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

Preclinical study report

1. Name of medicinal product (registration certificate №, if any):	ATTENTO® PLUS 20/5 /12,5
1) type of medicinal product according to which registration has been conducted or is planned to be conducted	Medicinal product with fixed combination
2) studies conducted	yes
2. Pharmacology:	
1) Primary pharmacodynamics	Not required for products where there is sufficiently documented human experience of their individual and combined use, according to the Guideline on the non-clinical development of fixed combinations of medicinal products, EMEA/CHMP/SWP/258498/2005, 24-Jan-2008
2) Secondary pharmacodynamics	As above
3) Safety pharmacology	As above
4) Pharmacodynamic interactions	As above
3. Pharmacokinetics:	
1) Analytical Methods and validation reports	Method Validation for the quantitation of RNH-6270 (research code of olmesartan, the active metabolite of olmesartan medoxomil), amlodipine, and hydrochlorothiazide in rat plasma by turbo ion spray LC/MS/MS. The method has been validated in the calibration range 10 to 10000 ng/mL for RNH-6270 and hydrochlorothiazide and 1 to 1000 ng/mL for amlodipine, with acceptable values of intra- and inter-assay precision and accuracy.
2) Absorption	Not required for products where there is sufficiently documented human experience of their individual and combined use and without pharmacokinetics interactions, according to the Guideline on the non-clinical development of fixed combinations of medicinal products, EMEA/CHMP/SWP/258498/2005, 24-Jan-2008
3) Distribution	As above
4) Metabolism	As above
5) Excretion	As above
6) Pharmacokinetic Interactions (preclinical)	As above

ПРЕДСТАВНИК ЗАЯВНИКА ДАМАСКІНА А.В

КОПІЯ ВІРНА

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

ПРЕДСТАВНИК
ЗАЯВНИКА
ДАМАСКІНА А.В

	in ion content were recorded in OM/HCTZ/AML-treated groups, but similar changes were also recorded in OM/HCTZ and AML groups. Treatment with OM/HCTZ/AML altered hematological parameters such as decrease in red blood cell count, hemoglobin, hematocrit and reticulocyte ratio, mean corpuscular volume, mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration; similar changes were also recorded in the OM/HCTZ-treated group. Treatment with OM/HCTZ/AML also induced clinical chemistry changes such as an increase in blood urea nitrogen, creatinine and potassium and a decrease in calcium. This latter change was also observed in the AML-treated group, whereas the increase in blood urea nitrogen, creatinine and potassium were recorded in the OM/HCTZ-treated group. Therefore, these and other clinical chemistry changes (increase in alkaline phosphatase activity, decrease in total proteins and globulin) observed in OM/HCTZ/AML-treated groups were attributable to either OM/HCTZ or AML. There were also several changes in relative (body weight-adjusted) organ weights following treatment with OM/HCTZ/AML but most of these changes were also recorded in either OM/HCTZ- or AML-treated groups and without histopathological correlate. An exception was the kidney, where thickening of the arterial wall of the afferent arterioles/interlobular arteries and regeneration of the renal tubules was evident in OM/HCTZ/AML- and OM/HCTZ-treated groups. Other histopathological findings occurring following OM/HCTZ/AML treatment, as well as after OM/HCTZ or AML treatments, as were observed in the adrenals and in the female reproductive tract, whereas mammary gland, intestinal and spleen findings could be attributed to AML or to OM, as per historical studies on this mono-component. Overall no new emerging toxicities were induced by the triple combination as compared with known toxicities attributed to individual agents. In toxicokinetics evaluation, the exposure to RNH-6270 (olmesartan) and HCTZ increased by co-administration with AML. The cause of increased exposure was considered to be associated with enhanced absorption of OM and HCT due to delayed OM/HCT evacuation via the relaxation of the intestinal smooth muscle, a consequence of exaggerated pharmacological effects of AML. However the recorded systemic exposures were approximately 10-times higher, or more, than the expected exposure at the highest

ПРЕДСТАВНИК ЗАЯВНИКА ДАМАСКІНА А.В

КОПІЯ ВІРНА

	recommended clinical dose, therefore the recorded toxicities are not expected to be clinically relevant.
3) Genotoxicity: in vitro	For fixed combinations of non-genotoxic substances, genotoxicity studies with the combination are not needed. according to the Guideline on the non-clinical development of fixed combinations of medicinal products, EMEA/CHMP/SWP/258498/2005, 24-Jan-2008
in vivo (including supportive toxicokinetics evaluation)	As above
4) Carcinogenicity:	For fixed combinations of compounds assessed as non-carcinogenic, carcinogenicity studies with the combination are not needed, according to the Guideline on the non-clinical development of fixed combinations of medicinal products, EMEA/CHMP/SWP/258498/2005, 24-Jan-2008
Long-term studies	As above
Short- or medium-term studies	As above
Additional studies	As above
5) Reproductive and Developmental Toxicity:	
Fertility and early embryonic development	When the single components have been adequately tested, and the reproductive/developmental toxicity profiles of these compounds are sufficiently characterised, additional studies with the combination are not needed, according to the Guideline on the non-clinical development of fixed combinations of medicinal products, EMEA/CHMP/SWP/258498/2005, 24-Jan-2008
Embryotoxicity	As above
Prenatal and postnatal toxicity	As above
Studies in which the offspring (juvenile animals) are dosed and/or further evaluated	As above. Furthermore, the product is indicated in adults only.
6) Local Tolerance	For a medicinal product to be administered orally and containing known excipients local tolerance studies are not required, according to the Guideline on non-clinical local tolerance testing of medicinal products, EMA/CHMP/SWP/2145/2000 Rev. 1, Corr. 1*, 22-Oct-2015
7) Additional Toxicity Studies:	As stated in EU CTD guideline (please refer to page 82, or 11 of Module 2), other toxicity studies are studies to clarify special problems, thus their presence is not mandatory. The repeat dose toxicity studies have not indicated the need to perform additional toxicity studies.
Antigenicity (production of antibodies)	As above
Immunotoxicity	As above
Mechanistic studies	As above
Dependence	As above

ПРЕДСТАВНИК ЗАЯВНИКА ДАМАСКІНА А.В

КОПІЯ ВІРНА

Metabolites toxicity	As above
Impurities toxicity	As above
Other	As above
5. Preclinical study conclusions	The results of the preclinical studies demonstrated that the combined administration of OM, AML and HCTZ neither augmented any existing toxicities of the individual agents nor induced any new toxicities and there were no toxicologically synergistic effects observed in the study. In addition, the rationale for no or limited new toxicity from the combination of OM, AML and HCTZ, which was based on the safety profile of the individual compounds or the dual combinations supports the fact that toxicologically synergistic effects relevant to humans are not expected with the co-administration of OM, AML and HCTZ.
Applicant (registration certificate holder)	(signature) Alessandro Lecci 04-May-2022 (full name)

{Procedure amended by new annex 29 according to MoH Ukraine Order № 1528 of 27.06.2019 }

ПРЕДСТАВНИК
ЗАЯВНИКА
ДАМАСКІНА А.В

Додаток 29
до Порядку проведення експертизи реєстраційних матеріалів на лікарські засоби, що подаються на державну реєстрацію (перереєстрацію), а також експертизи матеріалів про внесення змін до реєстраційних матеріалів протягом дії реєстраційного посвідчення
(пункт 4 розділу IV)

ЗВІТ
про доклінічні дослідження

1. Назва лікарського засобу (за наявності - номер реєстраційного посвідчення):	АТТЕНТО® ПЛЮС 20/5/12,5
1) тип лікарського засобу, за яким проводилася або планується реєстрація	Лікарський засіб з фіксованою комбінацією
2) проведені дослідження	так
2. Фармакологія:	
1) Первинна фармакодинаміка	Не вимагається для лікарських засобів з достатнім досвідом терапевтичного застосування індивідуально та в комбінаціях, відповідно до Настанови з доклінічної розробки комбінованих лікарських засобів з фіксованою комбінацією, EMEA/CHMP/SWP/258498/2005, від 24 січня 2008.
2) Вторинна фармакодинаміка	Як зазначено вище.
3) Фармакологія безпеки	Як зазначено вище.
4) Фармакодинамічні взаємодії	Як зазначено вище.
3. Фармакокінетика:	
1) Аналітичні методики та звіти щодо їх валідації	Валідація оцінки кількісного вмісту RNH-6270 (код в дослідженнях олмесартану, активного метаболіту олмесартану медоксомілу), амлодипіну та гідрохлоротіазиду в плазмі крові щурів методом РХ/МС/МС з турбо іонним розпиленням. Методика була валідована в каліброваному діапазоні 10–10 000 нг/мл для RNH-6270 та гідрохлоротіазиду і 1–1000 нг/мл для амлодипіну, отримані прийнятні показники внутрішньо- та між лабораторної прецизійності та точності.
2) Всмоктування	Не вимагається для препаратів з достатнім досвідом терапевтичного застосування індивідуально та в комбінаціях, відповідно до Настанови з доклінічної розробки комбінованих лікарських засобів з фіксованою комбінацією, EMEA/CHMP/SWP/258498/2005, від 24 січня 2008.
3) Розподіл	Як зазначено вище.
4) Метаболізм	Як зазначено вище.
5) Виведення	Як зазначено вище.
6) Фармакокінетичні взаємодії (доклінічні)	Як зазначено вище.

ПРЕДСТАВНИК ЗАЯВНИКА ДАМАСКІНА А.В

ПЕРЕКЛАД ВІРНИЙ

7) Інші фармакокінетичні дослідження	Як зазначено вище.
4. Токсикологія:	
1) Токсичність у разі одноразового введення	Не вимагається, згідно із Запитаннями та Відповідями до скасування необхідності дотримуватись вимог «Примітки до настанови щодо досліджень токсичного впливу при одноразовому застосуванні», EMA/CHMP/SWP/81714/2010, від 24 червня 2010
2) Токсичність у разі повторних введень	- Дослідження AN07-C0154-R01 (C-B394) для оцінки токсикокінетики (Дослідження: AN07-C0169-R01 (080137)): 28-денне багаторазове введення (ОМ/ГХТЗ/АМЛ 0/0/0 (контроль), 100/62,5/0, 100/62,5/10, 100/62,5/20, 50/31,25/20 та 0/0/20, через зонд, самцям та самицям щурів. Головною задачею цього дослідження був вибір адекватних доз для застосування в головному 3-місячному дослідженні результатів багаторазового введення (див. нижче). Загибель тварин була відсутня в усіх групах. Темпи збільшення маси тіла та споживання корму знизились в усіх групах введення ОМ/ГХТЗ/АМЛ, а також в групі введення дозою 100/62,5/0 (ОМ/ГХТЗ), хоча в цій групі ефект був меншим. Також і більшість результатів аналізів сечі, клінічного та біохімічного аналізу крові, а також результати гістопатологічних досліджень в групах введення ОМ/ГХТЗ/АМЛ були подібними до таких в групі введення ОМ/ГХТЗ і в окремих випадках в групі введення АМЛ (0/0/20). Деякі зміни, як представляється, були більш істотними в групах введення ОМ/ГХТЗ в порівнянні із групою ОМ/ГХТЗ, але ці зміни, переважно, були пов'язані зі ступенем зниження темпів приросту маси тіла. Результати токсикокінетичного аналізу свідчать по те, що показники експозиції RNH-6270 та ГХТЗ зростали при одночасному введенні з АМ, як наслідок збільшення фармакологічного впливу АМЛ (більша абсорбція ОМ та ГХТЗ внаслідок уповільнення шлунково-кишкового транзиту), що пояснює більше зниження темпів приросту маси тіла тварин, яким вводили ОМ/ГХТЗ/АМЛ. Таку збільшену абсорбцію ОМ та ГХТЗ, викликану АМЛ, в клінічних умовах не спостерігали. - Дослідження AN08-C0045-R01 (B-6493) для оцінки токсикокінетики (Дослідження: AN08-C0093-R01 (080761)): 3-місячне багаторазове введення (ОМ/ГХТЗ/АМЛ 0/0/0 (контроль), 100/62,5/0, 100/62,5/10, 100/62,5/20, 30/18,75/20 та 0/0/20, через зонд, самцям та самицям щурів. Смерті тварин в період введення були відсутні, аномальні клінічні ознаки чи офтальмологічні порушення виявлені не були в групах введення усіма дозами. Темпи збільшення маси тіла знизились в усіх групах введення ОМ/ГХТЗ/АМЛ, в порівнянні з показниками в групі введення ОМ/ГХТЗ (дозою 100/62,5/0) та АМЛ (0/0/20).

ПРЕДСТАВНИК ЗАЯВНИКА ДАМАСКІНА А.В

ПЕРЕКЛАД ВІРНИЙ

	Результати аналізу сечі свідчать про збільшення об'єму сечі та споживання води, збільшення осмотичного тиску, значення pH та зміни вмісту іонів у тварин з груп введення ОМ/ГХТЗ/АМЛ, такі саме зміни були зареєстровані і у тварин з груп введення ОМ/ГХТЗ та АМЛ. У тварин, яким вводили ОМ/ГХТЗ/АМЛ змінювались також і параметри клінічного аналізу крові, а саме, знижувався вміст еритроцитів, гемоглобіну, гематокритне число, індекс продукції ретикулоцитів, середній об'єм еритроцитів, середній вміст гемоглобіну в одному еритроциті та середня клітинна концентрація гемоглобіну; подібні зміни були виявлені також і у тварин з групи введення ОМ/ГХТЗ. Введення ОМ/ГХТЗ/АМЛ викликало також і зміни результатів біохімічного аналізу крові, а саме, збільшення концентрації азоту сечовини в крові, креатиніну та калію і зниження вмісту кальцію. Остання зміна була виявлена також і у тварин з групи введення АМЛ, тоді як збільшення концентрації азоту сечовини в крові, креатиніну та калію спостерігали і в групі введення ОМ/ГХТЗ. Отже, ці та інші зміни біохімічних показників (зростання активності лужної фосфатази, зниження вмісту загального білку та глобуліну), спостережене в групах введення ОМ/ГХТЗ/АМЛ, було викликане або ОМ/ГХТЗ, або АМЛ. Також були виявлені і інші зміни, наприклад, відносної маси органів (стандартизованих за масою тіла) в групах введення ОМ/ГХТЗ/АМЛ, проте більшість з цих змін була зареєстрована також і в групах введення ОМ/ГХТЗ чи АМЛ, втім відповідні гістопатологічні зміни були відсутні. Винятком були нирки, стовщення артеріальних стінок аферентних артеріол/міждольних артерій та регенерація ниркових канальців були виявлені в групі введення ОМ/ГХТЗ/АМЛ та ОМ/ГХТЗ. Інші зміни за результатами гістопатологічного аналізу в групах введення ОМ/ГХТЗ/АМЛ, а також ОМ/ГХТЗ чи АМЛ, стосувались надниркових залоз та репродуктивного тракту самиць, тоді як зміни молочних залоз, кишечника та селезінки могли бути викликані АМЛ чи ОМ, про що свідчать дані досліджень цих речовин при ізольованому введенні. В цілому, нові варіанти токсичного впливу, при введенні потрійної комбінації, в порівнянні з відомим токсичним впливом індивідуальних компонентів, виявлені не були. Токсикокінетична оцінка свідчить про те, що вплив RNH-6270 (олмесартану) та ГХТЗ зростає при одночасному введенні разом з АМЛ. Причина зростання експозиції, як вважають, пов'язана зі збільшенням абсорбції ОМ та ГХТ внаслідок уповільнення виведення ОМ/ГХТ, зумовлене релаксацією гладких м'язів кишечника, через підсилення фармакологічних ефектів АМЛ. Однак, спостережені показники системної експозиції були приблизно в 10 разів вищими, і навіть більше, ніж очікувані показники експозиції при введенні найвищою рекомендованою клінічною дозою, отже, не очікується, що такий токсичний

ПРЕДСТАВНИК ЗАЯВНИКА ДАМАСКІНА А.В

ПЕРЕКЛАД ВІРНИЙ

	вплив матиме клінічну значущість.
3) Генотоксичність: in vitro	Для лікарських засобів з фіксованою комбінацією не генотоксичних речовин необхідність проведення досліджень генотоксичності їхньої комбінації відсутня, згідно з вимогами Настанови з доклінічної розробки комбінованих лікарських засобів з фіксованою комбінацією, EMEA/CHMP/SWP/258498/2005, від 24 січня 2008.
in vivo (включаючи додаткову оцінку з токсикокінетики)	Як зазначено вище.
4) Канцерогенність:	Для лікарських засобів з фіксованою комбінацією речовин, класифікованих, як не канцерогенні, необхідність проведення досліджень канцерогенного впливу їхньої комбінації відсутня, згідно з вимогами Настанови з доклінічної розробки комбінованих лікарських засобів з фіксованою комбінацією, EMEA/CHMP/SWP/258498/2005, від 24 січня 2008.
Довгострокові дослідження	Як зазначено вище.
Короткострокові дослідження або дослідження середньої тривалості	Як зазначено вище.
Додаткові дослідження	Як зазначено вище.
5) Репродуктивна токсичність та токсичний вплив на розвиток потомства:	
Вплив на фертильність і ранній ембріональний розвиток	Якщо були проведені адекватні дослідження індивідуальних компонентів, і профіль токсичного впливу на репродуктивні функції / розвиток плоду цих сполук є достатньо характеризованими, необхідність проведення додаткових досліджень їхньої комбінації відсутня, згідно з вимогами Настанови з доклінічної розробки комбінованих лікарських засобів з фіксованою комбінацією, EMEA/CHMP/SWP/258498/2005, від 24 січня 2008.
Ембріотоксичність	Як зазначено вище.
Пренатальна і постнатальна токсичність	Як зазначено вище.
Дослідження, при яких препарат уводиться потомству (нестатевозрілим тваринам) та/або оцінюється віддалена дія	Як зазначено вище. На додаток, препарат призначений виключно для дорослих.
6) Місцева переносимість	Проведення досліджень місцевої переносимості лікарських препаратів, призначених для перорального застосування, які містять відомі допоміжні речовини, не вимагається, згідно з вимогами Настанови з доклінічних досліджень місцевої переносимості лікарських препаратів, EMA/CHMP/SWP/2145/2000, Ред. 1, виправлена 1*, від 22 жовтня 2015.
7) Додаткові дослідження токсичності:	Як зазначено в настанові EU CTD (див. стор. 82 чи 11 Модуля 2), іншими токсикологічними дослідженнями є дослідження для з'ясування особливих проблем, отже, їхнє проведення не є обов'язковим. Дані досліджень токсичного впливу при багаторазовому введенні не свідчать про потребу проведення додаткових

ПРЕДСТАВНИК ЗАЯВНИКА ДАМАСКІНА А.В

ПЕРЕКЛАД ВІРНИЙ

	токсикологічних досліджень.
Антигенність (утворення антитіл)	Як зазначено вище.
Імунотоксичність	Як зазначено вище.
Дослідження механізмів дії	Як зазначено вище.
Лікарська залежність	Як зазначено вище.
Токсичність метаболітів	Як зазначено вище.
Токсичність домішок	Як зазначено вище.
Інше	Як зазначено вище.
5. Висновки щодо доклінічного вивчення	Результатами доклінічних досліджень було продемонстровано, що при введенні ОМ, АМЛ та ГХТЗ не підсилюється відомий токсичний вплив індивідуальних компонентів і не виникає новий токсичний вплив, токсикологічні синергетичні ефекти в дослідженні виявлені також не були. На додаток, причина відсутності або обмеженості нового токсичного впливу при комбінованому застосуванні ОМ, АМЛ та ГХТЗ, що ґрунтується на профілях безпеки індивідуальних компонентів чи комбінацій двох з цих компонентів, підтверджує той факт, що токсикологічні синергетичні ефекти, важливі для людини, при одночасному застосуванні ОМ, АМЛ та ГХТЗ, не очікуються.

Заявник (власник реєстраційного посвідчення)

(*підпис від руки*)

(підпис)

Алессандро Леччі 04 травня 2022

(П. І. Б.)

Процедура, змінена та доповнена згідно з вимогами нового додатка 29 Міністерства охорони здоров'я України № 1528 від 27.06.2019.

ПРЕДСТАВНИК ЗАЯВНИКА ДАМАСКІНА А.В

ПЕРЕКЛАД ВІРНИЙ

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

Clinical study report 1

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

	(signature) Dr. Kai Schumacher (full name)

Clinical study report 2

1. Name of medicinal product (registration certificate №, if available)	ATTENTO ® PLUS 20/5/12.5 mg
2. Applicant	Menarini International Operations Luxembourg S.A., Luxembourg
3. Manufacturer	Daiichi Sankyo Europe GmbH, Germany (Manufacturing "in bulk", packaging, batch control and release) Berlin-Chemie AG, Germany (Packaging, batch control and release) Menarini - Von Heyden GmbH, Germany (Batch control and release)
4. Studies conducted:	yes
1) type of medicinal product, which has been or will be registered	Medicinal product with fixed combination
5. Title of clinical trial, code number of clinical trial	866-127 A randomized, open-label, three-way crossover study of different strengths of CS-866-hydrochlorothiazide combination tablets in healthy adult volunteers
6. Phase of clinical trial	Phase I
7. Period of clinical trial	07 Sep 2001-24 Sep 2001
8. Countries, where clinical trial has been conducted	USA
9. Number of trial subjects	planned: 18 actual:18 (completed)
10. Objective and secondary endpoints of clinical trial	Primary: to evaluate the comparative bioequivalence of hydrochlorothiazide (HCT) and the dose proportionality of CS-866 component following the oral administration of 3 different tablet formulations of CS-866 in combination with HCT.
11. Clinical trial design	Randomised, open-label, 3-way crossover comparison of single oral doses of CS-866 in combination with HCT administered to healthy male and female volunteers.
12. Main inclusion criteria	Healthy subjects between 18 and 45 years (inclusive) who were practicing and acceptable birth control (female subjects 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 had signed the informed consent form.
13. Investigational medicinal product, mode of administration and strength	Formulation A: CS-866/HCT 10/12.5 mg Market Image
14. Reference product, dose, mode of administration and strength	Formulation B: CS-866/HCT 20/12.5 Market Image Formulation C: CS-866/HCT 40/12.5 Market Image
15. Concomitant therapy	None
16. Criteria for evaluation efficacy	Assessment of the 90% Confidence intervals for the PK parameters $AUC_{0\text{-}lqc}$, $AUC_{0\text{-}inf}$ and C_{max}
17. Criteria for evaluation safety	Physical examination, vital signs, body weight, 12-lead ECGs, AEs, clinical laboratory parameters
18. Statistical methods	Analysis of covariance (ANCOVA) was performed on the natural

	log transformed PK values with subject (random effect), period and dose as factors and ln(dose) as covariates.
19. Demographic indices of studied population (sex, age, race, etc.)	TABLE 6.3: DEMOGRAPHIC INFORMATION ALL SUBJECTS TOTAL N (%) 18 (100%) GENDER N (%) MALE 9 (50%) FEMALE 9 (50%) RACE N (%) CAUCASIAN 9 (50%) BLACK 6 (33%) ASIAN 1 (6%) HISPANIC 2 (11%) OTHER 0 (0%) FRAME SIZE N (%) SMALL 3 (17%) MEDIUM 9 (50%) LARGE 6 (33%) AGE (yr.) MEAN (SD) 31.6 (8.02) RANGE 20.0 - 43.0 HEIGHT (in.) MEAN (SD) 67.7 (4.13) RANGE 60.0 - 74.0 WEIGHT (lb.) MEAN (SD) 160.8 (25.83) RANGE 114.0 -218.0
20. Efficacy results	Parameter / FORMULATION A (N=18) Mean (SD) / FORMULATION B (N=18) Mean (SD) / FORMULATION C (N=18) Mean (SD) AUC (0-lqc) (ng.h/mL) 1841.46 (468.44) 3625.93 (955.41) 5997.43 (1471.37) AUC (0-inf) (ng.h/mL) 1911.69 (516.00) 3760.58 (1046.34) 6195.01 (1541.33) CMAX (ng/mL) 316.42 (76.23) 637.17 (125.60) 958.69 (232.06) TMAX (hrs)[4] 1.50 2.00 2.00 T1/2 (hrs) 28.73 (21.93) 25.20 (24.10) 25.84 (16.85) TABLE 7.2.3.2: BIOEQUIVALENCE ANALYSIS OF HYDROCHLOROTHIAZIDE (HCTZ) PARAMETERS FORM A TO FORM B COMPARISON (N=18) RATIO OF A VS B (90% C.I.)[1] / FORM B TO FORM C COMPARISON (N=18) RATIO OF B VS C (90% C.I.)[1] / FORM A TO FORM C COMPARISON (N=18) RATIO OF A VS C (90% C.I.)[1] AUC 0-lqc (ng/mL)*hr 1.01 (0.95-1.08) 1.04 (0.98-1.11) 1.05 (0.99-1.13) AUC 0-inf (ng/mL)*hr 1.01 (0.95-1.07) 1.03 (0.97-1.09) 1.04 (0.98-1.10) Cmax (ng/mL) 1.03 (0.98-1.11) 1.02 (0.96-1.10) 1.06 (0.99-1.14) Tmax (hr) 0.00 (-0.25-0.25)[2] 0.00 (-0.25-0.25)[2] 0.00 (-0.25-0.25)[2] T1/2 (hr) 0.22 (-0.70-1.02)[2] -0.34 (-0.83-0.86)[2] 0.44 (-0.51-1.19)[2]
21. Safety results	Of the 18 subjects enrolled in the study, 13 reported a total of 38 TEAEs. Headache reported by 9 subjects (50%) was the most frequently reported AE. Other TEAEs reported by more than one subject were dizziness, somnolence and rash reported by 2 subjects each.
22. Conclusion (summary)	The 90% CIs for $AUC_{0\text{-}lqc}$, $AUC_{0\text{-}inf}$ and C_{max} for the proportionality parameters of CS-866 among the 3 dose strengths (10 mg, 20 mg and 40 mg) in the market image CS-866/HCT combination tablet formulations were within the boundary to establish dose proportionality. In addition, bioequivalence was observed for the HCT component (12.5 mg) among the 3 tablet formulations since the 90%CI of the ratios for $AUC_{0\text{-}lqc}$, $AUC_{0\text{-}inf}$ and C_{max} between the formulations were contained well within the standard boundaries (0.8, 1.25) to establish bioequivalence.
Applicant (registration certificate holder)	(signature) Dr. Kai Schumacher

	(full name)

Clinical study report 3

1. Name of medicinal product (registration certificate №, if available)	ATTENTO ® PLUS 20/5/12.5 mg
2. Applicant	Menarini International Operations Luxembourg S.A., Luxembourg
3. Manufacturer	Daiichi Sankyo Europe GmbH, Germany (Manufacturing "in bulk", packaging, batch control and release) Berlin-Chemie AG, Germany (Packaging, batch control and release) Menarini - Von Heyden GmbH, Germany (Batch control and release)
4. Studies conducted:	yes
1) type of medicinal product, which has been or will be registered	Medicinal product with fixed combination
5. Title of clinical trial, code number of clinical trial	866-126 A randomized, open-label, three-way crossover bioequivalence study of CS-866 tablets plus hydrochlorothiazide capsules or tablets and CS-866/hydrochlorothiazide combination tablets in healthy adult volunteers.
6. Phase of clinical trial	Phase I
7. Period of clinical trial	10 Aug 2001 to 28 Aug 2001
8. Countries, where clinical trial has been conducted	USA
9. Number of trial subjects	planned: 33 actual:30(completed)
10. Objective and secondary endpoints of clinical trial	To determine the bioequivalence of the clinical trial supply of CS-866 tablets and hydrochlorothiazide (HCT) capsules or tablets administered orally in combination versus oral administration of the market-image single-tablet formulation of CS-866/HCT.
11. Clinical trial design	A randomized, open-label, 3-way crossover comparison of single oral doses of CS-866 (20 mg) in combination with HCT (12.5 mg) administered to healthy male and female volunteers.
12. Main inclusion criteria	Volunteers for the study were healthy male and non-pregnant female subjects between 18-45 years (inclusive) who were practicing an acceptable form of birth control (females only), were within acceptable body weights and height ranges, had not used tobacco products in the last 12 months, had a negative urine drug/alcohol screen, and signed an informed consent form.
13. Investigational medicinal product, mode of administration and strength	20 mg CS-866/12.5 mg HCT market image combination tablet, single-dose, p.o. (formulation C)
14. Reference product, dose, mode of administration and strength	20 mg CS-866 investigational tablet + 12.5 mg HCT capsule, single-dose, p.o. (formulation A) 20 mg CS-866 investigational tablet + 12.5 mg NCT tablet, single-dose, p.o. (formulation B)

15. Concomitant therapy	None
16. Criteria for evaluation efficacy	$AUC_{0\text{-}Inf}$, $AUC_{0\text{-}lqc}$, C_{max}, k_{el} and $t_{1/2}$ for the CS-866 metabolite RNH-6270 and HCT
17. Criteria for evaluation safety	Physical examinations, vital signs, clinical adverse events and hematology, blood chemistry and urinalysis test results.
18. Statistical methods	Ln-transformed $AUC_{0\text{-}lqc}$, $AUC_{0\text{-}Inf}$ and C_{max} were analysed by ANOVA: The formulation differences and their corresponding 90% CIs were obtained from the analysis and were exponentiated to obtain the formulation bioequivalence ratios and their corresponding 90% CIs.
19. Demographic indices of studied population (sex, age, race, etc.)	

	ALL SUBJECTS
TOTAL	
N (%)	33 (100%)
GENDER N (%)	
MALE	17 (52%)
FEMALE	16 (48%)
RACE N (%)	
CAUCASIAN	12 (36%)
BLACK	14 (42%)
ASIAN	1 (3%)
HISPANIC	5 (15%)
OTHER	1 (3%)
FRAME SIZE N (%)	
SMALL	2 (6%)
MEDIUM	26 (79%)
LARGE	5 (15%)
AGE (yr)	
MEAN (SD)	26.5 (7.87)
RANGE	18.0 - 44.0
HEIGHT (in)	
MEAN (SD)	66.0 (4.07)
RANGE	59.0 - 73.0
WEIGHT (lb)	
MEAN (SD)	156.1 (25.96)
RANGE	114.0 -212.0

20. Efficacy results	The CS-866/HCT market image combination tablet (formulation C) and the investigational CS-866 tablet in combination with marketed HCT capsule (formulation A: US) or tablet (formulation B; Europe) were bioequivalent. The ratio point estimates for RNH-6270 were 1.04, 1.04 and 1.08 for $AUC_{0\text{-}lqc}$, $AUC_{0\text{-}Inf}$ and C_{max}, respectively, between formulations C and A. The 90% CI for all 3 ratios were contained within the standard bounds for bioequivalence. Similarly, RNH-6270 ratio point estimates were 1.07, 1.07 and 1.08 for $AUC_{0\text{-}lqc}$, $AUC_{0\text{-}Inf}$ and C_{max}, respectively between formulations C and B, and the 90% CI for all 3 ratios were contained well within the bounds for bioequivalence. Please see the summary PK for RNH-6270 below:

TABLE 7.2.3.1 SUMMARY OF PLASMA PHARMACOKINETIC PARAMETERS FOR RNH-6270

PARAMETER	FORMULATION A (N=30) MEAN (SD)	FORMULATION B (N=30) MEAN (SD)	FORMULATION C (N=33) MEAN (SD)	FORM C TO FORM A COMPARISON RATIO POINT ESTIMATE (N=30)	FORM C TO FORM A COMPARISON 90% CI (N=30)	FORM C TO FORM B COMPARISON RATIO POINT ESTIMATE (N=30)	FORM C TO FORM B COMPARISON 90% CI (N=30)
AUC 0-lqc (ng/mL)*hr	3483.06 (706.30)	3372.77 (781.04)	3623.65 (917.46)	1.04	0.98 - 1.10	1.07	1.01 - 1.13
AUC 0-Inf (ng/mL)*hr	3561.43 (845.38)	3459.21 (808.15)	3694.51 (872.01)	1.04	0.98 - 1.10	1.07	1.01 - 1.13
Cmax (ng/mL)	559.87 (129.03)	559.67 (115.80)	605.00 (136.81)	1.08	1.02 - 1.15	1.08	1.01 - 1.15
Tmax (hr)	2.00*	1.50*	2.00*	-		-	
t 1/2 (hr)	21.44 (17.80)	21.58 (18.47)	20.44 (16.27)	-		-	

Bioequivalence also was observed for HCT, with ratio point estimates and 90% CI of the ratios between formulations similar to those observed for RNH-6270. Please see the summary PK for HCT below:

	TABLE 7.2.3.2 SUMMARY OF PLASMA PHARMACOKINETIC PARAMETERS FOR HYDROCHLOROTHIAZIDE (HCTZ)

PARAMETER	FORMULATION A (N=36) MEAN (SD)	FORMULATION B (N=36) MEAN (SD)	FORMULATION C (N=36) MEAN (SD)	FORM C TO FORM A COMPARISON RATIO POINT ESTIMATE (N=36)	FORM C TO FORM A COMPARISON 90% CI (N=36)	FORM C TO FORM B COMPARISON RATIO POINT ESTIMATE (N=36)	FORM C TO FORM B COMPARISON 90% CI (N=36)
AUC 0-lqc (ng/mL)*hr	507.33 (135.63)	494.82 (137.85)	522.00 (121.38)	1.04	0.99 - 1.10	1.07	1.01 - 1.13
AUC 0-Inf (ng/mL)*hr	560.09 (140.16)	548.60 (134.39)	564.05 (117.99)	1.05	0.99 - 1.10	1.08	1.02 - 1.14
Cmax (ng/mL)	90.84 (29.93)	88.84 (27.84)	94.00 (31.91)	1.06	0.99 - 1.15	1.08	0.99 - 1.15
Tmax (hr)	2.00*	1.50*	1.50*	.		.	
T 1/2 (hr)	11.29 (7.22)	10.99 (2.98)	11.02 (2.89)	.		.	

21. Safety results	10 TEAEs were reported by 7 (21.9%) subjects who received 20 mg CS-866+12.5 mg HCT (formulation A), 23 TEAEs were reported by 6 (19.4%) subjects who received 20 mg CS-866+12.5 mg HCT tablet (formulation B) and 17 TEAEs were reported by 12 subjects who received the market image combination tablet (formulation C) Headache, dizziness and nausea were the most common TEAEs overall. One subject who experienced 14 of the 23 TEAEs after receiving formulation B was withdrawn due to nausea and vomiting. No serious TEAEs were reported.
22. Conclusion (summary)	The study demonstrated that the market-image combination tablet formulation of CS-866/HCT was bioequivalent to the clinical supplies used in US clinical studies (CS-866 + HCT capsules) and European clinical studies (CS-866 investigational tablets + HCT tablets). The 90% CI surrounding the ratio point estimates for $AUC_{0\text{-}lqc}$, $AUC_{0\text{-}Inf}$ and C_{max} for RNH-6270 and for HCT all were within the standard bounds (0.80, 1.25) for bioequivalence.
Applicant (registration certificate holder)	(signature) Dr. Kai Schumacher (full name)

Clinical study report 4

1. Name of medicinal product (registration certificate №, if available)	ATTENTO ® PLUS 20/5/12.5 mg
2. Applicant	Menarini International Operations Luxembourg S.A., Luxembourg
3. Manufacturer	Daiichi Sankyo Europe GmbH, Germany (Manufacturing "in bulk", packaging, batch control and release) Berlin-Chemie AG, Germany (Packaging, batch control and release) Menarini - Von Heyden GmbH, Germany (Batch control and release)
4. Studies conducted:	yes
1) type of medicinal product, which has been or will be registered	Medicinal product with fixed combination
5. Title of clinical trial, code number of clinical trial	866-139 A randomized, open-label, three-way crossover bioequivalence study of 20 mg CS-866 tablets plus 25 mg hydrochlorothiazide capsules or tablets and 20/25 mg CS-866/hydrochlorothiazide combination tablets in healthy adult volunteers.
6. Phase of clinical trial	Phase I
7. Period of clinical trial	30 Oct 2002 to 06 Dec 2002
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	To determine the bioequivalence of the market image, single tablet treatment of CS-866 – hydrochlorothiazide (Test, Treatment C) to the clinical trial supply of CS-866 (olmesartan medoxomil) tablets + hydrochlorothiazide capsules (Reference, treatment A) and the clinical trial 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 (20 mg) in combination with HCT (25 mg) administered to healthy male and female volunteers.
12. Main inclusion criteria	Volunteers in the study were healthy male and non-pregnant female subjects between 18-45 years (inclusive) who were practicing an acceptable form of birth control (females only), were within acceptable body 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: 20/25 mgCS-866/HCT market image combination tablet, single dose, p.o.
14. Reference product, dose, mode of administration and strength	Treatment A: 20 mg CS-866 investigational tablet + 2 x 12.5 mg HCT capsules, single dose, p.o.

	Treatment B: 20 mg CS-866 investigational tablet + 25 mg HCT tablet, single dose, p.o.
15. Concomitant therapy	None
16. Criteria for evaluation efficacy	$AUC_{0\text{-}Inf}$, $AUC_{0\text{-}lqc}$, C_{max}, T_{max}, k_{el}, $t_{1/2}$ of RNH-6270 (the active metabolite of CS-866).
17. Criteria for evaluation safety	Physical examination findings, vital sign measurements, clinical adverse events, hematology, blood chemistry, and urinalysis test results.
18. Statistical methods	Ln-transformed $AUC_{0\text{-}lqc}$, $AUC_{0\text{-}Inf}$ and C_{max} were analyzed by ANOVA. The treatment differences and their corresponding 90% CIs were obtained from the analyses and were exponentiated to obtain treatment bioequivalence ratios and their corresponding 90% CIs.
19. Demographic indices of studied population (sex, age, race, etc.)	

	ALL SUBJECTS
TOTAL N (%)	36 (100%)
GENDER N (%)	
MALE	26 (72%)
FEMALE	10 (28%)
RACE N (%)	
CAUCASIAN	5 (14%)
BLACK	23 (6 4%)
ASIAN	2 (6%)
HISPANIC	5 (14%)
OTHER*	1 (3%)
FRAME SIZE N (%)	
SMALL	6 (17%)
MEDIUM	30 (83%)
LARGE	0 (0%)
AGE (yrs.)	
MEAN (SD)	30.4 (7.61)
RANGE	18 .0 - 45.0
HEIGHT (in.)	
MEAN (SD)	68.8 (3.75)
RANGE	60.2 - 75.7
WEIGHT (lbs.)	
MEAN (SD)	159.7 (22.60)
RANGE	110.6 -196.0

20. Efficacy results

RNH-6270 PK Parameters

Parameter	Treatment A (n=32)[1] Mean (SD) Geomean (CV) Median	Treatment B (n=32)[1] Mean (SD) Geomean (CV) Median	Treatment C (n=32)[1] Mean (SD) Geomean (CV) Median
$AUC_{0\text{-}lqc}$ (ng.h/mL)	3715.75 (938.01) 3607.03 (25.09) 3541.64	3850.25 (923.37) 3744.95 (24.49) 3953.69	3665.78 (877.59) 3549.13 (27.17) 3652.95
$AUC_{0\text{-}Inf}$ (ng.h/mL)	3779.94 (957.46) 3668.99 (25.12) 3527.41	3935.83 (943.71) 3826.10 (24.84) 3995.84	3726.59 (900.12) 3605.36 (28.03) 3782.35
C_{max} (ng/mL)	631.94 (152.89) 615.10 (23.82) 619.78	666.37 (187.54) 643.27 (27.19) 646.85	635.06 (157.47) 618.24 (25.12) 656.78
$C_{max}/AUC_{0\text{-}Inf}$ (1/h)	0.17 (0.03)	0.17 (0.03)	0.17 (0.03)
T_{max} (hrs)	2.00	1.75	1.50
$T_{1/2}$ (hrs)	18.57 (10.68) 15.73	21.27 (21.65) 14.40	18.46 (8.90) 15.99

RNH-6270 Bioequivalence Analysis for PK Parameters

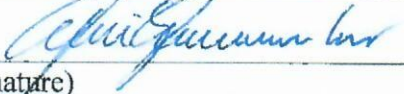
Parameter	Treatment C vs. Treatment A Ratio Point Estimate (90% CI)[1]	Treatment C vs. Treatment B Ratio Point Estimate (90% CI)[1]
$AUC_{0\text{-}lqc}$	0.99 (0.92, 1.05)	0.95 (0.89, 1.01)
$AUC_{0\text{-}Inf}$	0.98 (0.92, 1.05)	0.94 (0.88, 1.00)
C_{max}	1.01 (0.94, 1.08)	0.96 (0.90, 1.03)
$C_{max}/AUC_{0\text{-}Inf}$	1.02 (0.97, 1.07)	1.02 (0.97, 1.06)

HCTZ PK Parameters

Parameter	Treatment A (n=32)[1] Mean (SD) Geomean (CV) Median	Treatment B (n=32)[1] Mean (SD) Geomean (CV) Median	Treatment C (n=32)[1] Mean (SD) Geomean (CV) Median
$AUC_{0\text{-}lqc}$ (ng.h/mL)	1052.67 (308.34) 1010.57 (29.87) 1014.35	1019.44 (308.08) 970.81 (33.76) 997.66	969.20 (316.90) 911.52 (38.96) 949.27
$AUC_{0\text{-}Inf}$ (ng.h/mL)	1093.87 (306.37) 1054.38 (28.12) 1045.96	1061.46 (305.09) 1016.17 (31.64) 1036.65	1014.97 (314.30) 961.98 (35.94) 992.96
C_{max} (ng/mL)	172.56 (62.28) 163.35 (33.84) 155.45	159.59 (61.21) 148.43 (40.70) 146.90	147.51 (52.39) 138.20 (39.11) 140.90
$C_{max}/AUC_{0\text{-}Inf}$ (1/h)	0.16 (25.67)	0.15 (24.70)	0.15 (27.21)
T_{max} (hrs)	1.50*	2.00*	1.75*
$T_{1/2}$ (hrs)	10.48 (1.71) 10.15	10.50 (2.41) 10.26	11.26 (2.3) 11.46

HCTZ Bioequivalence Analysis for PK Parameters

Parameter	Treatment C vs. Treatment A Ratio Point Estimate (90% CI)[1]	Treatment C vs. Treatment B Ratio Point Estimate (90% CI)[1]
$AUC_{0\text{-}lqc}$	0.91 (0.85, 0.96)	0.94 (0.89, 1.00)
$AUC_{0\text{-}Inf}$	0.92 (0.87, 0.97)	0.93 (0.90, 1.01)
C_{max}	0.85 (0.77, 0.93)	0.93 (0.85, 1.02)
$C_{max}/AUC_{0\text{-}Inf}$	1.02 (0.97, 1.07)	1.02 (0.97, 1.06)

21. Safety results	Eight TEAEs were reported by 4 (11.8%) subjects who received 20 mg CS-866 + 25 (2 x 12.5) mg HCT capsules (treatment A), 13 TEAEs were reported by 5 (14.3%) subjects who received 20 mg CS-866 + 25 mg HCT tablets (treatment B), and two TEAEs were reported by 2 (5.9%) subjects who received the market image combination tablet (treatment C). Headache (n=7) was the most common AE reported overall. No subject was withdrawn from the study due to a TEAE. No serious TEAE was reported.
22. Conclusion (summary)	The total exposure and peak exposure to RNH-6270 were bioequivalent between the 20/25 mg CS-866/HCT market image tablet (treatment C), the 20 mg CS-866 + 25 (2 x 12.5) mg HCT capsule US clinical supplies (treatment A) and the 20 mg CS-866 + 25 mg HCT tablet European clinical supplies (treatment B). The total exposure of HCT was bioequivalent between the 20/25 mg CS-866/HCT market image tablet (treatment C), the 20 mg CS-866 + 25 (2 x 12.5) mg HCT capsule US clinical supplies (treatment A) and the 20 mg CS-866 + 25 mg HCT tablet European clinical supplies (treatment B). The point estimate (90% CI) for the ratio of the peak exposure of HCT between the 20/25 mg CS-866/HCT market image tablet (treatment C) and the 20 mg CS-866 + 25 (2 x 12.5) mg HCT capsule US clinical supplies (treatment A) was 0.85 (0.77, 0.93). This small decrease in peak exposure is not considered clinically significant. The ratio of absorption of HCT, as evidenced by $C_{max}/AUC_{0\text{-}Inf}$ was bioequivalent between the 20/25 mg CS-866/HCT market image tablet (treatment C), the 20 mg CS-866 + 25 (2 x 12.5) mg HCT capsule US clinical supplies (treatment A) and the 20 mg CS-866 + 25 mg HCT tablet European clinical supplies (treatment B).
Applicant (registration certificate holder)	 (signature) Dr. Kai Schumacher (full name)

Clinical study report 5

1. Name of medicinal product (registration certificate №, if available)	ATTENTO ® PLUS 20/5/12.5 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	SP-OLM-03-05 Treat-to target study of olmesartan medoxomil (OM) and an add-on treatment algorithm consisting of hydrochlorothiazide (HCT) and amlopidine besylate (AML) in patients with mild to moderate hypertension
6. Phase of clinical trial	Phase IV
7. Period of clinical trial	06 Apr 2006 to 08 Apr 2008
8. Countries, where clinical trial has been conducted	Austria, Belgium, France, Germany, Italy, the Netherlands, Portugal, Switzerland and the United Kingdom (58 clinical sites)
9. Number of trial subjects	planned: 694 actual: 601 (completed)
10. Objective and secondary endpoints of clinical trial	To evaluate the rates of subjects treated to target (STTT) overall and on each treatment combination step. STTT were defined as patients with mild to moderate hypertension achieving target BP defined as SeSBP of≤130 mmHg and mean SeDBP≤85 mmHg (non-diabetic patients) or SeSBP<130 mmHg and SeDBP<80 mmHg (diabetic patients).
11. Clinical trial design	This Phase IV trial was a non-comparative, sequential add-on, open-label, multinational, multicenter trial. **Washout – period I** (approx. 2 weeks): Period I consisted of a single screening visit in treatment naïve patients and a washout period for patients on antihypertensive medication(s). The goal was to reach the target BP defined as mean SeSBP≤130 mmHg (< 130 mmHg in diabetic patients) and mean SeDBP≤85 mmHg (<80 mmHg). To achieve this goal, patients were treated with an algorithm consisting of the following sequential steps: • **Period II**: OM 20 mg • **Period III**: OM 20 mg + HCT 12.5 mg (fixed combination) • **Period IV**: OM 20 mg + HCT 25 mg (fixed combination)

<table>
<tr><td></td><td>

- **Period V**: OM 20 mg and HCT 12.5 mg (fixed combination) + AML 5 mg
- **Period VI**: OM 20 mg and HCT 25 mg (fixed combination) + AML 10 mg.

</td></tr>
<tr><td>12. Main inclusion criteria</td><td>Male and female patients with mild to moderate hypertension defined as SeSBP of ≥ 140 mmHg and < 180 mmHg at trough and7or SeDBP ≥ 90 and < 110 mmHg.</td></tr>
<tr><td>13. Investigational medicinal product, mode of administration and strength</td><td>

- OM 20 mg
- OM 20 mg + HCT 12.5 mg (fixed combination)
- OM 20 mg + HCT 25 mg (fixed combination)
- OM 20 mg and HCT 12.5 mg (fixed combination) + AML 5 mg
- OM 20 mg and HCT 25 mg (fixed combination) + AML 10 mg.

</td></tr>
<tr><td>14. Reference product, dose, mode of administration and strength</td><td>None (non-comparative study)</td></tr>
<tr><td>15. Concomitant therapy</td><td>Standard antihypertensive therapy was allowed at study start and discontinued during the washout period.</td></tr>
<tr><td>16. Criteria for evaluation efficacy</td><td>Systolic and diastolic blood pressure: Measurements were taken on the same arm, by the same person, and at the same time of day and were made 3 times in the seated position. Subjects treated to target (STTT) were calculated from the means of the 3 SeSBP and SeDBP measurements.</td></tr>
<tr><td>17. Criteria for evaluation safety</td><td>Number, seriousness and severity of TEAEs, vital signs, 12-lead ECGs, physical examinations and, clinical hematology, blood chemistry and urinalysis results.</td></tr>
<tr><td>18. Statistical methods</td><td>To analyse the primary efficacy parameter, the STTT rate was estimated overall and on each treatment step, with a two-sided 95% CI using the normal approximation to the binominal distribution. A last observation carried forward (LOCF) approach was used on the full analysis set (FAS).</td></tr>
<tr><td>19. Demographic indices of studied population (sex, age, race, etc.)</td><td>

Gender [n (%)]	male	357 (51.4)
	female	337 (48.6)
Age [years]	n	694
	mean (SD)	58.16 (12.06)
	median	58.0
	range	20.0-88.0
Weight [kg]	n	694
	mean (SD)	82.16 (16.09)
	median	80.0
	range	38.0-157.4
BMI [kg/m²]	n	694
	mean (SD)	28.86 (4.69)
	median	28.24
	range	16.02- 50.24
[n (%)]	underweight (1)	8 (1.2)
	normal weight (2)	124 (17.9)
	overweight (3)	318 (45.8)
	obese (4)	244 (35.2)
Ethnicity [n (%)]	caucasian	678 (97.7)
	black	13 (1.9)
	asian	3 (0.4)
	other	0 (0.0)

</td></tr>
</table>

20. Efficacy results	Table 11.8: Number and percentage of subjects treated to target (primary efficacy parameter) overall and by visit (dose step) separately by analysis set (FAS and PPS)

Subjects treated to target	Full Analysis Set (N=691) n	%	95% CI	Per Protocol Set (N=457) n	%	95% CI
overall (Visit 1 to Visit 7, V-FE)	496	71.8	68.4-75.1	386	84.5	81.1-87.8
at Visit 3 (OLM 20 mg)	85	12.3	9.9-14.7	69	15.1	11.8-18.4
at Visit 4 (OLM/HCTZ 20/12.5 mg)	113	16.4	13.6-19.1	93	20.4	16.7-24.0
at Visit 5 (OLM/HCTZ 20/25 mg)	133	19.2	16.3-22.2	111	24.3	20.4-28.2
at Visit 6 (OLM/HCTZ/AML 20/25/5 mg)	103	14.9	12.3-17.6	72	15.8	12.4-19.1
at Visit 7 (OLM/HCTZ/AML 20/25/10 mg)	59	8.5	6.5-10.6	41	9.0	6.4-11.6

Table 11.9: Number and percentage of normalisers overall and by visit (dose step) separately by analysis set (FAS and PPS)

Normaliser	Full Analysis Set (N=691) n	%	95% CI	Per Protocol Set (N=457) n	%	95% CI
overall (Visit 1 to Visit 7, V-FE)	584	84.5	81.8-87.2	415	90.8	88.2-93.5
at Visit 3 (OLM 20 mg)	157	22.7	19.6-25.8	118	25.8	21.8-29.8
at Visit 4 (OLM/HCTZ 20/12.5 mg)	215	31.1	27.7-34.6	167	36.5	32.1-41.0
at Visit 5 (OLM/HCTZ 20/25 mg)	226	32.7	29.2-36.2	172	37.6	33.2-42.1
at Visit 6 (OLM/HCTZ/AML 20/25/5 mg)	165	23.9	20.7-27.1	108	23.6	19.7-27.5
at Visit 7 (OLM/HCTZ/AML 20/25/10 mg)	102	14.8	12.1-17.4	68	14.9	11.6-18.1

Table 11.10: Number and percentage of diastolic responders overall and by visit (dose step) separately by analysis set (FAS and PPS)

Diastolic Responder	Full Analysis Set (N=691) n	%	95% CI	Per Protocol Set (N=457) n	%	95% CI
overall (Visit 1 to Visit 7, V-FE)	647	93.6	91.8-95.5	441	96.5	94.8-98.2
at Visit 3 (OLM 20 mg)	253	36.6	33.0-40.2	178	38.9	34.5-43.4
at Visit 4 (OLM/HCTZ 20/12.5 mg)	362	52.4	48.7-56.1	261	57.1	52.6-61.6
at Visit 5 (OLM/HCTZ 20/25 mg)	336	48.6	44.9-52.4	237	51.9	47.3-56.4
at Visit 6 (OLM/HCTZ/AML 20/25/5 mg)	231	33.4	29.9-36.9	151	33.0	28.7-37.4
at Visit 7 (OLM/HCTZ/AML 20/25/10 mg)	141	20.4	17.4-23.4	89	19.5	15.8-23.1

Table 11.11: Number and percentage of systolic responders overall and by visit (dose step) separately by analysis set (FAS and PPS)

Systolic Responder	Full Analysis Set (N=691) n	%	95% CI	Per Protocol Set (N=457) n	%	95% CI
overall (Visit 1 to Visit 7, V-FE)	640	92.6	90.7-94.6	444	97.2	95.6-98.7
at Visit 3 (OLM 20 mg)	236	34.2	30.6-37.7	168	36.8	32.3-41.2
at Visit 4 (OLM/HCTZ 20/12.5 mg)	343	49.6	45.9-53.4	244	53.4	48.8-58.0
at Visit 5 (OLM/HCTZ 20/25 mg)	322	46.6	42.9-50.3	227	49.7	45.1-54.3
at Visit 6 (OLM/HCTZ/AML 20/25/5 mg)	230	33.3	29.8-36.8	152	33.3	28.9-37.6
at Visit 7 (OLM/HCTZ/AML 20/25/10 mg)	142	20.5	17.5-23.6	93	20.4	16.7-24.0

Table 11.12: Number and percentage of general responders overall and by visit (dose step) separately by analysis set (FAS and PPS)

General Responder	Full Analysis Set (N=691) n	%	95% CI	Per Protocol Set (N=457) n	%	95% CI
overall (Visit 1 to Visit 7, V-FE)	660	95.5	94.0-97.1	448	98.0	96.8-99.3
at Visit 3 (OLM 20 mg)	294	42.5	38.9-46.2	204	44.6	40.1-49.2
at Visit 4 (OLM/HCTZ 20/12.5 mg)	405	58.6	54.9-62.3	286	62.6	58.1-67.0
at Visit 5 (OLM/HCTZ 20/25 mg)	369	53.4	49.7-57.1	254	55.6	51.0-60.1
at Visit 6 (OLM/HCTZ/AML 20/25/5 mg)	251	36.3	32.7-39.9	162	35.4	31.1-39.8
at Visit 7 (OLM/HCTZ/AML 20/25/10 mg)	153	22.1	19.0-25.2	98	21.4	17.7-25.2

21. Safety results	Of the 694 patients receiving one or more of the study drugs, 271 (39%) experienced at least one TEAE, 137 patients (20%) at least one TEAE considered at least possibly related to the study drugs. 7 patients experienced an SAE and 3 additional patients before the start of study medication. None of the serious TEAEs was considered treatment-related. In 19 patients (3%) a TEAE led to discontinuation of the study medication. Study medication was more often than not often considered responsible for the discontinuation due to gastrointestinal, nervous system or ear disorders (dizziness, syncope, tinnitus).
22. Conclusion (summary)	Approximately three quarters (72%) of the study patients reached the BP target of SeBP 130/85 mg for non-diabetic patients and <130/80 mmHg for diabetic patients. Under monotherapy with OM 20 mg, 12% reached this target. Although the patients suffered from only mild (44%) to moderate (55%) hypertension, the majority

	required combination therapy of HCT and/or AML. Additional 36% of patients achieved the target after adding HCT 12.5 or 25 mg to OM; 23% after the addition of AML 5 or 10 mg to the OM + HCT combination. Whereas at baseline only 0.1% of patients showed normal or optimal BP, the conversion rates to these classes increased to approximately 30% at the later visits. At the last visit, only 13% of patients still had mild or moderate hypertension, whereas 21% were classified as high normal, 56% as normal and 10% even as optimal, i.e. two third of patients had normal or optimal blood pressure.
Applicant (registration certificate holder)	(signature) Dr. Kai Schumacher (full name)

1. Name of medicinal product (registration certificate №, if available)	ATTENTO ® PLUS 20/5/12.5 mg
2. Applicant	Menarini International Operations Luxembourg S.A., Luxembourg
3. Manufacturer	Daiichi Sankyo Europe GmbH, Germany (Manufacturing "in bulk", packaging, batch control and release) Berlin-Chemie AG, Germany (Packaging, batch control and release) Menarini - Von Heyden GmbH, Germany (Batch control and release)
4. Studies conducted:	yes
1) type of medicinal product, which has been or will be registered	Medicinal product with fixed combination
5. Title of clinical trial, code number of clinical trial	CS-8635-A-U103 A randomized, open-label, single-dose crossover study to determine the bioavailability of olmesartan, amlodipine and hydrochlorothiazide administered together as CS-8635 pilot formulation A or separately as Benicar HCT® (olmesartan and hydrochlorothiazide) plus Antacal® (amlodipine) in healthy subjects.
6. Phase of clinical trial	Phase I
7. Period of clinical trial	10 Jan 2008 to 03 Apr 2008
8. Countries, where clinical trial has been conducted	USA
9. Number of trial subjects	planned: 41 actual:28 (completed)
10. Objective and secondary endpoints of clinical trial	Primary: to determine the relative bioavailability of olmesartan, amlodipine and hydrochlorothiazide when administered as a fixed dose formulation (CS-8635 pilot formulation A) and as two-tablet regime (Benicar HCT® plus Antacal®). Secondary: to assess the safety and tolerability of CS-8635 pilot formulation A).
11. Clinical trial design	Open-label, randomized, 2-way crossover study
12. Main inclusion criteria	Subjects enrolled were healthy adult men and women aged 18-45 years (inclusive) who satisfied all inclusion/exclusion criteria
13. Investigational medicinal product, mode of administration and strength	Treatment A: CS-8635 (olmesartan medoxomil 40 mg/amlodipine besylate 10 mg/HCT 25 mg) pilot formulation A
14. Reference product, dose, mode of administration and strength	Benicar HCT® 40/25 mg tablets Antacal ® 10 mg tablets
15. Concomitant therapy	None
16. Criteria for evaluation efficacy	AUC_{0-t}, AUC, $_{0-Inf}$, AUC%extr, C_{max}, T_{max}, Lambda Z, $t_{1/2}$ and CL/F
17. Criteria for evaluation safety	Number and severity of TEAEs, physical examination, vital signs, 12-lead ECGs and laboratory measurements
18. Statistical methods	An analysis of variance (ANOVA) was performed on the ln-transformed AUC_{0-last}, AUC_{0-Inf} and C_{max} for olmesartan, amlodipine and hydrochlorothiazide. The

ANOVA model included sequence, treatment and period as fixed effects.

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

Trait		Treatment Sequence AB (N = 21)	BA (N = 20)	Overall (N = 41)
Gender N(%)	Male	18 (85.7%)	18 (90.0%)	36 (87.8%)
	Female	3 (14.3%)	2 (10.0%)	5 (12.2%)
Race N(%)	American Indian/ Alaskan Native	1 (4.8%)	0	1 (2.4%)
	Asian	0	2 (10.0%)	2 (4.9%)
	Black or African American	10 (47.6%)	16 (80.0%)	26 (63.4%)
	White	10 (47.6%)	2 (10.0%)	12 (29.3%)
Ethnicity N(%)	Hispanic or Latino	7 (33.3%)	4 (20.0%)	11 (26.8%)
	Not Hispanic or Latino	14 (66.7%)	16 (80.0%)	30 (73.2%)
Age (yr)	Mean ± SD	34.5 ± 7.97	30.0 ± 6.36	32.3 ± 7.49
	Median (Min – Max)	38.0 (21-44)	28.5 (22-42)	33.0 (21-44)
Height (cm)	Mean ± SD	176.2 ± 10.30	179.1 ± 8.57	177.6 ± 9.49
	Median (Min – Max)	178.0 (156-198)	179.5 (161-193)	178.0 (156-198)
Weight (kg)	Mean ± SD	84.08 ± 14.060	83.99 ± 13.379	84.03 ± 13.560
	Median (Min – Max)	82.70 (63.4-108.2)	85.50 (61.2-106.5)	84.90 (61.2-108.2)
BMI (kg/m²)	Mean ± SD	27.08 ± 3.885	26.16 ± 3.384	26.63 ± 3.634
	Median (Min – Max)	28.81 (19.1-32.0)	26.68 (19.7-31.2)	27.25 (19.1-32.0)

20. Efficacy results

Olmesartan	Treatment A N = 31	Treatment B N = 30
AUC_{last} (ng·h/mL)		
Arithmetic Mean ±SD	6632.3 ± 1775.48	6745.2 ± 1916.63
Geometric Mean (CV%)	6423.9 (25.7%)	6538.0 (24.6%)
AUC_{0-inf} (ng·h/mL)*		
Arithmetic Mean ±SD	6706.8 ± 1798.62	6793.5 ± 1911.67
Geometric Mean (CV%)	6493.7 (25.9%)	6588.7 (24.3%)
C_{max} (ng/mL)		
Arithmetic Mean ±SD	986.3 ± 316.35	938.8 ± 270.97
Geometric Mean (CV%)	941.4 (31.3%)	898.7 (25.0%)
T_{max} (h)		
Median (Min, Max)	1.9830 (0.983, 4.00)	1.742 (1.00, 3.00)
$t_{\frac{1}{2}}$ (h)*		
Arithmetic Mean ±SD	18.457 ± 10.2844	17.238 ± 8.3481
CL/F* (L/h)		
Arithmetic Mean ±SD	6.351 ± 1.5706	6.227 ± 1.3211

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

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

	Geometric LSMEANS				
PK Parameter	Treatment A (Test)	Treatment B (Reference)	Ratio of LSMEANS (%) (A/B)	90% C.I. for Ratio (%)	Intra-Subject CV (%)
AUC_{0-inf}	387.6	362.4	106.96	(102.93, 111.15)	8.5
AUC_{last}	346.0	323.2	107.05	(102.97, 111.30)	8.6
C_{max}	6.878	6.599	104.22	(99.59, 109.06)	10.0

Hydrochlorothiazide	Treatment A N = 31	Treatment B N = 31
AUC_{last} (ng·h/mL) Arithmetic Mean ±SD Geometric Mean (CV%)	1177.1 ± 234.22 1152.0 (22.1%)	1170.6 ± 229.05 1147.0 (21.4%)
AUC_{0-inf} (ng·h/mL) Arithmetic Mean ±SD Geometric Mean (CV%)	1202.8 ± 233.90 1178.7 (21.3%)	1195.2 ± 229.33 1172.0 (21.0%)
C_{max} (ng/mL) Arithmetic Mean ±SD Geometric Mean (CV%)	186.48 ± 53.543 178.48 (31.9%)	177.05 ± 40.209 172.14 (25.5%)
T_{max} (h) Median (Min, Max)	1.4830 (0.983, 3.00)	1.5000 (0.983, 3.00)
$t_{½}$ (h) Arithmetic Mean ±SD	10.843 ± 1.7363	10.457 ± 1.2373
CL/F (L/h) Arithmetic Mean ±SD	21.70 ± 5.130	21.81 ± 5.126

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

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

Clinical study report 7

1. Name of medicinal product (registration certificate №, if available)	ATTENTO ® PLUS 20/5/12.5 mg
2. Applicant	Menarini International Operations Luxembourg S.A., Luxembourg
3. Manufacturer	Daiichi Sankyo Europe GmbH, Germany (Manufacturing "in bulk", packaging, batch control and release) Berlin-Chemie AG, Germany (Packaging, batch control and release) Menarini - Von Heyden GmbH, Germany (Batch control and release)
4. Studies conducted:	yes
1) type of medicinal product, which has been or will be registered	Medicinal product with fixed combination
5. Title of clinical trial, code number of clinical trial	CS-8635-A-U104 A randomized, open-label, single-dose crossover study to determine the bioavailability of olmesartan, amlodipine and hydrochlorothiazide administered together as CS-8635 pilot formulation B or separately as Benicar HCT® (olmesartan and hydrochlorothiazide) plus Antacal® (amlodipine) in healthy subjects.
6. Phase of clinical trial	Phase I
7. Period of clinical trial	17 Jan 2008 to 14 Feb 2008
8. Countries, where clinical trial has been conducted	USA
9. Number of trial subjects	planned: 32 actual: 28 (completed)
10. Objective and secondary endpoints of clinical trial	Primary: to determine the relative bioavailability of olmesartan, amlodipine and hydrochlorothiazide when administered as a fixed dose triple component formulation (CS-8635 pilot formulation B) and as two tablet regimen (Benicar HCT® plus Antacal®). Secondary: to assess the safety and tolerability of CS-8635 pilot formulation B
11. Clinical trial design	Open-label, randomized, 2-way crossover study
12. Main inclusion criteria	Subjects enrolled were healthy adult men and women aged 18-45 years (inclusive) who satisfied all inclusion/exclusion criteria
13. Investigational medicinal product, mode of administration and strength	Treatment A: A single dose of CS-8635 pilot formulation B tablet (olmesartan medoxomil 40 mg/amlodipine besylate 10 mg/hydrochlorothiazide 25 mg)
14. Reference product, dose, mode of administration and strength	Treatment B: a single oral dose of Benicar HCT® (olmesartan medoxomil 40 mg/hydrochlorothiazide 25 mg) plus Antacal® (amlodipine besylate 10 mg)
15. Concomitant therapy	None
16. Criteria for evaluation efficacy	AUC_{0-t}, AUC, $_{0-Inf}$, AUC%extr, C_{max}, T_{max}, Lambda Z, $t_{1/2}$ and CL/F
17. Criteria for evaluation safety	Number and severity of TEAEs, physical examination, vital signs, 12-lead ECGs and laboratory measurements
18. Statistical methods	An analysis of variance (ANOVA) was

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

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

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

20. Efficacy results

Olmesartan	Treatment A N = 30	Treatment B N = 30
AUC_{last} (ng·h/mL) Arithmetic Mean ±SD Geometric Mean (CV%)	6710.5 ± 1777.29 6493.8 (26.4%)	6043.3 ± 1455.81 5874.0 (24.8%)
AUC_{0-Inf} (ng·h/mL)* Arithmetic Mean ±SD Geometric Mean (CV%)	6588.0 ± 1732.22 6384.0 (25.7%)	6092.5 ± 1483.37 5919.1 (25.0%)
C_{max} (ng/mL) Arithmetic Mean ±SD Geometric Mean (CV%)	1006.5 ± 337.39 957.4 (32.5%)	899.1 ± 277.48 856.9 (32.9%)
T_{max} (h) Median (Min, Max)	2.000 (1.00, 4.00)	1.992 (1.00, 4.00)
$t_{½}$ (h)* Arithmetic Mean ±SD	21.022 ± 14.2767	21.874 ± 14.6826
CL/F* (L/h) Arithmetic Mean ±SD	6.456 ± 1.5728	6.961 ± 1.7548

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

Amlodipine	Treatment A N = 30	Treatment B N = 30
AUC_{last} (ng·h/mL) Arithmetic Mean ±SD Geometric Mean (CV%)	325.6 ± 87.74 315.5 (25.6%)	308.9 ± 79.03 300.1 (24.6%)
AUC_{0-Inf} (ng·h/mL) Arithmetic Mean ±SD Geometric Mean (CV%)	355.8 ± 102.19 343.2 (27.4%)	338.3 ± 96.37 326.4 (27.3%)
C_{max} (ng/mL) Arithmetic Mean ±SD Geometric Mean (CV%)	7.035 ± 2.0205 6.779 (27.9%)	6.799 ± 1.5532 6.631 (23.0%)
T_{max} (h) Median (Min, Max)	8.009 (6.00, 12.00)	7.050 (4.00, 12.00)
$t_{½}$ (h) Arithmetic Mean ±SD	38.43 ± 6.728	38.41 ± 7.517
CL/F (L/h) Arithmetic Mean ±SD	30.15 ± 7.863	31.70 ± 8.366

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

	<table><tr><th>Hydrochlorothiazide</th><th>Treatment A N = 30</th><th>Treatment B N = 30</th></tr><tr><td>AUC_{last} (ng·h/mL) Arithmetic Mean ±SD Geometric Mean (CV%)</td><td>1171.6 ± 233.23 1148.9 (20.5%)</td><td>1188.4 ± 267.64 1160.9 (22.1%)</td></tr><tr><td>AUC_{0-inf} (ng·h/mL) Arithmetic Mean ±SD Geometric Mean (CV%)</td><td>1198.8 ± 236.04 1176.1 (20.2%)</td><td>1212.0 ± 267.40 1185.2 (21.6%)</td></tr><tr><td>C_{max} (ng/mL) Arithmetic Mean ±SD Geometric Mean (CV%)</td><td>179.96 ± 54.987 172.13 (31.1%)</td><td>178.9 ± 62.74 170.2 (31.8%)</td></tr><tr><td>T_{max} (h) Median (Min, Max)</td><td>1.5000 (0.967, 4.00)</td><td>1.5000 (0.983, 3.00)</td></tr><tr><td>$t_{½}$ (h) Arithmetic Mean ±SD</td><td>10.831 ± 1.3403</td><td>10.508 ± 1.3201</td></tr><tr><td>CL/F (L/h) Arithmetic Mean ±SD</td><td>21.68 ± 4.474</td><td>21.55 ± 4.491</td></tr></table> <table><tr><th></th><th colspan="2">Geometric LSMEANS</th><th></th><th></th><th></th></tr><tr><th>PK Parameter</th><th>Treatment A (Test)</th><th>Treatment B (Reference)</th><th>Ratio of LSMEANS (%) (A/B)</th><th>90% C.I. for Ratio (%)</th><th>Intra-Subject CV (%)</th></tr><tr><td>AUC_{0-inf}</td><td>1174</td><td>1169</td><td>100.39</td><td>(95.70, 105.32)</td><td>10.6</td></tr><tr><td>AUC_{last}</td><td>1147</td><td>1145</td><td>100.11</td><td>(95.34, 105.12)</td><td>10.8</td></tr><tr><td>C_{max}</td><td>171.2</td><td>169.5</td><td>101.01</td><td>(91.05, 112.06)</td><td>23.5</td></tr></table>
21. Safety results	The concomitant oral administration of olmesartan medoxomil 40 mg, amlodipine besylate 10 mg, and hydrochlorothiazide 25 mg was safe and well tolerated in this group of healthy subjects, and no differences in the frequency of TEAEs between the two formulations were observed.
22. Conclusion (summary)	The triple fixed dose combination (CS-8635 pilot formulation B) is bioequivalent to the Benicar HCT® plus Antacal® regimen
Applicant (registration certificate holder)	(signature) Dr. Kai Schumacher (full name)

Clinical study report 8

1. Name of medicinal product (registration certificate №, if available)	ATTENTO ® PLUS 20/5/12.5 mg **24**
2. Applicant	Menarini International Operations Luxembourg S.A., Luxembourg
3. Manufacturer	Daiichi Sankyo Europe GmbH, Germany (Manufacturing "in bulk", packaging, batch control and release) Berlin-Chemie AG, Germany (Packaging, batch control and release) Menarini - Von Heyden GmbH, Germany (Batch control and release)
4. Studies conducted:	yes
1) type of medicinal product, which has been or will be registered	Medicinal product with fixed combination
5. Title of clinical trial, code number of clinical trial	CS-8635-A-U101 A randomized, open-label, single dose, crossover study of olmesartan, amlodipine, and hydrochlorothiazide, to determine the bioavailability when administered as Benicar HCT® plus Norvasc® together versus separately in healthy volunteers
6. Phase of clinical trial	Phase I
7. Period of clinical trial	25 Jun 2007 to 03 Sep 2007
8. Countries, where clinical trial has been conducted	USA
9. Number of trial subjects	planned: 36 actual:32 (completed)
10. Objective and secondary endpoints of clinical trial	Primary; to determine bioavailability of olmesartan, amlodipine and hydrochlorothiazide when administered together as Benicar HCT® and Norvasc® and when administered alone. Secondary: to evaluate the safety and tolerability when Benicar® is coadministered with Norvasc®.
11. Clinical trial design	Open-label, randomised, single-dose 3 way crossover study.
12. Main inclusion criteria	Subjects enrolled were healthy men and women, aged 18-45 years (inclusive), who satisfied all inclusion/exclusion criteria
13. Investigational medicinal product, mode of administration and strength	Benicar HCT® (olmesartan medoxomil/hydrochlorothiazide)
14. Reference product, dose, mode of administration and strength	Norvasc® (amlodipine besylate)
15. Concomitant therapy	None
16. Criteria for evaluation efficacy	The following PK parameters were calculated for olmesartan, amlodipine and hydrochlorothiazide: AUC_{0-t}, AUC_{0-Inf}, AUC%extr, C_{max}, T_{max}, Lambda Z, $t_{1/2}$ and CL/F
17. Criteria for evaluation safety	Number and severity of TEAEs, physical examinations, vital signs, 12-lead ECGs, laboratory measurements.
18. Statistical methods	An analysis of variance (ANOVA) was performed on the ln-transformed AUC_{0-t}, AUC_{0-Inf} and C_{max} for OM, AML and HCT. The ANOVA model included sequence, treatment and period as fixed effects.

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

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

20. Efficacy results

Olmesartan	Treatment A N = 34	Treatment B N = 35
AUC_{0-t} (ng·h/mL) Arithmetic Mean ±SD Geometric Mean (CV%)	6134.4 ± 1676.74 5938.7 (25.8%)	6399.5 ± 1816.81 6068.9 (28.3%)
AUC_{0-inf} (ng·h/mL) Arithmetic Mean ±SD Geometric Mean (CV%)	6249.8 ± 1678.98 6055.8 (25.5%)	6501.9 ± 1837.56 6189.9 (28.8%)
C_{max} (ng/mL) Arithmetic Mean ±SD Geometric Mean (CV%)	912.5 ± 305.57 871.2 (30.7%)	1016.3 ± 317.94 957.4 (40.2%)
T_{max} (h) Median (Min, Max)	1.983 (1.00, 4.00)	1.983 (1.00, 3.00)
$t_{½}$ (h) Arithmetic Mean ±SD	17.394 ± 7.8206	16.257 ± 8.6458
CL/F (L/h) Arithmetic Mean ±SD	6.804 ± 1.6651	6.958 ± 3.6439

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

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

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

Hydrochlorothiazide	Treatment A N = 34	Treatment B N = 35
AUC_{0-t} (ng.h/mL) Arithmetic Mean ±SD Geometric Mean (CV%)	1043.4 ± 224.90 1020.7 (21.6%)	1052.7 ± 231.13 1021.8 (27.4%)
AUC_{0-inf} (ng.h/mL) Arithmetic Mean ±SD Geometric Mean (CV%)	1069.3 ± 224.78 1047.1 (21.0%)	1079.8 ± 229.12 1050.9 (25.8%)
C_{max} (ng/mL) Arithmetic Mean ±SD Geometric Mean (CV%)	161.51 ± 53.714 153.90 (31.8%)	164.78 ± 57.837 155.34 (37.0%)
T_{max} (h) Median (Min, Max)	1.5000 (0.983, 4.00)	1.5000 (0.983, 4.00)
$t_{½}$ (h) Arithmetic Mean ±SD	10.800 ± 1.4435	10.866 ± 2.0647
CL/F (L/h) Arithmetic Mean ±SD	24.38 ± 5.164	24.70 ± 8.513

	Geometric LSMEANS			
PK Parameter	Treatment A (Test)	Treatment B (Reference)	Ratio of LSMEANS (%) (A/B)	90% C.I. for Ratio (%)
AUC_{0-inf}	1051	1050	100.06	(95.01, 105.39)
AUC_{0-t}	1025	1021	100.33	(94.93, 106.05)
C_{max}	154.9	155.1	99.89	(91.97, 108.48)

21. Safety results	No serious or severe TEAEs occurred during the study. Overall, 16 subjects (44.4%) reported 62 TEAEs. No TEAE was considered definitely or probably drug-related. Overall, there was no clear difference for TEAEs between treatments A, B, and C.
22. Conclusion (summary)	The pharmacokinetics of olmesartan in the fixed dose combination (Benicar HCT®) are not affected by the co-administration of amlodipine. The PK of amlodipine are not affected by the fixed dose combination (Benicar HCT®). The PK of hydrochlorothiazide in the fixed dose combination (Benicar HCT®) are not affected by the co-administration of amlodipine. The concomitant administration of amlodipine besylate 10 mg, olmesartan medoxomil 40 mg and hydrochlorothiazide 25 mg was safe and well tolerated in this group of healthy male and female subjects.
Applicant (registration certificate holder)	(signature) Dr. Kai Schumacher (full name)

Clinical study report 9

1. Name of medicinal product (registration certificate №, if available)	ATTENTO ® PLUS 20/5/12.5 mg 27
2. Applicant	Menarini International Operations Luxembourg S.A., Luxembourg
3. Manufacturer	Daiichi Sankyo Europe GmbH, Germany (Manufacturing "in bulk", packaging, batch control and release) Berlin-Chemie AG, Germany (Packaging, batch control and release) Menarini - Von Heyden GmbH, Germany (Batch control and release)
4. Studies conducted:	yes
1) type of medicinal product, which has been or will be registered	Medicinal product with fixed combination
5. Title of clinical trial, code number of clinical trial	CS8635-A-U102 A randomized, open-label, single-dose crossover study to determine the bioavailability of olmesartan, amlodipine and hydrochlorothiazide when administered as CS-8663 plus Hydrochlorothiazide together versus separately in healthy subjects
6. Phase of clinical trial	Phase I
7. Period of clinical trial	21 June 2007 to 09 Aug 2007
8. Countries, where clinical trial has been conducted	USA
9. Number of trial subjects	planned: 36 actual:29 (completed)
10. Objective and secondary endpoints of clinical trial	Primary: to determine the bioavailability of olmesartan, amlodipine and hydrochlorothiazide when administered together as CS-8663 (olmesartan plus amlodipine besylate) and hydrochlorothiazide, and when administered alone Secondary: to evaluate the safety and tolerability when CS-8663 is co-administered with hydrochlorothiazide
11. Clinical trial design	Open label, randomized, single-dose, 3-way crossover study
12. Main inclusion criteria	Subjects enrolled were healthy adult men and women, aged 19-45 years (inclusive) who satisfied all inclusion/exclusion criteria
13. Investigational medicinal product, mode of administration and strength	CS-8663 (olmesartan medoxomil and amlodipine besylate) 40 mg/10 mg oral tablet
14. Reference product, dose, mode of administration and strength	Hydrochlorothiazide 25 mg oral tablet
15. Concomitant therapy	None
16. Criteria for evaluation efficacy	$AUC_{0\text{-}t}$, $AUC_{0\text{-}Inf}$, AUC%extr, C_{max}, T_{max}, Lambda Z, $t_{1/2}$ and CL/F
17. Criteria for evaluation safety	Number and severity of TEAEs, physical examination, vital signs, 12-lead ECGs and laboratory measurements
18. Statistical methods	An analysis of variance (ANOVA) was performed on ln-transformed $AUC_{0\text{-}t}$, $AUC_{0\text{-}Inf}$ and C_{max}. The ANOVA model included sequence, treatment and period as fixed effects

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

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

20. Efficacy results

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

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

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

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

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

	Geometric LSMEANS

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

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