3	(Reference)	(A/B)	(%)	
	AUC <sub>84</sub>	343.7	386.4 341.4	99.18	(95.50, 103.00)	
	Cutax	7.269	7.399	98.25	(97.37, 104.11)	
			1.011	70.23	(93.62, 103.11)	
	Hydrochlor	othiazide	Treats	ment A = 32	Treatment C N = 33	
	AUC, (ng.h/mL)				.,	
	Arithmetic Mean Geometric Mean	(CV%)		± 202.82 (19.1%)	1127.8 ± 251.41 1102.0 (21.9%)	
	AUCs of (ng.h/ml Arithmetic Mean	4)		202.63		
	Geometric Mean C <sub>max</sub> (ng/mL)			(18.7%)	1153.5 ± 249.21 1128.7 (21.3%)	
	Arithmetic Menn			£ 50.355	162.92 ± 45.449	
	Geometric Mean		150.38	(34.9%)	156.92 (28.3%)	
	Median (Min, Ma t <sub>s</sub> (h)		1.742 (1.	00, 8.97)	1.9830 (0.983, 4.03)	
	Arithmetic Mean ±SD		11.151 ± 1.6693		10.839 ± 1.4503	
	CL/F (L/h)	1017	11.121	1.0073	10.839 ± 1.4503	



		Geometric						
	PK Parameter	Treatment A (Test)	Treatment C (Reference)	Ratio of LSMEANS (%) (A/C)	90% C.I. for Ratio (%)			
	AUC <sub>0.inf</sub>	1083	1131	95.74	(92.79, 98.79)			
	AUC64	1056	1104	95.64	(92.64, 98.74)			
	Cnn	152.7	158.7	96.24	(88.85, 104.24)			
21. Safety results	Overall, 2 considere were note the overa slight inc amlodipin (24.2%) s	20 subjected definited betwee the number rease apparent combinations of the combination o	ets reportely or properties of subjustment in the contraction of the c	ted 60 TEA robably dru ments A, B jects with a Treatment herapy): W ment A and TEAEs tha	d during the study. AEs. No TEAE was ag-related. Differences and C with respect to at least 1 TEAE, with a B (olmesartan and ithin each treatment, 8 10 (31.3%) subjects it were considered 8%) subjects in			
	Treatmen	t C expe	rienced '	TEAEs rela	ated to the study drug.			
22. Conclusion (summary)	The pharmathe fixed co-admin amlodipin (CS-8663 hydrochlogaffected by the company of the company	macoking dose correction is tration in a dmirely are not orothiazing the correction of old	etics (PK nbination of hydro iistered at affected de. The land administration	A) of olmes in (CS-8663 ochlorothia is the fixed by the co-PK of hydration of the contraction of the contrac	artan administered as 3) are not affected by zide. The PK of dose combination administration of ochlorothiazide are not the fixed dose iil and amlodipine			
	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	Schum	iljen	wunter				

{Procedure amended by new annex 30 according to MoH Ukraine Order N 1528 of 27.06.2019 }

