CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-093

ADMINISTRATIVE DOCUMENTS

ITEM 13

PATENT INFORMATION

1.0 Patent Information

The patent information for candesartan cilexetil and the combination of candesartan cilexetil and hydrochlorothiazide is provided in this section. Six (6) patents have been identified as pertinent to candesartan cilexetil (NDA 20-838, approved on June 4, 1998 under section 505 of the Federal Food, Drug, and Cosmetic Act) and/or the combination of candesartan cilexetil and hydrochlorothiazide (the subject of this application for which approval is being sought) and their indication for the treatment of hypertension.

Patent information as per Title 21 CFR § 314.53(c)(1) is summarized below. In addition, a declaration statement is provided in accordance with Title 21 CFR § 314.53(c)(2).

Patent Number	Patent Expiration Date	Type of Patent	Patent Owner	Authorized Representative to Receive Notice of Patent Certification
*5,196,444	April 18, 2011	drug substance; drug product; method of use	Takeda Chemical Industries, Ltd.	AstraZeneca LP
*5,534,534	July 9, 2013	drug product	Takeda Chemical Industries, Ltd.	AstraZeneca LP
*5,703,110	April 18, 2011	drug substance; drug product; method of use	Takeda Chemical Industries, Ltd.	AstraZeneca LP
*5,705,517	April 18, 2011	drug substance; drug product; method of use	Takeda Chemical Industries, Ltd.	AstraZeneca LP
5,721,263	February 24, 2015	drug product; method of use	Takeda Chemical Industries, Ltd.	AstraZeneca LP
5,958,961	June 6, 2014	drug product; method of use	Takeda Chemical Industries, Ltd.	AstraZeneca LP

*Patent previously identified under NDA 20-838 (candesartan cilexetil)

2.0 Patent Declaration Statement

DECLARATION

The undersigned declares that U.S. Patent Numbers 5,196,444, 5,534,534, 5,703,110, 5,705,517, 5,721,263 and 5,958,961 cover the formulation, composition, and/or method of use of candesartan cilexetil (NDA 20-838, approved on June 4, 1998 under section 505 of the Federal Food, Drug, and Cosmetic Act) and/or the combination of candesartan cilexetil and hydrochlorothiazide. The combination product of candesartan cilexetil and hydrochlorothiazide is the subject of this application for which approval is being sought.

Cindy M. Lancaster

Cindy M. Lancaster, M.S., M.B.A.
Director, Regulatory Affairs
AstraZeneca LP

EXCLUSIVITY SUMMARY FOR NDA # 21-093 SUPPL #_____

Trade Name ATACAND HCT Generic Name candesartan cilexetil-hydrochlorothiazide

Applicant Name AstraZeneca LP HFD # 110

Approval Date If Known 9/5/00

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /✓/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /✓/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /✓/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /✓/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request? 3

e) Has pediatric exclusivity been granted for this Active Moiety?

NO

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /___/ NO /X/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /X/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-838 candesartan cilexetil

NDA# 011-835 hydrochlorothiazide

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /X/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /✓/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /✓/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /✓/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /✓/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies: SH-AHK-0004, AM124, EC408, AM153 and EC403

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /X/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /X/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # ____ YES /X/ ! NO /___/ Explain: _____

Investigation #2

IND # _____ YES /___/ ! NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /__/ NO /X/

If yes, explain: _____

_____

/S/

_____ 5/17/00

Signature Date

Title: CSO

/S/

_____ 7/19/00

Signature of Office/ Date

Division Director

cc: Original NDA Division File HFD-93 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

NDA/BLA # 21-093 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8

HFD-110 Trade and generic names/dosage form: Atacand HCT (candesartan cilexetil - hydrochlorothiazide) TABLETS Action: AP (AE) NA

Applicant AstraZeneca, LP Therapeutic Class 45

Indication(s) previously approved N/A

Pediatric information in labeling of approved indication(s) is adequate ___ inadequate X

Indication proposed in this application treatment of hypertension

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ___Yes (Continue with questions) ___No (Sign and return the form)

IN WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

__Neonates (Birth-1month) __Infants (1month-2yrs) __Children (2-12yrs) __Adolecents(12-16yrs)

__1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

__2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

__3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

- __a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
- __b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.
- __c. The applicant has committed to doing such studies as will be required.
  - __ (1) Studies are ongoing,
  - __ (2) Protocols were submitted and approved.
  - __ (3) Protocols were submitted and are under review.
  - __ (4) If no protocol has been submitted, attach memo describing status of discussions.
- __d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

✓ __4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

__5. **If none of the above apply, attach an explanation, as necessary.**

ARE THERE ANY PEDIATRIC PHASE 4 COMMITMENTS IN THE ACTION LETTER? ___ Yes ✓ No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from DR Fredd Medical Review (e.g., medical review, medical officer, team leader)

/S/

Signature of Preparer and Title

6/19/00

Date

Orig NDA/BLA # 21-093
HFD 110/Div File
NDA/BLA Action Package
~~HFD-006/KRoberts~~

(revised 10/20/97)

FOR QUESTIONS ON COMPLETING THIS FORM, CONTACT KHYATI ROBERTS, HFD-6 (ROBERTSK)

HFD-104/TCRescenzi

6/19/00
TO: NDA 21093, Candesartan/HCTZ for Hypertension
FROM: Stephen Fredd, M.D. SF
SUBJECT: Request for Full Waiver of Pediatric Use Requirement

AstraZeneca requested a full waiver for pediatric for pediatric use information on 4/28/00. While that request contained sufficient information to establish that the CC/HCTZ combination would not be used in a substantial number of pediatric patients, they did not provide any response to the requirement under 21CFR314.55(c)(2) that the new drug would not provide a meaningful therapeutic benefit over existing therapies. To address this point, our FR notice suggests evaluation the labeling for other drugs for this use to see if a substantial number have already been labeled.

The sponsor has now made a comprehensive submission addressing this requirement. They note that NIH in an update of the 1987 task force report on high blood pressure in children and adolescents states that children generally have secondary hypertension. Therefore the search for and elimination of the cause is essential. For those needing control of blood pressure, diuretics and beta-blockers were historically used, but these now are not the preferred agents. ACE inhibitors are now recommended, but are not to be used when bilateral renal artery stenosis is present. The sponsor notes that Merck was recently granted pediatric exclusivity for Enalapril with the expectation that pediatric labeling for that drug will soon be available. The angiotensin II receptor antagonists were not addressed in the NIH report.

The review of pediatric labeling for antihypertensives notes that Aldomet, Chlorothiazide and Hydrochlorothiazide have some dosing guidance in pediatric patients in the labeling. While this is does not represent a large number of antihypertensive drugs labeled for pediatric use, many are currently under study, including Candesartan cilexetil.

The sponsor has now adequately addressed both criteria for the granting of a full pediatric waiver, and I recommend that the waiver be granted.

CC:Dr. Lipicky
Mr. Fromm

ITEM 16

DEBARMENT CERTIFICATION

1.0 DEBARMENT CERTIFICATION

As required by Section 306(k)(1) of the Generic Drug Enforcement Act [21 U.S.C. 335a(k)(1)], we hereby certify that, in connection with this application, AstraZeneca LP (formerly Astra Pharmaceuticals, L.P. until June 1, 1999 and also known as Astra Merck, Inc. until July 1998) did not and will not use in any capacity the services of any person debarred under subsection 306(a) or (b) of the Act.

CSO Approval/Labeling Review

Application: NDA 21-093
Atacand HCT (candesartan cilexetil/hydrochlorothiazide)
16/12.5 and 32/12.5 mg Tablets

Applicant: AstraZeneca LP

Background: An approvable letter was issued for NDA 21-093 on July 19, 2000. Subsequent to the approvable letter several issues have come up that needed resolution:

1) On July 31, 2000, the sponsor proposed revisions in the **CLINICAL TRIALS** and **DOSAGE and ADMINISTRATION** sections of the package insert.

Resolution: Dr. Lipicky reviewed the sponsor's modifications and said that they were acceptable. I relayed our acceptance of those modifications to AstraZeneca on August 7, 2000.

2) The sponsor expressed difficulty in meeting the dissolution method and specifications for the 16-12.5 and 32-12.5 mg tablets of candesartan cilexetil-hydrochlorothiazide.

Resolution: A teleconference was held on July 28, 2000 between AstraZeneca and Drs. Marroum, Nguyen, and Srinivasachar to discuss the dissolution specifications and methods. AstraZeneca proposed a higher speed for dissolution but Dr. Marroum felt that the higher speed would not be discriminating enough to evaluate the tablet dissolution characteristics. He did say, however, that if the sponsor was having difficulty getting dissolution at the . recommended by the Division they should send in data to Division documenting those failures.

On August 24, 2000 the sponsor notified the Division that several batches of the 16-12.5 mg of candesartan cilexetil-hydrochlorothiazide had failed using the dissolution specifications as outlined in the approvable letter. They asked if the specification: could be changed to or the 16-12.5 mg dosage form. Dr. Marroum said this change was acceptable but asked the sponsor to submit the actual data documenting the failures to the Division for review. AstraZeneca submitted the dissolution data documenting the failures to the Division on August 25, 2000. Dr. Dorantes reviewed the dissolution data and confirmed the timeframe for the 16-12.5 mg strength of candesartan cilexetil-hydrochlorothiazide was acceptable.

3) The Division, in the approvable letter, asked the sponsor to provide the results from the conditions prior to launch and for their commitment to monitor moisture content and tablet hardness on the first three commercial batches and to obtain Agency concurrence before terminating these tests on future annual batches.

Resolution: AstraZeneca, in their submission of final printed labeling on August 14, 2000, confirmed their commitment to of the tablets and to monitor moisture and hardness on the first three commercial batches of both tablet strengths. They indicated, if successful, they would send results of the prior to launch as a "General Correspondence" to the NDA. Results of the moisture and tablet hardness tests would be submitted as a "General Correspondence" to the NDA after launch and the company will obtain Division approval before discontinuing the testing on future annual batches.

4) The sponsor proposed editorial changes in the **Fetal/Neonatal Morbidity and Mortality** and **Carcinogenesis, Mutagenesis, Impairment of Fertility** subsections of the package insert.

Resolution: Dr. Proakis, in a telephone conversation with AstraZeneca on July 27, 2000, said the proposed editorial changes were acceptable.

Comments/Recommendation: There are no other unresolved issues pending for this NDA. An approval letter will be drafted for Dr. Lipicky's signature.

/S/

Edward Fromm
Consumer Safety Officer

Ef/8-18-00

cc: NDA 21-093
HF-2 (MedWatch)
HFD-110
HFD-110/EFromm
HFD-110/Blount

JUL 19 2000

CSO NDA Overview
July 10, 2000

NDA 21-093 Atacand HCT (candesartan cilexetil/hydrochlorothiazide) 16/12.5 and 32/12.5 mg Tablets

Sponsor: AstraZeneca LP

Classification: 4S

Date of Application: September 28, 1999
Date of Receipt: September 28, 1999
User Fee Goal Date: July 28, 2000

Background

AstraZeneca has submitted this NDA for the combination product candesartan cilexetil/HCTZ for the treatment of hypertension. Candesartan monotherapy was approved for the treatment of hypertension under NDA 20-838 on June 4, 1998. Studies for the combination were performed under (for use in hypertension and congestive heart failure).

Meetings
November 19, 2000: Filing meeting.

June 30, 1997: End-of-Phase II meeting for candesartan cilexetil/hydrochlorothiazide.

Review

Medical/Statistical Review
Medical Reviewer: Stephen Fredd, M.D. (safety and efficacy)
Raymond Lipicky, M.D. (secondary review)
Statistical Reviewer: Kooros Mahjoob, Ph.D.

Labeling: see Dr. Fredd's and Mahjoob's 3-15-00 review for labeling recommendations.
Conclusion: Fredd/Majoob: approvable
Lipicky: approvable (see Division Director's Memo)

Biopharmaceutics Review:
Reviewer: Nhi Nguyen, PharmD.
Labeling: None
Conclusion: approvable, but asked the sponsor to change the dissolution method and specifications for the 16/12.5 mg and 32/12.5 mg Tablets (see Dr. Nguyen's 6-21-00 review).

Chemistry
Reviewer: Joseph Piechocki, Ph.D.
Labeling: acceptable
cGMP Inspections: Acceptable, September 20, 1999, June 22, 2000
Methods validation: has not been requested yet
Environmental Assessment: exclusion granted

Conclusion: approvable, but asked that the drug product be tested under a launch and also asked for commitments to monitor content and tablet hardness on the first three commercial batches and obtain Agency concurrence before terminating these tests on future annual batches (see Dr. Piechocki's 6-27-00 review and Dr. Srinivasachar's 7-10-00 memorandum to that review).

Pharmacology

Reviewer: Anthony Proakis, Ph.D.

Labeling: see Dr. Proakis' January 6, 2000 review; he recommended changes in the **WARNINGS**, *Fetal/Neonatal Morbidity* subsection, **PRECAUTIONS**, *Carcinogenesis, Mutagenesis, Impairment of Fertility* subsection and the **OVERDOSAGE** section.

Conclusion: approvable

Statistics (preclin): Not needed

Safety Update: In a May 25, 2000 submission, the firm states that there were no trials ongoing at the time of NDA submission and none have been initiated, so there are no additional data available to comprise a four-month Safety Update to the NDA.

Patent info: included in package

Pediatric info: waiver granted

DSI: Dr. Fredd said DSI audits were unnecessary.

Debarment Certification: included in package

OPDRA Tradename Review: OPDRA said, "since ATACAND has already been previously approved and the HCT is commonly used with other combination products containing hydrochlorothiazide, we have no objection." March 3, 2000

/S/

Edward J. Fromm

cc:
NDA 21-093
HFD-110
HFD-110/E.Fromm/Blount
ef/7-10-00

DEC 20

Minutes of a NDA Filing Meeting

Date: November 19, 1999

Applications: NDA 21-093
Atacand HCT (candesartan cilexetil/hydrochlorothiazide)
16/12.5 and 32/12.5 mg Tablets

Applicant: AstraZeneca LP

Primary Goal Date: July 28, 2000

Secondary Goal Date: September 28, 2000

Participants:

Robert R. Fenichel, M.D., Ph.D., HFD-110, Deputy Division Director
Steven Fredd, M.D., HFD-110, Deputy Director
Norman Stockbridge, M.D.,Ph.D., Medical Team Leader
Abraham Karkowsky, M.D., Ph.D., HFD-110, Medical Team Leader
Charles Resnick, Ph.D., HFD-110, Pharmacology Team Leader
Anthony Proakis, Ph.D., HFD-110, Pharmacologist
Kasturi Srinivasachar, Ph.D., Team Leader, Chemistry, Division of New Drug Chemistry I (HFD-810)
Patrick Marroum, Ph.D., HFD-860, Clinical Pharmacology and Biopharmaceutics, Team Leader
Hong Zhao, Ph.D., HFD-860, Clinical Pharmacologist and Biopharmaceuticist
Khin Maung U, M.D., Ph.D., Division of Scientific Investigations
Natalia Morgenstern, HFD-110, Chief, Project Management Staff
Edward Fromm, HFD-110, Consumer Safety Officer

Background

AstraZeneca has submitted this NDA for the combination product candesartan cilexetil/HCTZ for the treatment of hypertension. Candesartan cilexetil monotherapy was approved for the treatment of hypertension under NDA 20-838 on June 4, 1998. Studies for the combination for the treatment of hypertension were performed under

Meeting

Pharmacology

Reviewer: Anthony Proakis, Ph.D.

Dr. Proakis had no objections to filing the NDA. He has completed his initial review and expects to have a final version by January 31, 2000.

Chemistry

Reviewer: Joe Piechocki, Ph.D. (absent)

Dr. Srinivasachar had no objections to filing the NDA. Dr. Srinivasachar indicated that Dr. Piechocki would be done with his review by April 15, 2000. Dr. Srinivasachar said a focus of the review would be whether there was an interaction between candesartan cilexetil and hydrochlorothiazide.

A facility inspection will be requested.

Biopharmaceutics

Reviewer: Hong Zhao, Ph.D., Raman Baweja, Ph.D.

Dr. Zhao had no objections to filing the NDA. She indicated that she would be requesting more dissolution data from the company. The review is expected to be completed by April 15, 2000.

Clinical/Statistical

Medical Officer: Stephen Fredd, M.D.

Statistician: Kooros Mahjoob, Ph.D.

The medical officer and statistician will be doing a joint review. They did not object to filing the NDA. The review is expected to be completed by March 30, 2000.

Dr. Fredd indicated that because the studies were not optimally designed he would pool the results to see if there was a dose-response relationship. The submission was also poorly organized, incompletely detailed, but reviewable.

DSI

DSI audits are not necessary. Dr. U. noted that DSI sometimes conducts audits on their own volition when they suspect investigator misconduct.

Secondary Medical Review

Reviewer: Raymond Lipicky, M.D.

Dr. Lipicky expects to complete his review by April 30, 2000.

Conclusion

The application will be filed.

Addendum

On December 15, 1999, the Biopharmaceutics reviewers for Atacand HCT were changed from Dr. Hong Zhao and Dr. Raman Baweja to Dr. Nhi Nguyen.

/S/

Minutes Preparation

Edward Fromm

Concurrence Chair:

/S/

Robert R. Fenichel, M.D., Ph.D.

ef/11-30-99

Rd: JPiechocki/12-7-99
KSrinivasachar/12-7-99
PMarroum/12-7-99
HZhao/12-8-99
AProakis/12-8-99
CResnick/12-8-99
SFredd/12-9-99
NMorgenstern-12/14/99

cc: NDA 21-093
HFD-110
HFD-110/EFromm/SMatthews

JUL 16 1997

Minutes
June 30, 1997
End-of-Phase 2 Meeting
candesartan cilexetil/hydrochlorothiazide
Astra Merck Inc.

Pre-meeting submission: June 9, 1997,

Attending:

Astra Merck:

Elliott Berger, Ph.D.	Regulatory Affairs
Robert Cobuzzi, Ph.D.	Clinical Development
Joanne Curley, R.Ph.	Chemistry and Manufacturing
Daniel Cushing, Ph.D.	Regulatory Affairs
Denise Hardison, M.S.	Biostatistician
Larrye Loss, Pharm. D.	Clinical Development
Eric Michelson, M.D.	Clinical Development
Maria Sunzel, Ph.D.	Clinical Development

Astra Hassle:

Eva Lindgren	Product Team Leader
Gunnar Olsson, M.D.	Clinical Development
Bertil Olofsson, Ph.D.	Biostatistics

FDA:

Raymond Lipicky, M.D.	HFD-110	Division Director
Norman Stockbridge, M.D., Ph.D.	HFD-110	Group Leader/Medical
Steven Caras, M.D., Ph.D.	HFD-110	Medical Officer
James Hung, Ph.D.	HFD-710	Statistician
Ameeta Parekh, Ph.D.	HFD-860	Group Leader/Biopharmaceutics
Florian Zielinski, Ph.D.	HFD-810	Chemist
Kathleen Bongiovanni	HFD-110	Regulatory Health Project Manager

Background: Astra-Merck asked to come in to discuss their clinical development program for a candesartan cilexetil/hydrochlorothiazide combination product.

Discussion Points: The following are questions from the pre-meeting submission and the responses:

Q1: CMC question: covered by telephone by Drs. Florian Zielinski and Daniel Cushing prior to the meeting. See telecon dated June 25, 1997.

Q2: Is it necessary to conduct a separate study of the potential interaction with food?

Dr. Parekh told the firm that we recommend a standard food study because it is a new formulation, but it is not required. Without a study, the labeling would state what is known about the effect of food on each component and that no studies have been performed with the

combination. She recommended a single-dose cross-over study, using a high-fat meal and the highest strength of the combination product.

Dr. Parekh noted that the firm has ongoing bioequivalence and drug interaction studies, but they are not using the highest strength of the combination, as we generally recommend. She asked the firm to consider obtaining plasma levels from planned studies in patients taking the highest dose of the combination. A-M said that candesartan monotherapy had linear kinetics, so they thought their studies would be acceptable. Dr. Parekh asked them whether they know that the kinetics remain linear in combination. Dr. Lipicky said that they could submit animal data to support their position. Dr. Lipicky also noted that if there are no dose-related adverse events with candesartan, there is little to worry about.

Hydrochlorothiazide

A-M noted that the HCTZ used in the clinical trials was not a marketed product, and they have not performed any bioequivalence studies on that HCTZ and an approved product. Dr. Lipicky said that such a study would not be necessary. [Dr. Parekh disagreed and spoke to A-M and Dr. Lipicky after the meeting to clarify this issue, and Drs. Lipicky and Parekh agreed that A-M should perform a bioequivalence study. See Dr. Parekh's review dated July 7, 1997.]

Q3: Is the extent of population exposure, including time of exposure and numbers of patients included in subgroups, sufficient to support a general claim for the treatment of hypertension?

Dr. Lipicky agreed that the extent of exposure is sufficient.

Q4: Does the data from the factorial study, EC403, support the additivity of the combination of candesartan cilexetil and hydrochlorothiazide?

Drs. Hung and Lipicky noted that they do not have sufficient data to support a statement on the additivity of the effects.

A-M asked whether EC403 and the other studies would support the approval of the 8/12.5 and 16/12.5 combinations. Dr. Lipicky said that they would (assuming appropriate results).

Q5: Does the Agency concur with our working position that the maximum dose of candesartan cilexetil (monotherapy) is 32 mg?

Dr. Lipicky said that we are not yet able to answer that question, since the monotherapy NDA is still under review.

Q6: Does study #153 (combination of 32 mg candesartan cilexetil and 12.5 mg HCTZ versus mono components), along with the other studies in the development plan, provide sufficient data to support the proposed Dosage and Administration presented in section II of this information package?

Dr. Lipicky said that the results of the trials would determine the labeling, and he would be able to comment on the labeling after the results are reviewed. He said that it is likely that they would have a "Therapy Guided by Clinical Effect" section.

Substitution for HCTZ Alone

A-M asked whether the labeling could say to substitute the combination for 25 mg HCTZ alone for patients who experience adverse effects. Dr. Lipicky said that their labeling would be unlikely to say that 25 mg of HCTZ is the highest dose that one should take. If a physician would like to switch a patient on 25 mg of HCTZ to the combination with the same blood pressure lowering effect, there is not a dose of the combination available to achieve that. In study EC403, 25 mg HCTZ lowered diastolic blood pressure by 3.6 mm Hg compared to placebo, and 4/12.5 lowered blood pressure by 6.5 mm Hg, so the combination causes almost double the effect. A-M said that they will have additional data on the effect of HCTZ alone and the combination in the same trial.

Low Dose for the Combination

Dr. Lipicky noted that the data from the factorial trial show that the doses of the combination are different from placebo, but they do not appear to be different from each other. He suggested that they further explore the low end of the dose range. A-M noted that in a previous meeting, we told them that we believe that 2 mg of candesartan gave a less than significant effect.
Dr. Lipicky acknowledged that one is using a crystal ball when choosing doses. He noted that some physicians prefer to start patients on low doses, where others prefer to start with a large dose. Additional information would not be an approvability issue, but would allow one to write more complete instructions for the use of the product.

Higher Dose for the Combination

Dr. Lipicky suggested that rather than studying 32 mg candesartan and 12.5 mg HCTZ, they perform a study with 32 mg candesartan and 25 mg HCTZ. He said that, assuming adequate results, they would then know something about the use of 32/25, and the study with their additional data would support the marketing of a 32/12.5 combination product.

Dr. Lipicky said that the current studies would support a 16/25 combination product.

Congestive Heart Failure

A-M asked if they could bring up a recent issue with their study, on the use of candesartan and Dr. Lipicky agreed. The Safety Committee has discussed stopping the study with the Executive Committee; the Safety Committee believes that there is a low probability of a favorable outcome for the study. The study has no prespecified stopping rules. A-M asked what they should do. Dr. Lipicky told them that they would need to make their own decision about the trial.

Conclusions:

- We recommended that A-M perform a standard food study with the highest strength of the combination product.
- We requested information to show that the kinetics of candesartan and HCTZ remain linear over the therapeutic range when combined.
- The extent of population exposure is sufficient.
- Assuming adequate results, the completed and on-going studies would support approval of 8/12.5, 16/12.5, and 16/25 mg combinations. If the firm conducts an additional study

on 32/25, it would support a 32/12.5 and a 32/25 combination product.

- Labeling will depend on the results of the clinical trials.
- The firm should decide what to do with the trial.

/S/

Signature, minutes preparer: _____
Kathleen F. Bongiovanni 7-16-97

/S/

Concurrence Chair: _____
Raymond Lipicky, M.D.

cc:
HFD-110
HFD-110/SFredd
HFD-110/KBongiovanni
HFD-110/SBenton
kb/7/3/97; 7/16/97.
R/D: AParekh/7/7/97; JHung/7/11/97; FZielinski/7/11/97; SCaras/7/15/97; NStockbridge/7/15/97.

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: **NDA 21093/000**
Stamp: **28-SEP-1999** Regulatory Due: **28-JUL-2000**
Applicant: **ASTRAZENECA**
725 CHESTERBROOK BLVD
WAYNE, PA 190875677

Priority: **4S** Org Code: **110**
Action Goal: District Goal: **29-MAY-2000**
Brand Name: **ATACAND HCT(CANDESARTAN CILEXETIL HCTZ)1**
Established Name:
Generic Name: **CANDESARTAN CILEXETIL HCTZ**
Dosage Form: **TAB (TABLET)**
Strength: **16/12.5 AND 32/12.5**

FDA Contacts:
E. FROMM (HFD-110) 301-594-5300 , Project Manager
J. PIECHOCKI (HFD-110) 301-594-5300 , Review Chemist
K. SRINIVASACHAR (HFD-110) 301-594-5376 , Team Leader

Overall Recommendation:

ACCEPTABLE on 22-JUN-2000 by M. EGAS (HFD-322) 301-594-0095
ACCEPTABLE on 03-NOV-1999 by M. EGAS (HFD-322) 301-594-0095

Establishment:
DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **01-NOV-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**
Responsibilities: **FINISHED DOSAGE STABILITY TESTER**

Establishment:
DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **22-JUN-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
Responsibilities: **FINISHED DOSAGE STABILITY TESTER**

Establishment: **9615999**
ASTRA PRODUCTION TABLETS AB
SODERTALJE, , SW
DMF No:
AADA No:

Profile: **TCM** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Responsibilities: **FINISHED DOSAGE MANUFACTURER**

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

FINISHED DOSAGE STABILITY TESTER

Milestone Date: **02-NOV-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment:

DMF No:
AADA No:

Profile: **TCM** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **01-NOV-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **FINISHED DOSAGE PACKAGER**

Establishment:

DMF No:
AADA No:

Profile: **TCM** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **01-NOV-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **FINISHED DOSAGE PACKAGER**

Establishment:

DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **01-NOV-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

Establishment: **9610307**
TAKEDA CHEMICAL INDUSTRIES L

HIKARI, YAMAGUCHI, JA

DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**

Responsibilities: **DRUG SUBSTANCE**

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

MANUFACTURER

Last Milestone: **OC RECOMMENDATION**
Milestone Date: **01-NOV-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 21093/000
Stamp: 28-SEP-1999
Regulatory Due: 28-JUL-2000
Applicant: ASTRAZENECA
725 CHESTERBROOK BLVD
WAYNE, PA 190875677
Priority: 4S
Org Code: 110

Action Goal:
District Goal: 29-MAY-2000
Brand Name: ATACAND HCT(CANDESARTAN CILEXETIL HCTZ)1
Estab. Name:
Generic Name: CANDESARTAN CILEXETIL HCTZ

Dosage Form: (TABLET)
Strength: 16/12.5 AND 32/12.5

Application Comment: FIRST TIME INSPECTION FOR THIS PRODUCT (on 29-OCT-1999 by J. PIECHOCKI (HFD-110) 301-594-5300)
SATABILITY TESTING FACILITY (on 19-JUN-2000 by J. PIECHOCKI (HFD-110) 301-594-5300)

FDA Contacts: E. FROMM (HFD-110) 301-594-5300 , Project Manager
J. PIECHOCKI (HFD-110) 301-594-5300 , Review Chemist
K. SRINIVASACHAR (HFD-110) 301-594-5376 , Team Leader

Overall Recommendation: ACCEPTABLE on 22-JUN-2000 by M. EGAS (HFD-322) 301-594-0095
ACCEPTABLE on 03-NOV-1999 by M. EGAS (HFD-322) 301-594-0095

Establishment:

DMF No: AADA:
Responsibilities: FINISHED DOSAGE STABILITY TESTER
Profile: CTL OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	29-OCT-1999				PIECHOCKI
OC RECOMMENDATION	01-NOV-1999			ACCEPTABLE BASED ON PROFILE	EGASM

Establishment:

DMF No: AADA:
Responsibilities: FINISHED DOSAGE STABILITY TESTER
Profile: CTL OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	19-JUN-2000				PIECHOCKI
SUBMITTED TO DO	19-JUN-2000	GMP			EGASM
DO RECOMMENDATION	22-JUN-2000			ACCEPTABLE BASED ON FILE REVIEW	EGASM
SHOULD HAVE BEEN SUBMITTED WITH THE REST OF THE EER IN 10/99, SITE WOULD HAVE BEEN AC THEN.					
OC RECOMMENDATION	22-JUN-2000			ACCEPTABLE DISTRICT RECOMMENDATION	EGASM

Establishment: 9615999
ASTRA PRODUCTION TABLETS AB
SODERTALJE, , SW

DMF No: AADA:
Responsibilities: FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE STABILITY TESTER

Profile: TCM OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	29-OCT-1999				PIECHOCKI
SUBMITTED TO DO	01-NOV-1999	GMP			EGASM
DO RECOMMENDATION	02-NOV-1999			ACCEPTABLE BASED ON FILE REVIEW	EGASM
BASED ON EI OF 11/97					
OC RECOMMENDATION	02-NOV-1999			ACCEPTABLE DISTRICT RECOMMENDATION	FERGUSONS

Establishment:

DMF No: AADA:
Responsibilities: FINISHED DOSAGE PACKAGER
Profile: TCM OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	29-OCT-1999				PIECHOCKI
OC RECOMMENDATION	01-NOV-1999			ACCEPTABLE BASED ON PROFILE	EGASM

Establishment:

DMF No: AADA:
Responsibilities: FINISHED DOSAGE PACKAGER
Profile: TCM OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	29-OCT-1999				PIECHOCKI
OC RECOMMENDATION	01-NOV-1999			ACCEPTABLE BASED ON PROFILE	EGASM

Establishment:

DMF No: AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
Profile: CSN OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	29-OCT-1999				PIECHOCKI
OC RECOMMENDATION	01-NOV-1999			ACCEPTABLE BASED ON PROFILE	EGASM

Establishment: 9610307
TAKEDA CHEMICAL INDUSTRIES LTD
HIKARI, YAMAGUCHI, JA

DMF No: AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
Profile: CSN OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	29-OCT-1999				PIECHOCKI
OC RECOMMENDATION	01-NOV-1999			ACCEPTABLE BASED ON PROFILE	EGASM

Methods Validation

As of July 10, 2000, the Methods Validation is pending.

CSO Filing Review

Application:	NDA 21-093 Atacand HCT (candesartan cilexetil/hydrochlorothiazide) 16/12.5 and 32/12.5 mg Tablets
Applicant:	AstraZeneca LP
Application Date:	September 28, 1999
Receipt Date:	September 28, 1999
Primary Goal Date:	July 28, 2000
Secondary Goal Date:	September 28, 2000

Background

AstraZeneca has submitted this NDA for the combination product candesartan/HCTZ for the treatment of hypertension. Candesartan monotherapy was approved for the treatment of hypertension under NDA 20-838 on June 4, 1998. Studies for the combination for the treatment of hypertension were performed under

Meetings

End-of Phase 2: June 30, 1997.

Reviewers:

Chemistry:	Joe Piechocki, Ph.D.
Biopharm:	Hong Zhao, Ph.D., Raman Baweja, Ph.D.
Pharmacology:	Anthony Proakis, Ph.D.
Statistics:	Kooros Mahjoob, Ph.D.
Clinical:	Stephen Fredd, M.D.

Review

This NDA was submitted on paper; in addition, the firm has provided one set of (CRTs) Case Report Tabulations and (CRFs) Case Report Forms in electronic format. A copy of the CRFs has been given to Dr. Fredd.

The sponsor has submitted a Debarment Certification and Financial Interests and Arrangements of Clinical Investigators Certification.

The index to the NDA is inadequate. The volume numbering system starts with volume 1 at the beginning of each section, making it incompatible with the FDA Document Room numbering system.

There are eleven controlled trials that support efficacy for this NDA:

4 Group I trials (Studies AM153, EC408, AM124 and SH-AHK-0004) are the primary adequate and well-controlled trials that support the efficacy of Candesartan/HCTZ in the treatment of essential hypertension. These trials were all multicenter, randomized, double-blind, parallel-group, placebo-controlled trials of candesartan and HCTZ, alone and in combination, for 8 to 12 weeks in patients with essential hypertension.

7 Group II-Supportive Controlled Trials (Studies SH-AHK-0011, EC016, SH-AHK-0012, SH-AHK-0006, EC407, AM117 and EC403). These trials include design features that excluded them from Group I. These features included entry criteria specifying particular subpopulations for study (non-responders to monotherapy, severely hypertensive patients), absence of a placebo control group, titration of study treatment (either forced or response-dependent), and absence of parallel component monotherapy groups.

Summary of Deficiencies

The index is inadequate. The applicant has submitted a revised index that is compatible with the FDA's numbering system.

Recommendation

Provided that the reviewers have not identified reasons for refusing to file, I recommend that the application be filed.

/S/

Edward Fromm
Consumer Safety Officer

cc: NDA 21-093
HFD-110
HFD-110/Fromm

Financial Certification

1.0 CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

In accordance with 21 CFR part 54, this section provides financial information for the four primary efficacy studies AM124, AM153, EC408, and SH-AHK-0004. No other studies in this NDA are considered by the sponsor to be covered studies as defined by 21 CFR § 54.2(e).

These studies were completed prior to February 2, 1999. This certification is subject to the revisions in the requirements for financial disclosure set forth by FDA at 63 Fed. Reg. 72171 (Dec. 31, 1998). Consequently, information was collected regarding financial interests described in 21 CFR §§ 54.2(a) compensation, 54.2(c) proprietary interests, and 54.2(b) non publicly traded equity interests. Through due diligence, it was determined that there were no disclosable financial interests, therefore, Form FDA 3454 is being provided along with the list of investigators for AM124, AM153, EC408 and SH-AHK-0004.

It should be noted that Form FDA 3454 as published does not reflect the changes implemented in the December 31, 1998 revision. Therefore, Form FDA 3454 has been modified to line out the reference to significant payments.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. ~~I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).~~ 63 Fed Reg. 72171 (Dec. 31, 1998)

Clinical Investigators		
	See attached	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Steven J. Miller, Ph.D.	Director, Regulatory Liaison
FIRM/ORGANIZATION: AstraZeneca LP	
SIGNATURE: Steven J. Miller	DATE: September 8, 1999

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FORM FDA 3454 (3/99)

Candesartan Cilexetil-HCTZ - NDA 21-093
Item 19: Other

Financial Disclosure/Certification Due Diligence

Product: ATACAND HCT™ (candesartan cilexetil-HCTZ)

Protocol/Study Number: AM124 **Sponsor: Astra Merck Inc.**

Site No.	Name of Investigator/ Subinvestigator	Name/Address of Institution
001	**Jeffrey Adelglass, MD** Julius Wolfram, MD Steven P. Peskind, MD Jane Bartlett, RNC, MSN John Brenner, DO Michael Adamo, DO	Dallas Clinical Research, Inc. 9 Medical Parkway, Suite 202 RHD Professional Plaza 4 Dallas, TX 75324
002	**Allen B. Adolphe, MD**	Not Applicable 3901 Georgia NE, Suite C4 Albuquerque, NM 87110
003	**Scott D. Bleser, DO**** **Richard J. Sievers, DO** Nayesh R. Patel, MD	Bellbrook Medical Center 4336 State Route 725 Bellbrook, OH 45305
042	**Robert E. Broker, MD** David C. Silkiner, MD Gretchen H. Johnson, MD Harry I. Geisberg, MD W. Travis Ellison, MD Newman W. Harter, MD Marshall Meadors, III, MD M. Glenn Abernathy, MD C. Don Bryant, MD Melanie Lee, NP W. John Henry, III, MD John M. Milas, MD	MedQuest 552-A Memorial Drive Ext. Greer, SC 29651
004	**Stephen R. Carlson, MD** Timothy L. Burke, MD Jay R. Knuths, MD	The Duluth Clinic 400 East Third Street Duluth, MN 55805
006	**Jerome D. Cohen, MD** Jamie Ostdiek, PAC Jane Finn, RN	St. Louis University Health Sciences Center 3525 Caroline Avenue St. Louis, MO 63104
040	**James L. Conrad, MD** David C. Moll, MD Richard T. Price, MD Nicola DeMarco, RN Nancy Feracco, RN	Trivalley Primary Care Pennridge Office 1301 N. Fifth Street Perkasie, PA 18944
007	**Robert Davidson, MD** Suhail Ahmad, MD	University of Washington Scribner Kidney Center 2150 N. 107th, Suite 160 Seattle, WA 98133
010	**D. Michael Elnicki, MD** Dawn Bell, PharmD	West Virginia University School of Medicine Section of General Internal Medicine Robert C. Byrd Health Science Center Morgantown, WV 26506-9160
009	**Michael D. Ezekowitz, MD, PhD** Ira Cohen, MD Helen Noel, MEd, RNP	VA Connecticut Health Care System Scientific Projects, Human Studies, Research 151 950 Campbell Avenue West Haven, CT 06516

Financial Disclosure/Certification Due Diligence

Product: ATACAND HCT™ (candesartan cilexetil-HCTZ)

Protocol/Study Number: AM124 **Sponsor: Astra Merck Inc.**

Site No.	Name of Investigator/ Subinvestigator	Name/Address of Institution
011	**John Flack, MD**** **Vardaman Buckalew, Jr, MD** Michael V. Rocco, MD Carla Yunis, MD, MPH Carlos M Ferrario. MD Serguei V. Novikov, MD Paula J. Hess, RN Judy Holbrook, LPN Mizpah Shepherd Lowell Hedquist	Wake Forest University Hypertension Center Bowman Gray School of Medicine Medical Center Boulevard Winston-Salem, NC 27157
041	**Arthur J. Green, MD** George A. Scharyj, MD Benigno Burton Bobon, MD James Wayne Roberts, MD Richard M. Harris, PA Alan Einstein, DO Veneda Tasson, BSN, RNC	The Crucible Group, Inc 2864 Thornridge Drive Atlanta, GA 30340.
012	**Edgardo Hernandez-Lopez, MD** Luis F. Rodriquez-Ospina, MD Ruben D. Abreu, MD Jose Escabi-Mendoza, MD	Department of Veterans Affairs VA Medical Center One Veterans Plaza San Juan, PR 00927-5800
013	**Charles Huh, MD**** **W. Thomas Garland, MD** Jeffrey Kalades, MD	Lawrence Clinical Research 3100 Princeton Pike Building 1, 3rd Floor Lawrenceville, NJ 08648
014	**Dearing W. Johns, MD** Christopher M. Rembold, MD Carlos R. Ayers, MD Dennis L. DeSilvey, MD	University of Virginia School of Medicine Cardiovascular Division Box 146, UVA Health Sciences Center Charlottesville, VA 22908
015	**Mark S. Kipr.es, MD** Sherwyn Schwartz, MD Jerome Fischer, MD Beverly Orsak, RN Jan Roman, RN Wilhelm Muller, PA Lillian Tilles, NP Chuck Hunt, NP	Diabetes and Glandular Disease Clinic, P.A. 8042 Wurzbach, Suite 420 San Antonio, TX 78229
016	**Stephanie Ladson-Wofford, MD** Sundeep Dillon, MD	Ohio State University Medical Center Division of Nephrology 2-North Means Hall 1654 Upham Drive Columbus, OH 43210-1228
037	**Kenneth C. Lasseter, MD**	Clinical Pharmacology Associates 2060 NW 22nd Avenue Miami, FL 33142
017	**Jon H. Levine, MD** Cameron Shearer, MD	Clinical Research Associates 2222 State Street, Suite D

Financial Disclosure/Certification Due Diligence

Product: ATACAND HCT™ (candesartan cilexetil-HCTZ)

Protocol/Study Number: AM124 **Sponsor: Astra Merck Inc.**

Site No.	Name of Investigator/ Subinvestigator	Name/Address of Institution
	Stephan C. Sharp, MD Richard D. Pinson, MD Linda Moore. Schipani, RN, MSN Roz McGuire, RN Carol Madison, RN	Nashville, TN 37203
018	**Barry M. Massie, MD** Ibrahim Abdalla, MD Nancy Brana, RN, NP Susan Ammon, RN Elaine M. Der, RN, NP	VA Medical Center Cardiology Department (111C) 4150 Clement Street San Francisco, CA 94121
019	**R. Eric McAllister, MD, PhD**	Ukiah Valley Medical Center 230-A Hospital Drive Ukiah, CA 95482
020	**William E. Miller, MD** Deborah A. Maichle, RN, MSN, CS	Medical Center of Delaware 501 W. 14th Street Wilmington, DE 19801
021	**Rafael Montoro, MD** Leonardo V. Lopez, MD	Clinical Therapeutics Corporation 470 Baltimore Way PO Box 144192 Coral Gables, FL 33114
036A	**Joel M. Neutel, MD** Deanna Cheung, MD David Abrahamson, MD	Orange County Research Center 1310 W. Stewart Drive, Suite 212 Orange, CA 92668
036B	**David H. Smith, MD** Deanna Cheung, MD David Abrahamson, MD	Memorial Research Medical Clinic 2865 Atlantic Avenue, Suite 227 Long Beach, CA 90806-1711
022	**John E. Pappas, MD** Larry Burns, MD Joseph Gerhardstein, MD William Burkhart, MD Robert Burkhart, MD Barry Schumer, MD Terrence O'Neil, MD Akintokuno Owoeye, MD Sonya Caldwell, PA Julie McGinnis, PA Elizabeth Jones, PA Ralph Caldroney, MD Charles Johnson, DO	Central Kentucky Research Associates, Inc. 2366 Nicholasville Road, Suite 602 Lexington, KY 40503
023	**Richard A. Preston, MD**	Miami VA Medical Center Chief Hypertension Clinic 1201 NW 16th Street Miami, FL 33125
024	**Max Reif, MD** John H. Galla, MD	University of Cincinnati Medical Center Hypertension Section

Financial Disclosure/Certification Due Diligence

Product: ATACAND HCT™ (candesartan cilexetil-HCTZ)

Protocol/Study Number: AM124 **Sponsor: Astra Merck Inc.**

Site No.	Name of Investigator/ Subinvestigator	Name/Address of Institution
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026	**Gary Sander, MD, PhD** Ali Amkieh, MD R. Dean Yount, MD Thomas D. Giles, MD	LSUMC Section of Cardiology 1542 Tulane Avenue, Room 437 New Orelans, LA 70112
027	**Bruce Spinowitz, MD** Chaim Charytan, MD	Nephrology Associates, P.C. 56-45 Main Street Flushing-Queens, NY 11355
028	**William Edward Strauss, MD** Richard P. Shannon, MD Michelle McGillivray, MSN Pat Owen, NP	West Roxbury VA Medical Center 1400 VFW Parkway West Roxbury, MA 02132
029	**Harry J. Ward, MD** Ronald Fong, MD M. Edwina Barnett, MD, PhD	King/Drew Medical Center Division of Nephrology and Hypertension 12021 S. Wilmington Avenue Los Angeles, CA 90059
030	**Mervyn Weerasinghe, MD** Shelly Kafka, MD Patricia Larrabee, RN, NP Sandra VanCamp, RN, NP Lydia St. Hilaire, RN Donna Sorokti, MA	Rochester Clinical Research 500 Helendale Road, Suite 180 Rochester, NY 14609
031	**Matthew R. Weir, MD** Iris Keys, MD Janice James, RN Sue Hall, RN Deanna Wright, LPN Ashley Saunders, BA Nancy Frazier, RN Dale Toce, MD Elijah Saunders, MD Todd Crocenzi, MD Barbara Jean Shaneman, LPN Susan Yi, CRNP Towanda Maker, RN John Belperiio, MD	University of Maryland Hospital Nephrology Division 22 South Green Street, Room N3W143 Baltimore, MD 21201-1595
032	**Jeffrey W. Work, MD** Marc Ehrich, MD Benjamin Simon, MD Ronald Danzig, MD Harris Schoenfeld, MD	Cardiology Consultants Medical Group of the Valley, Inc. 18370 Burbank Boulevard, Suite 707 Tarzana, CA 91356
033	**Steven A. Yarows, MD** David K. Vallance, MD Yun-Ching Chen, MD	Not Applicable 128 Van Buren Chelsea, MI 48118

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Product: ATACAND HCT™ (candesartan cilexetil-HCTZ)

Protocol/Study Number: AM124 **Sponsor: Astra Merck Inc.**

Site No.	Name of Investigator/ Subinvestigator	Name/Address of Institution
	Judy L. Williams, LPN Karen S. Cummings, PAC	
034	**Christen A. Zuschke, MD** Michael L. Sternberg, MD Barbara C. Mitchell, MD T. Phillip Bell, MD Marilyn Williamson, RN	University of South Alabama Department of Emergency Medicine Division of Clinical Research 3401 Medical Park Drive #3, Suite 107 Mobile, AL 36693
035	**Randall M. Zusman, MD** Beverly Buczynski, RN	Massachusetts General Hospital 15 Parkman Street, #482 Boston, MA 02114

* This site was shipped study medication but did not enroll any patients.
** Investigator left site and signed over responsibilities to second investigator listed.
Investigators are in bold print, Subinvestigators are in regular print

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Product: Atacand HCT™ (candesartan cilexetil-HCTZ)

Protocol/Study No: 153 **Sponsor: Astra Merck Inc.**

Site No.	Name of Investigator/ Subinvestigator	Name/Address of Institution
001	**Maurice Archuleta, MD**	Rocky Mountain Clinical Research
001	Debra Ann Friesen, MD	Rocky Mountain Clinical Research
001	Gail Danhaur, RN	Rocky Mountain Clinical Research
001	Pam Deak, RN	Rocky Mountain Clinical Research
002	**Robert Bettis, MD**	Edmonds Family Medicine Clinic
002	Paul Bagnulo, MD	Edmonds Family Medicine Clinic
002	Teresa Hildebrand, MD	Edmonds Family Medicine Clinic
002	Victoria Fields-Vocelka, Pa	Edmonds Family Medicine Clinic
002	Martin Proudfoot, MD	Edmonds Family Medicine Clinic
002	Robin Colbath, ARNP	Edmonds Family Medicine Clinic
002	Martha Bennet, MD	Edmonds Family Medicine Clinic
002	Roger Olsson, MD	Edmonds Family Medicine Clinic
002	Zohreh Safai, MD	Edmonds Family Medicine Clinic
002	Laura Lippman, MD	Edmonds Family Medicine Clinic
002	Mark Hanson, MD	Edmonds Family Medicine Clinic
002	Jeffrey Schlameus, MD	Edmonds Family Medicine Clinic
002	Daniel Weakly, MD	Edmonds Family Medicine Clinic
002	Karol Davis, MD	Edmonds Family Medicine Clinic
002	Sandra Goss, MD	Edmonds Family Medicine Clinic
002	Joseph Petrin, MD	Edmonds Family Medicine Clinic
002	Kathryn Upton, MD	Edmonds Family Medicine Clinic
002	Mary Tolberg, MD	Edmonds Family Medicine Clinic
002	Ross Carey, MD	Edmonds Family Medicine Clinic
002	Donald Moe, MD	Edmonds Family Medicine Clinic
002	Sandra Borg, MD	Edmonds Family Medicine Clinic
002	Suzanne Quistgaard, MD	Edmonds Family Medicine Clinic
002	Rocky Mazzeo,MD	Edmonds Family Medicine Clinic
003	**Neville Bittar, MD**	Gemini Scientific
003	Margaret Spatola, CCRC	Gemini Scientific
004	**Kenneth Blaze, DO**	Sheridan Health Corp.
004	Jonathan Jaffee, MD	Sheridan Health Corp.
004	Anne Gordon, PA	Sheridan Health Corp.
004	Darlene Stevens, ARNP	Sheridan Health Corp.
005	**Robert E. Broker, MD**	MedQuest Centers for Research
005	David C. Silkiner, MD	MedQuest Centers for Research
005	Gretchen H. Johnson, MD	MedQuest Centers for Research
005	Katherine T. Lewis, MD	MedQuest Centers for Research
005	Francis E. Heidt,MD	MedQuest Centers for Research
006	**Lance D. Dworkin, MD**	Rhode Island Hospital
006	Diane Mignano, RN	Rhode Island Hospital
006	Douglas G. Shemin, MD	Rhode Island Hospital
006	Elias Kanaan, MD	Rhode Island Hospital
006	Michael J. Mahler, MD	Rhode Island Hospital
007	**Chester L. Fisher, Jr. MD, MPh**	Tidewater Physicians Multispecialty Group
007	Elizabeth Hollingsworth, PhD	Tidewater Physicians Multispecialty Group
007	Robert E. Caven, MD	Tidewater Physicians Multispecialty Group

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Protocol/Study No: 153 **Sponsor: Astra Merck Inc.**

Site No.	Name of Investigator/ Subinvestigator	Name/Address of Institution
008	**Dan Henry, MD**	Foothill Family Clinic
008	Bruce Callister, PAC	Foothill Family Clinic
008	Peter Chapa, PAC	Foothill Family Clinic
008	Shane Christensen, MD	Foothill Family Clinic
008	Susan Edwards, MD	Foothill Family Clinic
008	Jack Taylor, MD	Foothill Family Clinic
008	Deeborah Gobelman, PAC	Foothill Family Clinic
008	Jamie Longe, MD	Foothill Family Clinic
008	Donna Mason-Thompson, FNP	Foothill Family Clinic
008	Sharon Strong, MD	Foothill Family Clinic
008	Stephen Wood, MD	Foothill Family Clinic
009	**Robert Holloway, MD**	InSite Clinical Trials, LLC
009	Leslie K. Ross, PA-C	InSite Clinical Trials, LLC
009	Ratna Kanummury, PA-C	InSite Clinical Trials, LLC
009	Jan King, RN	InSite Clinical Trials, LLC
010	**John Holmes, MD**	Heart of America Research
011	**Laurence Horowitz, MD**	University of Colorado
011	Eli A. Rosenthal, MD	University of Colorado
011	Mary Ann St. John, RN	University of Colorado
011	Dianne Wolf, RN	University of Colorado
011	Lois Clegg, RN	University of Colorado
012	**Mark Jabro, MD**	Sharp Rees-Stealy Medical Group
012	Dr. James Morgan	Sharp Rees-Stealy Medical Group
012	Dr. Steve Green	Sharp Rees-Stealy Medical Group
012	Dr. Anthony Sacks	Sharp Rees-Stealy Medical Group
012	Dr. Leo Toupin	Sharp Rees-Stealy Medical Group
012	Dr. Alicia Benjamin	Sharp Rees-Stealy Medical Group
012	Dr. Cyril Light	Sharp Rees-Stealy Medical Group
012	Diana Jacquez	Sharp Rees-Stealy Medical Group
013	**Carl Johnson, MD**	Baptist Health Center, Fair Park
013	Lee Walker, MD	Baptist Health Center, Fair Park
014	**Bobby Quentin Lanier, MD**	Lanier Education And Research Network
014	Peter J. Damico, MD	Lanier Education And Research Network
015	**Jon H. Levine, MD**	Clinical Research Associates, Inc.
015	Richard D. Pinson, MD	Clinical Research Associates, Inc.
015	Stephan C. Sharp, MD	Clinical Research Associates, Inc.
015	Cameron Shearer, MD	Clinical Research Associates, Inc.
015	Linda Moors Schipani, Rn, MSN	Clinical Research Associates, Inc.
015	Rosalyn E. McGuire, RN	Clinical Research Associates, Inc.
015	Eileer. Lawrence, RN	Clinical Research Associates, Inc.
015	Dawn Benefield, RN	Clinical Research Associates, Inc.
015	Karen Wilson, RN	Clinical Research Associates, Inc.
016	**James H. Mersey, MD**	Mersey Clinical Research, Inc.
016	James A. Dicke, MD	Mersey Clinical Research, Inc.
016	Joanna B. Tyzack, MD	Mersey Clinical Research, Inc.
017	**Donald W. Middleton, Jr., MD**	Clinical Studies, New Bedford
017	Phyllis J. Troia, MD	Clinical Studies, New Bedford

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Site No.	Name of Investigator/ Subinvestigator	Name/Address of Institution
017	Carole Means, RN	Clinical Studies, New Bedford
017	Janice Munroe	Clinical Studies, New Bedford
017	Linda Smith	Clinical Studies, New Bedford
017	Michele Ketchum	Clinical Studies, New Bedford
018	**Vincent Miscia**	Consultants in Cardiology
018	John T. Haas	Consultants in Cardiology
019	**William J. Mroczek, MD**	Clinical Research at the Cardiovascular Center
019	Jonathan Klein, MD	Clinical Research at the Cardiovascular Center
019	Laraine T. Field, MD	Clinical Research at the Cardiovascular Center
019	Farid Jalinous, MD	Clinical Research at the Cardiovascular Center
019	William B. Barham, MD	Clinical Research at the Cardiovascular Center
020	**Joel M. Neutel, MD**	Orange County Research Center
020	David HG Smith, MD	Orange County Research Center
020	Madonna Nicolai, RN, MN, CFNP	Orange County Research Center
021	**Vecihi Batuman**	Tulane University
021	Sanjay Shah, MMD	Tulane University
021	Jhon Guzman-Rivera MD	Tulane University
021	Brian Morares, MD	Tulane University
021	L. Lee Hamm, MD	Tulane University
021	Camie Kulivan, RN, BSN	Tulane University
021	Wendy Naquin, RN, BSN	Tulane University
022	**Vasilios Papademetriou, MD**	Georgetown Univerity Medical Center
022	Christopher Wilcox, MD, PhD	Georgetown Univerity Medical Center
025	**Max Reif, MD**	University of Cincinnati
025	John H. Galla, MD	University of Cincinnati
025	Vicki Carter, MSN, RN	University of Cincinnati
025	Maria Layne, MSN, RN	University of Cincinnati
026	**John Rubino, MD**	Raleigh Medical Group
026	James W. Jacobs, MD.	Raleigh Medical Group
026	Robert Hodges Bilbro, MD	Raleigh Medical Group
026	Charles Alan Eure, MD	Raleigh Medical Group
026	William M. Dunlap, MD	Raleigh Medical Group
026	Gerald Wayne Blake, MD	Raleigh Medical Group
026	Lisa Dejarnette, MD	Raleigh Medical Group
026	Martin Van Cleeff, MD	Raleigh Medical Group
026	Susan L. Crittenden, MD	Raleigh Medical Group
026	Gerald David Leve, MD	Raleigh Medical Group
026	Mina Levin, MD	Raleigh Medical Group
026	Scott C. Bilbro, MD	Raleigh Medical Group
026	Elizabeth Anne Campbell, MD	Raleigh Medical Group
027	**Douglas Schumacher, MD**	Hill Top Research, Ltd.
027	Gerald Lane, DO	Hill Top Research, Ltd.
027	Thomas Petryk, MD	Hill Top Research, Ltd.
027	Jeffrey Fisher, M.S., PA-C	Hill Top Research, Ltd.
028	**Charles J. Sigmund, Jr., Dr.**	St. Louis Center for Clinical Research
028	Horst Zekert, MD	St. Louis Center for Clinical Research
028	C.E. Hogan, MD	St. Louis Center for Clinical Research

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Site No.	Name of Investigator/ Subinvestigator	Name/Address of Institution
030	**Frank Snyder, MD**	Lovelace Scientific Research
030	Martin J. Conway, MD	Lovelace Scientific Research
030	Diana W. Koster, MD	Lovelace Scientific Research
030	Harriette Barber, CNP	Lovelace Scientific Research
031	**James Snyder, M.D.**	Southwest Medical Associates
031	Gail Donohou, APN-C	Southwest Medical Associates
031	Joan Rogers, RN	Southwest Medical Associates
031	Ruth Parr, RN	Southwest Medical Associates
031	Nancy Thacker, LPN	Southwest Medical Associates
032	**M. Scott Touger, M.D.**	Hill Top Research, Inc.
032	Charles B. Crow, III, M..D.	Hill Top Research, Inc.
032	Gordon T. Connor, M.D.	Hill Top Research, Inc.
032	Tilly Cross, RN	Hill Top Research, Inc.
032	Lynn Fridy, CCRC	Hill Top Research, Inc.
032	Rhonda Boone, RN	Hill Top Research, Inc.
033	**John J. Upchurch, M.D.**	UAB Clinic - Roebuck
033	Lyman W. Fritz, M.D.	UAB Clinic – Roebuck
033	Lisa D. Columbia, M.D.	UAB Clinic – Roebuck
033	Kay Welch, CCRC	UAB Clinic – Roebuck
033	Gail Wingo, RN, CCRC	UAB Clinic – Roebuck

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Protocol/Study No: EC408 **Sponsor: Takeda Euro R&D Centre**

Site No.	Name of Investigator	Site
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Protocol/Study No: EC408 **Sponsor: Takeda Euro R&D Centre**

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32	Dr. med. Holmer Drews	Langgstraße 22, 63075 Offenbach
33	Dr. med. Ingomar Naudts	Ludwig Erhard Platz 11, 63110 Dudenhofen
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35	Dr. med. H. P. Wendl	Bahnhofstraße 14, 76855 Annweiler
36	Dr. med. Wilgard Pohl	Industriestraße 52, 01129 Dresden
37	Dr. med. Andreas Preusche	Altenberger Straße 40, 01762 Schmiedeberg
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39	Dr. med. Klaus Colberg	Kurhausstraße 14, 23795 Bad Segeberg
40	Dipl. Med. Petra Walsinger	Bahnhofstraße 7, 12555 Berlin
41	Priv. Doz. Dr. med. Uwe Desaga	Mittelweg 123, 20148 Hamburg
42	Dr. med. Christa Link	Nobelstraße 50, 18059 Rostock
44	Dr. med. Henrik Sachs	Dörrenbachstraße 22a, 98528 Suhl
45	Dr. med. Heiner Loos	Ulmenallee 15-17, 16356 Ahrensfelde
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47	Dr. med. Ronald Raabe	Kniprodestraße 21, 10407 Berlin
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Protocol/Study No: EC408 **Sponsor: Takeda Euro R&D Centre**

Site No.	Name of Investigator	Site
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53	Dr. med. Andreas Schreckenberg	Hauptstraße 55, 28844 Weyhe
54	Dr. med. Jürgen Ebeling	Winterhuder Marktplatz 21, 22299 Hamburg
55	Dr. med. Stefan Reichelt	Turmstraße 56, 07381 Pößneck
56	Dr. med. Thomas Scholl	Bahnhofstraße 17, 24534 Neumünster

Prof. Dr. med. Heinz Letzel was the Coordinating Investigator

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Protocol/Study No: SH-AHK-0004 **Sponsor: Astra Hässle AB**

France

Site No.	Name of Investigator	Site
1	Dr. Jacques Tondut	Angers
2	Dr. Pierre Duchene	Feneu
3	Dr. Michel Lambert	Angers
4	Dr. P. Igigabel	Tierce
5	Dr. Jean-Charles Deletre	Cande
6	Dr. Christian Deleuze	Brissac-Quince
7	Dr. Michel Behar	Longpont-Sur-Orge
8	Dr. Alain Bolo	Paris
9	Dr. Daniel Delbecq	Paris
10	Dr. Jëan-Marie Halmenschlager	Paris
11	Dr. Denis Smila	Yerres
12	Dr. Christian Coperc	Roanne
13	Dr. Marc Fleury	Roanne
14	Dr. Paul-Louis Jacquier	Commelle Vernay
15	Dr. Joël Richard	Creumeaux
16	Dr. Daniel Varona	Boen-Sur-Lignon
17	Dr. Michel Chelly	Ablon-Sur-Seine

Professor Albert Mimran, Médecine Interne et Hypertension artérielle, Hôpital Lapeyronie, 371, av. Du doyen Giraud, 34295 Montpellier cedex 5 was the Coordinating investigator for France.

Poland

Site No.	Name of Investigator/Sub-Investigator	Site
21	**Dr. Andrzej Wiecek** Dr. Joanna Witkowicz-Kulhawik Dr. Michal Nowicki	Katowice
23	**Dr. Halina Adamska-Dyniewska** Dr. Julitta Chojnowksa Jezierska Dr. Bozenna Gajewska Dr. Grzegprz Zabielski Dr. Bala Tadeusz Dr. Zbignia Pieloch Dr. Stanislaw Dziekarski	Lódz
24	**Dr. Ryszard Kwiecinski** Dr. Grazyna Bogdanowicz Dr. Henryk Zygadlo	Opole
25	**Dr. Grazyna Rzepecka** Dr. Mariola Rabsztyn-Lebensztejn Dr. Witold Nizinski Dr. Janusz Kobiela	Sosnowiec
26	**Dr. Marek Skura** Dr. Katarzyna Zach	Tarnów
27	**Dr. Krzysztof Wrabec** Dr. Tamara Parczewska Dr. Elzbieta Nowak Dr. Jerzy Lewczuk Dr. Wieslawa Sawa	Wroclaw

Professor Andrzej Wiecek, Dept. of Nephrology, Silesian School of Medicine, ul. Francuska 20, 40-027 Katowice was the Coordinating investigator for Poland.

Hungary

Site No.	Name of Investigator/Sub-Investigator	Site
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42	**Dr. Anikó Somogyi** Dr. Péter Pusztai Dr. Szanett Mólnar	Budapest
43	**Dr. Kornél Simon** Dr. Tibor Túri	Szekésfehérvar
44	**Dr. Klára Sándori** Dr. Eva Simon Dr. Judit Bakay Dr. Boatrix Papp	Sopron
45	**Dr. Peter Vályi** Dr. Mária Krizmanich Dr. József Németh	Csoma
46	**Dr. Istvan Czuriga** Dr. Zoltán Bedó	Debrecen
47	**Dr. György Abraham**	Szeged
48	**Dr. Miklós Csanádi** Dr. Attíla Thury	Szeged
49	**Dr. Miklós Hódi** Dr. László Sághy Dr. Iren Kiss	Szeged
50	**Dr. Sándor Timár** Dr. Attila Kiss Dr. Mónika Boskó Dr. Ervin Parkas	Kecskemét
51	**Dr. Béla Ózе** Dr. Lászlo Kássa Dr. Árpád Szoboszlay	Cegléd

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Czech Republic

Site No.	Name of Investigator/Sub-Investigator	Site
61	**Dr. Renata Cífková** Dr. Véra Adámková Dr. Marie Jozifková Dr. Helena Pistulková	Praha
62	**Dr. Miroslav Soucek** Dr. Ivan Rihácek Dr. Jaroslav Julinek Milos Stefja	Brno
63	**Dr. Otto Mayer** Dr. Hana Polivková	Plzen

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