- Lot number, expiration and lot size for each formulation used in all studies
- Raw data along with summary study results for all PK studies
- Dissolution studies with proposed methods and specifications for aliskiren
- Study results for any clinical study that conducted PK should also be submitted to section 6 of the NDA

Dr. Velazquez stated that studies 03HTN, CRD08, and CRD09 should be submitted to section 6 since it looks like PK was performed. The sponsor stated that these studies were performed with a Speedel formulation, and that they were not going to be utilized to make any product claims. So they will not be submitting these studies. The Division agreed.

The sponsor confirmed that the food-effect study has not been performed because they were waiting on the selection and decision of the final "to be marketed" formulation. They said they will be initiating that study shortly.

The sponsor also confirmed that they have not initiated their proposed study in the elderly population, and they had some additional drug-drug interactions studies they were planning on conducting in accordance with Table 3 of page 6 of their meeting package.

There was a discussion regarding the dissolution studies that would be required based on the SUPAC IR Guidance. Novartis agreed that studies 1201, 2203, 2204 and 2308 listed in the meeting package were the pivotal studies that they planned to submit to support approval. Dr. Velazquez noted that the film-coat and some of the other ingredients varied between the formulations used in these studies. In addition, the tablets for some of the studies were placed into capsules and others into capsules with fillers. Novartis explained the tablets were placed into capsules for blinding purposes and that it did not affect the dissolution. Novartis stated that they have looked at the formulation specifications very closely, and they believe that they fall within either a Level I or Level II SUPAC classification. The Division and Novartis both agreed to re-evaluate the compositions of the formulations used to determine what SUPAC level change they fall under for both the "blinded" and the other formulations used in order to determine what studies would be required per the SUPAC IR Guidance. If the data show that there is a Level III change, a bioequivalence study would be required along with dissolution studies.

Clinical

Dr. Marciniak noted that the PK data for aliskiren are highly variable between and within individuals, and there have been two strokes reported in young individuals. We are concerned that there could be a link between the high variability and the risk for stroke. We recommend that Novartis look at the effect over the entire dosing intervals using ambulatory blood pressure monitoring and the intra-individual variability preferably at the peak dose. Novartis explained that they would provide ABPM data describing intra-individual intervals but they would not have multiple measurements for individuals from day to day. Novartis stated that the intra-individual variability for their aliskiren formulation is lower than the formulation used in the studies conducted by Speedel. The Division recommended that Novartis summarize and submit these data with the NDA. Novartis agreed.

The Division recommended that Novartis look at the issues of rebound and sustained effect after long-term use. Novartis stated that they would have withdrawal data describing both of these issues.

Office of Drug Safety

Dr. Marciniak explained that the Office of Drug Safety (ODS), according to the latest PDUFA, is to be included in the Pre-NDA discussions for all new molecular entities. The Office for Drug Safety reviewed

the Pre-NDA meeting package and forwarded their comments and resource guidance to the Division for inclusion in the Pre-NDA meeting minutes. A copy of these comments were faxed to the sponsor immediately prior to the meeting (Novartis did not have an opportunity to review the fax prior to the meeting).

ODS comments and recommendations are a follows:

- If the sponsor and/or FDA believe that there are product risks that merit more than conventional professional product labeling (i.e. package insert (PI) or patient package insert (PPI)) and postmarketing surveillance to manage risks, then the Sponsor is encouraged to engage in further discussions with FDA about the nature of the risks and the potential need for a Risk Minimization Action Plan (RiskMAP).

- If the NDA/BLA application includes RiskMAPs or pharmacovigilance plans and will be submitted in the Common Technical Document format, please submit as follows:
  RiskMAPs
  2.5.5 Overview of Safety with appropriate cross references to section
  2.7.4 Summary of Clinical Safety
  and any other relevant sections of the Common Technical Document for the NDA/BLA application.
  Pharmacovigilance plans
  2.5.5 Overview of Safety, with any protocols for specific studies provided in 5.3.5.4 Other Clinical Study Reports or other sections as appropriate
  (e.g., module 4 if the study is a nonclinical study).

  If the application is not being submitted as a Common Technical Document, include proposed RiskMAPs in the
  NDA Clinical Data Section (21 CFR 314.50 (d)(5)) or
  BLA Clinical Data Section (21 CFR 601.25(b)(3))
  and clearly label and index them.

- For the most recent publicly available information on CDER's views on RiskMAPs, please refer to the following Guidance documents:

  Premarketing Risk Assessment: http://www.fda.gov/cder/guidance/6357fnl.htm

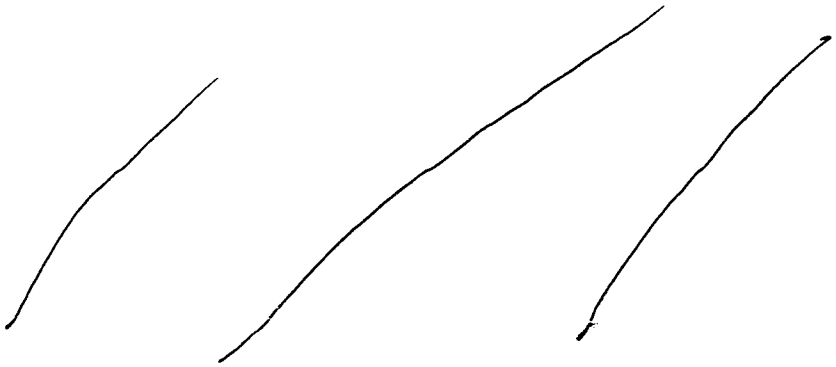
  Development and Use of Risk Minimization Action Plans:
  http://www.fda.gov/cder/guidance/6358fnl.htm>

  Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment:
  http://www.fda.gov/cder/guidance/6359OCC.htm

- If there is any information on product medication errors from the premarketing clinical experience, ODS requests that this information be submitted with the NDA/BLA application.

- The sponsor is encouraged to submit the proprietary name and all associated labels and labeling for review as soon as available.

5. **As previously stated, we currently expect to submit our original NDA in the first quarter of 2006. The dossier will include safety exposures consistent with what we agreed to at our end of phase 2 meeting.**



Additional Topic for Discussion

Conclusions/Recommendations

Novartis agreed to address and provide the data related to the biopharmaceutical issues discussed above.

Novartis and the Division agreed to reassess the dissolution requirements for the aliskiren formulations used to support approval in accordance with the SUPAC Guidance. Additional discussions between the Novartis and the Division would be arranged as needed.

Novartis plans to submit their NDA during the first quarter of 2006.

Meeting Recorder: *{See appended electronic signature page}*
Daryl Allis, R.N., M.S., F.N.P.

Concurrence Chair: *{See appended electronic signature page}*
Thomas Marciniak, M.D.

Draft	04/21/05	Final	04/26/05
RD:			
Gershon	04/25/05		
Velazquez	04/25/05		
Marciniak	04/25/05		

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Daryl L. Allis
4/26/05 09:00:26 AM
A copy of the minutes will be faxed to
the sponsor following Dr. Marciniak's signature.

Thomas Marciniak
4/26/05 10:01:19 AM

J

10 Page(s) Withheld

1 Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 62,976

Novartis Pharmaceuticals Corporation
Attention: Kimberly D. Dickerson, Pharm.D.
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Dickerson:

We refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Aliskiren (SSP-100) Capsules.

We acknowledge receipt of your September 22, 2004 request, serial number 059, on September 23, 2004, for a special carcinogenicity protocol assessment. The protocol title is "*26-week oral (dietary) carcinogenicity study in CB6F1 –rasH2 mice*". We are reviewing your submission and will respond in writing within 45 days of its receipt. If during the course of our review, you submit a revised version of this protocol, the original request will be considered withdrawn and the new submission considered a new request for special protocol assessment.

If you have any questions, please call:

Mr. Daryl Allis
Regulatory Health Project Manager
(301) 594-5332

Sincerely,

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Edward Fromm
9/29/04 10:08:06 AM

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION

US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

Transmitted to FAX Number:	973-781-3320
Attention:	**Ms. Catherine Ford**
Company Name:	Novartis Pharmaceuticals Corporation
Phone:	862-778-3378
Subject:	Minutes: Teleconference 9/22/04
Date:	September 28, 2004
Pages including this sheet:	6

From:	**Daryl Allis**
Phone:	**301-594-5309**
Fax:	**301-594-5495**
Email:	**allisd@cder.fda.gov**

You are responsible for notifying us of any significant differences in understanding that you may have regarding the meeting outcomes (as reflected in the minutes).

Please let me know you received this. Thank you.

Minutes of a Teleconference

Meeting Date:	September 22, 2004
Application:	IND 62,976
Drug:	Aliskiren (SPP 100) Tablets
Sponsor:	Novartis Pharmaceuticals Corporation
Type of Meeting:	B
Classification:	EOP 2: Chemistry
Meeting Request:	August 18, 2004
Sponsor Notified:	August 31, 2004 (Telephone)
Confirmation Faxed:	September 1, 2004
Briefing Package Date:	August 18, 2004
Meeting Chair:	Kasturi Srinivasachar, Ph.D.
Meeting Recorder:	Daryl Allis

Attendees:

Division of Cardio-Renal Drug Products

Kasturi Srinivasachar, Ph.D.	Team Leader, Chemistry, HFD-810
Javher Advani, Ph.D.	Chemist, HFD-810
Lydia Velazquez, Pharm.D.	Biopharmaceutist, HFD-860
Charles Resnick, Ph.D.	Team Leader, Pharmacology, HFD-110
Gowra Jagadeesh, Ph.D.	Pharmacologist, HFD-110
Daryl Allis, R.N., M.S., F.N.P.	Regulatory Health Project Manager, HFD-110

Novartis Pharmaceuticals Corporation

Catherine Ford	Global Regulatory CMC
Kimberly Dickerson, Pharm.D.	Drug Regulatory Affairs
Daniel Wasmuth, Ph.D.	Technical Research and Development
Stefan Hirsch, Ph.D.	Technical Research and Development

Background

Novartis Pharmaceuticals Corporation is developing Aliskiren (SPP 100), a renin inhibitor, for the once daily treatment of hypertension. Aliskiren is a potent and selective inhibitor of human renin, the enzyme responsible for the production of angiotensin I. Angiotensin I is converted by angiotensin converting enzyme (ACE) to angiotensin II, one of the most potent known vasoconstrictors. These effects on the renin-angiotensin system provide the pharmacologic rationale for renin inhibition in the treatment of hypertension. Novartis plans to develop film-coated tablet formulations containing 150 and 300-mg of Aliskiren.

Early studies in healthy volunteers and patients were conducted by Speedel Pharmaceuticals of Bridgewater, NJ. The ownership of IND # 62,976 was transferred to Novartis Pharmaceuticals Corporation effective September 1, 2002. Previous correspondence and meetings between the Division and sponsors include:

- Pre-IND meeting, November 8, 2000
- Pre-IND CMC meeting November 9, 2000

- EOP 2 meeting, February 11, 2004
- Special Protocol Assessment: Clinical response letter, June 3, 2004
- Special Protocol Assessment: Type A meeting, July 12, 2004

Novartis Pharmaceuticals Corporation requested this meeting to obtain Agency feedback on specific Chemistry, Manufacturing and Controls issues as recommended in the EOP 2 meeting on February 11, 2004.

Discussion Points

1. **Is the FDA satisfied that the Aliskiren drug substance intermediate — is not mutagenic and is properly controlled during our drug substance synthesis?**

   Dr. Resnick noted that — has been identified by Novartis as an — and, therefore, a suspect mutagen/carcinogen. If not for this identification, the presence of — would not be an issue for the Division, as levels in the drug substance are below the threshold for requiring qualification studies. Therefore, he agreed with the sponsor's approach to dealing with the issue, i.e., demonstrating that — is not mutagenic, rather than documenting levels in drug substance of no more than — (sponsor's current assay not sensitive enough to quantify levels this low). Novartis reported that an Ames test on the intermediate in question provided no evidence of mutagenic potential Dr. Resnick stated that for a negative Ames test alone to be considered sufficient evidence that the — in question is not a mutagen, the sponsor would need to provide documentation that virtually all — test positive in this bacterial mutagenicity assay. Furthermore, the Ames Test that is being cited as evidence of lack of mutagenic potential for — has not been fully reported to the Agency (only a brief summary provided) and that test has been described as having not being conducted in conformance with GLPs. In addition, problems with precipitation prevented the test from being carried out at doses as high as those usually achieved in this assay. In summary, the Agency is not satisfied that a lack of mutagenic potential has been demonstrated for — and the sponsor should reconsider the alternative approach of developing an assay sensitive enough to document levels in the drug substance that are low enough to satisfy the agency, whether or not — possesses mutagenic potential.

   Novartis asked whether the full Ames Test study report would provide the additional data that the FDA needs to determine if the carcinogenicity/mutagenicity concerns were resolved. Dr. Resnick stated that it was a possibility, provided that they could convince us that an Ames Test alone is sufficient for documenting the lack of mutagenic potential for an — Novartis agreed to submit the full study report, discuss these issues internally, and request additional conversations with the Division to determine if additional testing will be required.

2. **Does the FDA agree with the Novartis selection of drug substance starting materials?**

   Novartis has proposed — regulatory starting materials. Dr. Srinivasachar stated that — is the simplest and the most straight forward of the — The Division has some reservations about — The background briefing information indicated that there were no impurities listed for — and therefore no information on carry-over of impurities to the drug substance for this proposed starting material. Novartis stated that there is an — present and they would provide the appropriate specifications to include listing and quantifying the impurities. Dr. Srinivasachar noted that — would lead to a — impurity in the drug substance and asked whether Novartis expected the same amount in the drug substance. Novartis stated that the — has been qualified and is controlled at — The Division agreed that, at this point, this was acceptable but we would need to look at the data for all batches. Novartis agreed they would provide the additional data for all batches.

In summary, the proposed starting materials are acceptable to the Division even though

The Sponsor was asked to look at the proposed specifications for to ascertain whether these are comprehensive. Novartis would look at the suppliers and the routes of synthesis to ensure that all possible impurities are covered, and evaluate and tighten the specifications, as appropriate, prior to filing the NDA.

3. **Does the FDA agree that the drug dissolution data which are provided in Section 3.3.2 of the briefing book are adequate to support the minor change in tabled**

Dr. Velazquez noted that Novartis has defined the proposed changes as a SUPAC IR, Level 1 change in the components and composition for the tablets. The Division, however, believes the change in the would be a Level 2 change (change greater than 1.0% according to the guidance). Based on a level 2 change in components and composition, Novartis stated that they believe Aliskiren has low permeability and high solubility which would require Level 2, Category B dissolution. They asked whether the FDA agreed on their dissolution methods and specifications. Dr. Velazquez stated that there are two issues that require Agency assessment. One is determining whether Aliskiren is a low permeability and high solubility compound; which if correctly categorized would categorize them as a level 2 change. The second issue would be assessing the dissolution data submitted (to include raw data) to establish a dissolution method and specification. The Agency does not set dissolution methods and specifications prior to NDA approval. The sponsor should submit all their data supporting all the issues just discussed at NDA submission for assessment.

Novartis asked whether there were concerns related to the proposed changes. The Division stated there were no concerns.

Additional Discussion

Stability Testing

Novartis stated that they have started the stability studies on the low and high strengths of Aliskiren and they did not plan of submitting the data prior to the NDA. Dr. Srinivasachar stated that would be acceptable and a Special Protocol Assessment for Stability Protocols would not be necessary as long as the compound was not out of the ordinary and they followed the standard ICH and Agency guidelines. Novartis asked if they could provide a background briefing book and request a teleconference, if needed. The Division agreed.

Conclusions/Recommendations

The Division recommends that Novartis:

- Submit the full study report for the Ames test for our review and make a case for considering an Ames Test, by itself, as sufficient for determining the mutagenic/carcinogenic potential of an
- In lieu of the above, develop an assay sensitive enough to document levels of in the drug substance that are low enough to satisfy the agency that there is a negligible safety concern for
- Reassess the suppliers and the routes of synthesis of the proposed starting materials to ensure that all possible impurities are covered, and evaluate and tighten the specifications, as appropriate, prior to filing the NDA.

- Reassess the change [redacted] consider the proposed change as a Level 2 change, and submit the raw dissolution data for a Level 2, Category B change with the NDA.

- Request a teleconference to discuss the stability testing protocol, if needed

Signature Recorder: *{See appended electronic signature page}*
Daryl Allis, R.N., M.S., F.N.P.

Concurrence, Chair: *{See appended electronic signature page}*
Kasturi Srinivasachar, Ph.D.

Draft: **Final:** 09/28/04

RD:

Jagadeesh	09/24/04
Resnick	09/24/04
Velazquez	09/27/04
Advani	09/27/04
Srinivasachar	09/28/04

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Daryl L. Allis
9/28/04 12:50:39 PM
A copy of the minutes will be faxed to
the sponsor following Dr. Srinivasachar's final signature.

Kasturi Srinivasachar
9/28/04 01:05:18 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 62,976

Novartis Pharmaceuticals Corporation
Attention: Dr. Kimberly D. Dickerson
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Dickerson:

Please refer to your submission dated July 21, 2004, requesting a deferral of pediatric studies for Aliskiren (SPP-100) Tablets.

We have reviewed the submission and agree that a deferral of pediatric studies in patients <1 month to 16 years of age is justified for Aliskiren for the treatment of hypertension because additional safety and efficacy data need to be collected for this "first-in-class" drug product and the drug would be ready for approval in adults before studies in pediatric patients would be completed.

Accordingly, pediatric studies are deferred for your application under 21 CFR 314.55 until 2 years after the approval for use in adults.

If you have any questions, please call:

Mr. Daryl Allis
Regulatory Project Manager
301-594-5309

Sincerely

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Acting Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Norman Stockbridge
8/26/04 02:20:54 PM

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION

US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

Transmitted to FAX Number:	973-781-3590
Attention:	Kimberly Dickerson, Pharm.D.
Company Name:	Novarits Pharmaceuticals Corporation
Phone:	862-778-4576
Subject:	Teleconference Minutes
Date:	July 28, 2004
Pages including this sheet:	5

From:	**Daryl Allis**
Phone:	**301-594-5309**
Fax:	**301-594-5495**
Email:	**allisd@cder.fda.gov**

You are responsible for notifying us of any significant differences in understanding that you may have regarding the meeting outcomes (as reflected in the minutes).

Please let me know when you receive this. Thank you.

Minutes of Teleconference

Date of Meeting:	July 12, 2004
IND Application:	62,976
Drug:	Aliskiren (SPP-100) Tablets
Sponsor:	Norvartis Pharmaceuticals Corporation
Request Date:	June 24, 2004
Sponsor Notified:	June 25, 2004
Confirmation Date:	June 25, 2004 (fax)
Package Received:	July 1, 2004
Meeting Type:	A
Classification:	Special Protocol Response
Purpose:	Clarify the Division's responses to the Special Protocol Assessment
Meeting Chair:	Norman Stockbridge, M.D., Ph.D.
Meeting Recorder:	Daryl Allis

FDA Participants

Norman Stockbridge, M.D., Ph.D.	Acting Director, Division of Cardio-Renal Drug Products, HFD-110
Shari Targum, M.D.	Acting Team Leader, Medical Officer, HFD-110
Lydia Velazquez, Pharm.D.	Clinical Pharmacologist & Biopharmaceutist, HFD-860
James Hung, Ph.D.	Team Leader, Statistician, HFD-710
Daryl Allis, M.S., F.N.P.	Regulatory Health Project Manager, HFD-110

Novartis Participants

Adrian Birch	Executive Director, Drug Regulatory Affairs
Yann Tong Chiang, Ph.D.	Director, Biostatistics
Kimberly Dickerson, Pharm.D.	Assistant Director, Drug Regulatory Affairs
Martin Lefkowitz, M.D.	Executive Director, Clinical Research & Development
Catherine Schreiber, R.Ph., M.A.	Executive Director, Project Management
Sujata Vaidyanathan, Ph.D.	Sr. Lead Pharmacokineticist, Early Clinical Development
Steven Zelenkofske, D.O.	Director, Clinical Research and Development
Jin Zhu, Ph.D.	Associate Director, Biostatistics

Background

Novartis Pharmaceuticals Corporation (Novartis) is developing Aliskiren (SPP 100), an oral formulation renin inhibitor, for the indication of safe and effective once daily therapy for the treatment of hypertension, alone or in combination with other antihypertensive agents. Aliskiren is a potent and selective inhibitor of human renin, the enzyme responsible for the production of angiotensin I. Novartis submitted a request for Special Protocol Assessment on April 19, 2004 for their Phase 2 clinical protocol entitled "An 8 week double-blind, multicenter, randomized, multifactorial, placebo-controlled, parallel-group study to evaluate the efficacy and safety of aliskiren administered alone and in combination with hydrochlorothiazide in patients with essential hypertension." The Division provided a Written Response dated June 3, 2004. Novartis requested this Type A meeting to clarify further

62,976 Aliskiren
SPA T-con 7/12/04
issues related to persistence of antihypertensive effect, lack of rebound effect, and their plans to address the Division's recommendations regarding the statistical analysis plan, dose response and pharmacokinetics of aliskiren and hydrochlorothiazide.

Topics for Discussion

Persistence of Antihypertensive Effect and Lack of Rebound Effect
Novartis noted that the End-of-Phase 2 minutes stated that a randomized withdrawal would be descriptive for persistence effect, and the Division's Written Response to the Special Protocol Assessment stated that the persistence of antihypertensive effect must be documented as well as the lack of a rebound effect. Novartis asked whether a randomized withdrawal study would be required for registration. Dr. Stockbridge stated we need evidence that the drug is effective weeks after patients have been on the drug and the cleanest way to get this information is from a randomized withdrawal study following 6-12 months of therapy. Novartis asked if they could show the persistent effect by adding the randomized withdrawal to an open label safety study. The Division agreed.

Novartis indicated that if the randomized withdrawal would be required, they planned to perform ambulatory blood pressure monitoring (ABPM) 2 weeks after withdrawal of therapy in those patients who had 24-hour ABPM recorded at baseline and at least once during the core double blind active treatment phase of the study and cuff blood pressure recordings and adverse events would be evaluated at weeks 1, 2, and 4 following abrupt withdrawal. Dr. Stockbridge stated that we were not sure whether the ABPM needed to be measured or when it should be measured in addition to the cuff blood pressures. The Division agreed the cuff blood pressures at 1, 2, and 4 weeks as described above would be adequate.

Novartis noted that not all drugs have done randomized withdrawal studies and they asked if this was a "first in a class" issue. Dr. Stockbridge agreed that the "n^{th}" drug in a class might not have done randomized withdrawal studies and concurred that being "first drug in a class" carries additional responsibilities.

Statistical Analysis
The Division agreed to the proposed statistical plan. Dr. Hung confirmed that Novartis still planned to use ANCOVA for the primary analysis for aliskiren and hydrochlorothiazide. He suggested that if there is no treatment by treatment interaction, then the ANCOVA without the treatment by treatment interaction term is a better analysis. He recommended that if there is a suspicion of treatment by treatment interaction, they consider the average (AVE) test. He said that from his experience, this test seems more powerful than the maximum (MAX) test.

Dose Response
Dr. Stockbridge noted the Division had previously recommended that Novartis consider testing aliskiren at 600-mg or higher to adequately describe the dose response. Novartis stated that the dose response would be further characterized in an additional study as previously recommended by the Division. The Division agreed.

Pharmacokinetics
Novartis stated the pharmacokinetics (PK) of aliskiren and hydrochlorothiazide would be evaluated in other studies because of sampling handling difficulties (plasma samples have to be [redacted] prior to shipping). They believe their additional studies would fully characterize the PK rather than including sparse sampling in the proposed Phase 2 study. The Division agreed but suggested Novartis might consider collecting the PK sparse sampling at 1 or 2 sites that had the capabilities for proper sample handling as an alternative.

Conclusions/Recommendations

- Novartis agreed to conduct the randomized withdrawal study as discussed above.
- The Division recommends that ANCOVA should be used for testing the primary endpoints and the AVE test should be used if a large negative aliskiren-by-hydrochlorothiazide interaction is detected to assess the global assessment of combinations versus their respective monotherapies.

Meeting Recorder: *(See Appended Electronic Page)*
Daryl Allis, M.S., F.N.P.

Concurrence Chair: *(See Appended Electronic Page)*
Norman Stockbridge, M.D., Ph.D.

Draft	07/14/04	Final	07/27/04
RD:			
Hung	07/15/04		
Velazquez	07/23/04		
Targum	07/23/04		
Stockbridge	07/23/04		

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Daryl L. Allis
7/28/04 11:30:18 AM
A copy of the minutes will be faxed to
the sponsor after Dr. Stockbridge's final signature.

Norman Stockbridge
7/28/04 03:42:06 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 62,976

Novartis Pharmaceuticals Corporation
Attention: Kimberly D. Dickerson, Pharm.D.
Assistant Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Dickerson:

We refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for aliskiren (SPP-100) Tablets.

We also refer to your April 19, 2004, request, serial number 027, for a special clinical protocol assessment, received April 21, 2004. The protocol is entitled "An 8 week double-blind, multicenter, randomized, multifactorial, placebo-controlled, parallel-group study to evaluate the efficacy and safety of aliskiren alone and in combination with hydrochlorothiazide in patients with essential hypertension."

We have completed our review of your submission and, based on the information submitted, have the following responses to your questions.

Statistical:

1. For the analysis of the second primary objective (combination treatment), the proposed ANCOVA analysis seems to be reasonable if there is no large treatment by treatment interaction. The pattern of the interaction needs to be examined for the cells of nonzero dose combinations of the 4 by 4 factorial design, in addition to the test of the aliskiren-by-HCTZ interaction. If large treatment by treatment interactions are suspected, then some type of global assessment of dose combinations versus their respective components are needed (e.g. Hung, Chi & Lipisky, 1993, Biometrics). The protocol needs to propose an approach to global assessment.

2. You state that if the overall assessment of the combination treatment is positive, then the pairwise comparisons will be made by an ANCOVA model. The statistical test will be made at a 2-sided significance level of 0.05 for each comparison, and the combination dose is considered superior than monotherapy if the result is in favor of the combination. This is acceptable if these analyses are exploratory in nature. If you are seeking a claim for a specific dose, then a statistical approach needs to be proposed to control the total type I error rate at 0.05 level for all the pairwise comparisons involved.

In addition, we have the following comments.

Medical:

1. The dose range of aliskiren must be delineated. If bridging bioequivalence studies for the phase 2 study formulations are not done, then 600mg and possibly a higher dose should be included in the pivotal trials as recommended in the End-of Phase 2 (EOP2) meeting held on February 11, 2004.

2. The bioavailability of aliskiren is highly variable. The effects of this variability would be expected to be greater at peak than at trough. There have been reports of Serious Advent Events (SAEs) of hypotension in the clinical studies. The BP response must be characterized throughout the interdosing interval and should be correlated with drug levels.

3. Persistence of antihypertensive effect must be documented, as well as the lack of a rebound effect. This could be done through a randomized withdrawal following the primary endpoint determination in one of the trials as recommended at the EOP2 meeting.

Clinical Pharmacology & Biopharmaceutics

1. The protocol did not include pharmacokinetic (PK) and/or pharmacodynamic (PD) assessments. The interaction between aliskiren and hydrochlorothiazide could be evaluated in this study by using a sparse sampling approach.

2. In the presence of an adverse event, it is recommended that a blood sample for aliskiren assay be collected as close as possible to the occurrence of the adverse event.

If you wish to discuss our responses, you may request a meeting. Such a meeting will be categorized as a Type A meeting (refer to our "*Guidance for Industry; Formal Meetings With Sponsors and Applicants for PDUFA Products*"). Copies of the guidance are available through the Center for Drug Evaluation and Research from the Drug Information Branch, Division of Communications Management (HFD-210), 5600 Fishers Lane, Rockville, MD 20857, (301) 827-4573, or from the internet at http://www.fda.gov/cder/guidance/index.htm. This meeting would be limited to discussion of this protocol. If a revised protocol for special protocol assessment is submitted, it will constitute a new request under this program.

If you have any questions, please call:

Mr. Daryl Allis
Regulatory Health Project Manager
(301) 594-5309

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Acting Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Norman Stockbridge
6/3/04 08:18:44 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 62,976

Novartis Pharmaceuticals Corporation
Attention: Kimberly D. Dickerson, Pharm.D.
Assistant Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Dickerson:

We refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Aliskiren (SPP-100).

We acknowledge receipt of your May 18, 2004, request, serial number 033, on May 19, 2004, for a special clinical protocol assessment. The protocol is entitled "A randomized, double blind, multiple oral dose study to evaluate the effects of SPP100 on cardiac subject versus placebo with positive control (Avelox)."

Your submission does not qualify for special protocol assessment. The proposed protocol does not fit within the criteria for special protocol assessment because the data from the proposed trial would not relate to efficacy claims that would be part of an original new drug application.

We recommend that you refer to our "*Guidance for Industry: Special Protocol Assessment*" for information on the types of protocols that qualify for this program. Copies of the guidance are available through the Center for Drug Evaluation and Research from the Drug Information Branch, Division of Communications Management (HFD-210), 5600 Fishers Lane, Rockville, MD 20857, (301) 827-4573, or from the internet at http://www.fda.gov/cder/guidance/index.htm.

If you have any questions, please call

Mr. Daryl Allis
Regulatory Health Project Manager
(301) 594-5309

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Acting Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Norman Stockbridge
5/27/04 06:39:18 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 62,976

Novartis Pharmaceuticals Corporation
Attention: Kimberly D. Dickerson, Pharm D.
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Dickerson:

We refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Aliskiren (SPP-100) Tablets.

We acknowledge receipt of your April 19, 2004, request, serial number 027, on April 21, 2004, for a special clinical protocol assessment. The protocol title is "*An 8 week double-blind, multicenter, randomized, multifactorial, placebo-controlled, parallel-group study to evaluate the efficacy and safety of aliskiren administered alone and in combination with hydrochlorothiazide in patients with essential hypertension.*" We are reviewing your submission and will respond in writing within 45 days of its receipt. If during the course of our review, you submit a revised version of this protocol, the original request will be considered withdrawn and the new submission considered a new request for special protocol assessment.

If you have any questions, please call:

Mr. Daryl Allis
Regulatory Health Project Manager
(301) 594-5309

Sincerely,

{See appended electronic signature page}

Zelda McDonald
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Zelda McDonald
4/28/04 10:33:36 AM

Minutes of an End-of-Phase 2 Meeting

Date of Meeting:	February 11, 2004
IND Application:	62,976
Drug:	Aliskiren (SPP-100) Tablets
Sponsor:	Norvartis Pharmaceuticals Corporation
Request Date:	December 23, 2003
Sponsor Notified:	January 5, 2005 (telephone)
Confirmation Date:	January 6, 2004 (fax)
Package Received:	January 15, 2004
Meeting Type:	End-of-Phase 2
Classification:	B
Purpose:	Discuss the Phase 3 development plan to support approval
Meeting Chair:	Robert Temple, M.D.
Meeting Recorder:	Daryl Allis

FDA Participants

Robert Temple, M.D.	Director, Office for Drug Evaluation I
Douglas C. Throckmorton, M.D.	Director, Division of Cardio-Renal Drug Products, HFD-110
Thomas Marciniak, M.D.	Team Leader, Medical Officer, HFD-110
Karen Hicks, M.D.	Medical Officer, HFD-110
Patrick Marroum, Ph.D.	Team Leader, Clinical Pharmacologist, HFD-860
Angelica Dorantes, Ph.D.	Clinical Pharmacologist, HFD-860
James Hung, Ph.D.	Team Leader, Statistician, HFD-710
Charles Resnick, Ph.D.	Team Leader, Pharmacology, HDF-110
Kasturi Srinivasachar, Ph.D.	Team Leader, Chemistry, HFD-810
Daryl Allis, M.S., F.N.P.	Regulatory Health Project Manager, HFD-110

Novartis Participants

Martin Bedigian, M.D.	Director, Clinical Research & Development
Adrian Birch	Executive Director, Drug Regulatory Affairs
Yann Tong Chiang, Ph.D.	Director, Biostatistics
Kimberly Dickerson, Pharm.D.	Assistant Director, Drug Regulatory Affairs
Martin Lefkowitz, M.D.	Executive Director, Clinical Research & Development
Ian Michael Nicholls, B.Sc.	Registered Toxicologist, Toxicology/Preclinical Safety
Catherine Schreiber, R.Ph., M.A.	Executive Director, Project Management
Sujata Vaidyanathan, Ph.D.	Sr. Lead Pharmacokineticist, Early Clinical Development
Daniel Wasmuth	Chemical and analytical Development
Steven Zelenkofske, D.O.	Director, Clinical Research and Development

62,976 Aliskiren
EOP 2

Background

Novartis Pharmaceuticals Corporation is developing Aliskiren (SPP 100), an oral formulation renin inhibitor, for the indication of safe and effective once daily therapy for the treatment of hypertension, alone or in combination with other antihypertensive agents. Aliskiren is potent and selective inhibitor of human renin, the enzyme responsible for the production of angiotensin I. Angiotensin I is converted by angiotension converting enzyme (ACE) to angiotensin II, one of the most potent known vasoconstrictors. Blocking renin prevents the production of angiotension peptides by the renin-ACE pathway. Renin inhibitors block the renin-angiotensin system (RAS) at a higher level in the cascade than ACE inhibitors and have a different effect on the components of the RAS. After the administration of a renin inhibitor the formation of both angiotensin I and II is blocked, thereby preventing the formation of angiotensin peptides by ACE and non-ACE pathways. These effects on the RAS provide the pharmacologic rationale for renin inhibition in the treatment of hypertension. Novartis plans to develop a film-coated tablet formulation containing 150 and 300 mg, respectively.

Early studies in healthy volunteers and in patients conducted under IND 62,976 were done by Speedel Pharmaceuticals of Bridgewater, NJ. The ownership of the IND was transferred to Novartis Pharmaceuticals Corporation effective September 1, 2002. Previous meetings between the Division and Speedel Pharmaceuticals include:
Pre-IND meeting, November 8, 2000
Pre-IND CMC meeting November 9, 2000

Novartis Pharmaceuticals Corporation requested this meeting to obtain Agency feedback on the clinical development program to support approval of Aliskiren. They are seeking the Agency's acceptance of Phase III programs which would establish Aliskiren as an effective and safe antihypertensive agent:
As a monotherapy, and as a free-add on agent in combination with other antihypertensive agents

Topics for Discussion

Chemistry, Manufacturing and Controls
Dr. Srinivasachar noted that one of the intermediates in the manufacturing process contains a [redacted] He asked whether this was carried over to the drug substance. [redacted] are known genotoxic carcinogens; therefore, Novartis needs to develop an assay to measure residual amounts of the [redacted] in the drug substance to provide assurance that this compound is not present even in trace amounts (less than [redacted]

Renin Activity Suppression and Comparative Drugs
Dr. Temple noted that Aliskiren has a half-life of approximately 24 hours. He asked Novartis to explain why the plasma renin activity was not suppressed after 24 hours post administration. They stated that the initial dose did not suppress the renin activity for 24 hours but with repeated doses they found it was suppressed by day 8.

Dr. Temple stated that showing an additive effect to drugs acting on the renin-angiotension system (RAS) did not seem helpful unless it is shown at maximum doses of those drugs. Before including language on the use of this drug with other classes of drugs that affect the RAS (beta-blockers, ACE-inhibitors, ARBs), the sponsor will need to conduct studies comparing the effects of the combination of them with Aliskiren with the two monotherapies at maximum doses.

QT Effects
Novartis stated they have a negative signal for QT effects in their present studies. They, however, are planning to do a thorough, definitive QT study with a placebo and active control in healthy volunteers in accordance with the Guidance, and they will submit these data with the NDA. Dr. Throckmorton stated that if Novartis uses a positive control and the results are negative, they do not need to collect additional ECGs during the clinical trials for further QT evaluation.

Pediatric Studies
Novartis requested a deferral for pediatric studies

. Mr. Allis, Project Manager, will provide the sponsor with the appropriate regulatory pathway forward for granting a deferral for pediatric studies.

Preclinical study program

1. **Does FDA agree that the completed and planned preclinical study program is sufficient to support registration?**

Novartis will be starting a dose ranging study for a transgenic mouse carcinogenicity study next week and they will submit a Special (carcinogenicity) Protocol Assessment request when completed. The results of a 90-day dose range-finding study and a carcinogenicity study protocol for a two year study in rats went to the Executive Carcinogenicity Advisory Committee in May 2003.

The Agency agrees that the completed and planned preclinical study program would be sufficient to support registration.

Clinical pharmacology and pharmacokinetic study program

2. **Does FDA agree that the data obtained from the DDI studies using 150 mg are adequate for addressing DDI label information given that the therapeutic doses in the phase III program will be between 75 and 300 mg?**

Yes, but in vitro metabolic studies showing that Aliskiren is not a substrate of CYP450 and does not induce/inhibit CYP1A2, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4, and the possibility of having metabolic drug interactions with other drugs cleared by the above isoenzymes is unlikely. Therefore, some of the newly proposed DDI studies may not be needed, with the exception of HCTZ that will be used in the proposed combination therapy.

Additionally, if the currently ongoing in vitro P-glycoprotein study shows that Aliskiren inhibits and/or is a substrate of P-glycoprotein, additional in vivo DDI studies would be needed.

3. **Does FDA agree that Novartis is not required to further demonstrate comparability between the Phase 2 and the Phase 3 formulation?**

The provided information shows that the formulations do not meet the SUPAC criteria for a biowaiver. If this is correct, then dissolution data alone cannot be used to support the link between the Phase 2 and Phase 3 (to-be-marketed) formulations. Dr. Marroum explained that if they had a greater than a 10% difference in total excipients between the two formulations they would need a bioequivalence study. The formulation data provided in the meeting package appears to be in excess of 10%. They would need to link the formulation used in the Phase 2 study to the formulation they plan to market and use in the Phase 3 study if they plan to use the data from the Phase 2 study in determining safety and efficacy.

The sponsor stated that they would reassess their formulation comparability to determine whether they are a level 1 or 2, as referred in the Guidance and present a case for not needing a bioequivalence (BE) study. If they determine they are a level 3, they understand that they would need a BE study.

Dr. Temple suggested that they could consider adding a 600-mg Aliskiren dose to the Aliskiren/ Valsartan and the Aliskiren/ hydrochlorothiazide (HCTZ) studies rather than linking the to-be-marketed formulation to the Phase 2 studies. If this course is taken, then the sponsor will have the full range of doses explored using the to-be-marketed formulation, along with the earlier study to be used as confirmatory evidence.

4. Does FDA agree that the clinical pharmacology program is adequate to support registration?

There was a lengthy discussion regarding the pharmacokinetics (linear versus non-linear), metabolic pathways, food effect and drug-drug interactions. Novartis stated that early, small studies (N =6) showed a hint of non-linearity between the high and low doses. They are completing a larger study to characterize the pharmacokinetics fully.

Novartis stated that they believe Aliskiren does not inhibit or induce cytochromes. They are presently conducting a study that will describe the metabolic pathway information to include P-glycoprotein transport data. They will request additional conversation with Dr. Marroum, Team Leader, Clinical Pharmacology, when these data are available.

Novartis stated they know there is a food interaction, and they are planning to conduct a study without instruction related to food and they will analyze the blood pressure (BP) effect. The Agency suggested that Novartis should consider sparse sampling for determining food effects, or if they measure drug blood levels and can demonstrate that the levels are above the levels that matters, then the food effect does not matter. Dr. Throckmorton noted that other drug labels have included language that recommends taking the drug consistently with or without food.

The Agency stated that we need data that show interactions in regard to race, age, gender, hepatic impairment and food effect. We do not believe that we need data for renal impairment because less than 10% of the drug is excreted in the urine. Studies showing additional interactions would be up to the sponsor. The labeling would describe the effect or indicate it was not studied.

The Agency recommended that Novartis collect sparse samples in the Phase 3 clinical trials for Population PK and PK/PD analyses to investigate the various covariates (i.e., concomitant medications, food, gender, age, race, etc.) that might have an effect on Aliskiren's exposure.

Clinical study program

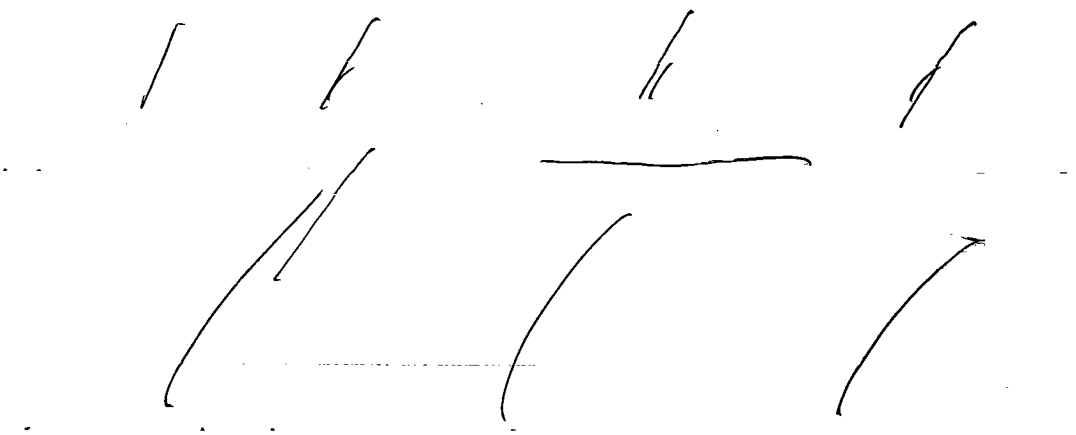
5. Does FDA agree that the proposed Phase 3 program in addition to the available Phase 2 clinical data can form the basis for the approval of Aliskiren for the treatment of essential hypertension for use in monotherapy and in free combination with other antihypertensive agents?

The Agency agrees but recommends that Novartis consider adding a 600-mg dose and/or higher dose to the Aliskiren/ HCTZ study to show no additional effect at higher doses in addition to the 2201 study that used a 600-mg dose showing no additional effect.

Novartis asked what is the Agency's discomfort with only a single dose explored above their proposed top dose at 300 mg. Dr. Throckmorton stated that just doubling the dose with a drug that is highly variable does not characterize the dose response curve fully. We prefer another dose point to demonstrate the doses are equal, worse or better. In addition, this provides useful data that there is no utility for going higher. If one is risk adverse, we would recommend 2 additional cells that would include both a 600-mg and higher dose.

Dr. Throckmorton suggested that Novartis consider a randomized withdrawal at the end of one of the clinical trials to demonstrate continued antihypertensive effect off drug. The sponsor could use ABPM or cuff measurements, however, the recorder would need to be blinded for cuff measurements. The labeling would describe the trial design and data results. The sponsor asked how long the withdrawal period should be and if the dose matters.
Dr. Throckmorton stated that the withdrawal period needed to be long enough to assure complete washout and monitor the blood pressure for several weeks off drug (dictated by how long the drug takes to achieve pharmacodynamic steady-state).

6.



7. Does FDA agree that the program of the free combination studies, their design and duration of combination treatment is adequate to support registration of Aliskiren for use in free combination with other antihypertensive agents?

The Agency agrees but recommends including higher doses of Aliskiren as discusses in number 5. The use of Aliskiren with other agents that affect the RAS system will need to be studied as was discussed in the opening remarks above.

8. Does FDA agree that the proposed safety database is of adequate scope for approval of a new chemical entity in hypertension (number and duration of patient exposures, and number of exposures at each dose)? Is the anticipated exposure to 150 mg and 300 mg sufficient to support registration of doses?

The Agency agrees.

9. Does the FDA agree that the proposed study design (A2303) in patients with severe hypertension satisfies the requirements for the evaluation of severe patients? Does FDA agree with the definition of severity as defined by Novartis?

The Agency does not separate out severe, moderate or mild hypertension. To date, antihypertensive agents that work in one surely have worked in all hypertension and the labeling would support the use with hypertension generally.

10. Does FDA agree that clinical efficacy and safety data in the elderly can be provided by analyzing the subset of elderly patients in our total clinical database?

The Agency agrees.

11.

Regulatory

12. **Does FDA agree that the data package of previous, ongoing and proposed studies, if successful, will support approval of the proposed indication: -**
." Does FDA agree that the data package of previous, ongoing and proposed studies, if successful, would support approval of our desired labeling (see Appendix 3)?

The Agency agrees, but we generally do not include in the labeling.

Conclusions/Recommendations

The Division recommends the sponsor consider the following:

- Contact the Division for further discussions regarding the CMC issues
- Submit a Special Protocol Assessment Request for the Transgenic mouse study when available
-
- Submit a proposed statistical analysis plan for review
- Conduct the studies to characterize the PK/PD and P-glycoprotein transport fully and request additional conversation with Dr. Marroum

The Division will contact the sponsor and provide a regulatory pathway for requesting a deferral for pediatric studies.

Meeting Recorder: Daryl Allis, M.S., F.N.P.

Concurrence Chair: Robert Temple, M.D.

Draft	02/13/04	Final	03/04/05
RD:			
Srinivasachar	02-13-04		
Resnick	02/13/04		
Hung	02-13-04		
Dorantes	02-13-04		
Marroum	02/18/04		
Hicks	02/18/04		
Marciniak	02/19/04		
Throckmorton	02/24/04		
Temple	03/01/04		

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Daryl L. Allis
3/4/04 09:45:50 AM
A copy of the minutes will be faxed to
the sponsor following Dr. Temple's concurrence and signature.

Robert Temple
3/4/04 07:00:11 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs

FACSIMILE TRANSMITTAL SHEET

DATE: May 29, 2003

To: Adrian Birch	**From:** Adele Seifried
Company: Novartis	HFD-024
Fax number: (973) 781-3590	**Fax number:** 301-594-5147
Phone number: (862) 778-3589	**Phone number:** 301-594-5666

Subject: Response to Carcinogenicity Special Protocol Assessment Request - Final CAC Report - IND 62,976

Total no. of pages including cover: 4

Comments:

Document to be mailed: ☐ YES ☑ NO

Executive CAC

Date of Meeting: May 20, 2003

Committee: Joseph Contrera, Ph.D., HFD-901, Acting Chair
David Jacobson-Kram, Ph.D., HFD-024, Member
Abby Jacobs, Ph.D., HFD-540, Member
John Leighton, Ph.D., HFD-150, Alternate Member
Charles Resnick, Ph.D., HFD-110, Team Leader

Presenting Reviewer: Gowra Jagadeesh, Ph.D., HFD-110

Author of Draft: Charles Resnick, Ph.D.

IND # 62976
Drug: aliskiren hemifumarate
Sponsor: Novartis Pharmaceuticals Corporation

Background: Aliskiren hemifumarate is a renin inhibitor being investigated for safety and efficacy as an antihypertensive agent. The anticipated maximum human dose is 300 mg/day. The carcinogenic potential of aliskiren hemifumarate is to be assessed by daily dietary administration to Wistar rats for 104 weeks. The animals will be housed in pairs, and food and water will be available ad libitum. Dietary drug concentrations are intended to provide doses of 0, 250, 750 or 1500 mg aliskiren/kg/day (50 rats/sex/group). Doses were selected based on the results of a 90-day dietary administration study and an 8-week rising dose dietary administration study (two weeks at each dosage level) in the same strain of rat. For toxicokinetics study, blood will be drawn from the retro-orbital plexus of surviving animals during study weeks 4 and 39. Additional rats (5/sex/group) will be sacrificed after one year for evaluation of GI irritant effects. Complete necropsies will be performed and histopathologic examinations of all protocol listed tissues will conducted on all animals.

The 90-day dose range-finding study does not address doses beyond 1000 mg/kg/day, a dose at which there was no significant effect on body weight gain (94 and 92% of control weight gain for males and females, respectively) or other evidence of dose-limiting toxicity at the end of the study. The results of the 8 week rising dose study are inconsistent with those of the former study, particularly as far as the body weight effect at 1000 mg/kg/day in females is concerned (female group mean weight gain ranged from 52-68% of control weight gain at doses ranging from 1000 to 2500 mg/kg/day with no relationship to dose level). On the other hand, a clearly dose-related decrease in weight gain (84-38% of control) was observed for males as the dose was raised from 1000 to 1500 to 2000 to 2500 mg/kg/day. On the basis of the 90-day study, the MTD for aliskiren hemifumarate in the Wistar rat is greater than 1000 mg aliskirin/kg/day for both males and females. Results of the 8-week rising dose study, although inconsistent with those of the 90-day study, suggest that dose levels cannot go much higher than 1000 mg/kg/day without encountering excessive reduction in body weight gain. The division considers the sponsor's choice of 1500 mg/kg/day as the high dose for the 2-year study to be a reasonable choice.

Executive CAC Recommendations and Conclusions

- The Committee concurs with the doses proposed by the sponsor (1500, 750 & 250 mg/kg/day) based on data from both the 90-day dose range-finding study and the 8-week rising dose toxicity study.

- The Committee recommends that satellite animals, rather than main study animals, be used for toxicokinetics evaluation.

- The Committee recommends that the animals in this feeding study be individually housed rather than housed in pairs.

Joseph Contrera, Ph.D.
Acting Chair, Executive CAC

cc:\
/HFD-110
/CResnick, HFD-110
/GJagadeesh, HFD-110
/DAllis, HFD-110
/ASeifried, HFD-024

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Joe Contrera
5/28/03 01:15:36 PM

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Adele Seifried
5/29/03 08:44:53 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 62,976

Novartis Pharmaceuticals Corporation
Attention: Mr. Adrian L. Birch
Executive Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Mr. Birch:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Aliskiren (SPP-100).

The sponsor of an IND is required, under 21 CFR 312.33, to submit an annual progress report within 60 days of the anniversary date that the IND went into effect. Such reports aid us in the evaluation of the safety and effectiveness of the drug with respect to the plan of study. We have not received this year's report; we request that you submit your report within 30 days.

Your report should contain the following information:

1. Individual Study Information

   A brief summary of the status of each study in progress and each study completed or discontinued since your last annual report. The summary should include the following information for each study:

   a. The title of the study (with any appropriate study identifiers such as protocol number), its purpose, a brief statement identifying the patient population, and a statement as to whether the study is ongoing, completed, or discontinued.

   b. The total number of subjects initially planned for inclusion in the study; the number entered into the study to date, tabulated by age group, gender, and race; the number whose participation in the study was completed as planned; and the number who dropped out of the study for any reason.

   c. If the study has been completed, or if interim results are known, a brief description of any available study results.

2. Summary Information

Information obtained during the previous year's clinical and nonclinical investigations, including:

a. A narrative or tabular summary showing the most frequent and the most serious adverse experiences by body system.

b. A summary of all IND safety reports submitted since your last annual report.

c. A list of subjects who died during participation in the investigation, with the cause of death for each subject.

d. A list of subjects who dropped out during the course of the investigation in association with any adverse experience, whether or not thought to be drug related.

e. A brief description of what, if anything, was obtained that is pertinent to an understanding of the drug's actions, including, for example, information about dose response, information from controlled trials, and information about bioavailability.

f. A list of the preclinical studies (including animal studies) completed, discontinued, or in progress during the past year and a summary of the major preclinical findings.

g. A summary of any significant manufacturing or microbiological changes made since your last annual report.

3. A description of the general investigational plan for the coming year. The general investigational plan should contain the information required under 21 CFR 312.23(a)(3)(iv).

4. If the investigator brochure has been revised, a description of the revision and a copy of the new brochure.

5. A description of any significant Phase 1 protocol modifications made since the last annual report and not previously reported to the IND in a protocol amendment.

6. A brief summary of significant foreign marketing developments since the last annual report, such as approval for marketing in any country, withdrawal or suspension from marketing in any country, or refusal of a regulatory authority to approve a marketing application.

7. If desired, a log of any outstanding business with respect to the IND for which you request or expect a reply, comment, or meeting.

If you are not currently conducting any clinical studies under this IND but plan to in the future, you may request in the annual report that the IND be inactivated. That action will relieve you of the responsibility of annual reporting. When you decide to resume studies under the inactive IND, you must submit a protocol amendment containing the proposed general investigational plan for the coming year and appropriate protocols. If the protocol amendment relies on information previously submitted, it should reference that information. You must wait 30 days after FDA receives your protocol amendment before initiating your clinical studies unless you are notified earlier that the study may begin.

If your studies have been completed or have never been initiated and you do not plan future studies, you should request in your annual report that the IND be withdrawn. Please note that withdrawal of an IND does not constitute abandonment of the application as used in 21 CFR 314.430(g). A determination of abandonment is made at the time a request is received under the Freedom of Information Act and after consultation with you.

A request for withdrawal or inactivation should include the reason the study was discontinued, assurance that all investigators have been informed, and steps taken with respect to the unused supplies of the drug.

Your report should be submitted in triplicate, identified by the above IND number, to either of the following addresses:

U.S. Postal Service:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room, 5002
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room, 5002
1451 Rockville Pike
Rockville, Maryland 20852

If you have any questions, please contact:

Alisea Sermon, Pharm.D.
Regulatory Health Project Manager
(301)-594-5334

Sincerely yours,

Zelda McDonald
Acting Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Zelda McDonald
10/30/02 11:21:56 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 62,976

Novartis Pharmaceuticals Corporation
Attention: Mr. Adrian Birch
One Health Plaza
East Hanover, NJ 07936

Dear Mr. Birch:

We acknowledge receipt of your August 22, 2002, correspondence notifying the Food and Drug Administration of the change in sponsorship for the following Investigational New Drug Application (IND):

IND Number Assigned: 62,976

Name of Drug: Aliskiren (SPP100)

Name of New Sponsor: Novartis Pharmaceuticals Corporation

Name of Former Sponsor: Speedel Pharmaceuticals, Inc.

We will update our files to list you as the sponsor of this IND. However, we require the following information to complete the file for the change of sponsorship:

1. The date that the new sponsorship became effective and a letter or other documentation from the former sponsor showing that all rights have been assigned or transferred to the new sponsor.

2. A completed form FDA 1571 signed by the new sponsor or the new sponsor's authorized agent, including the name and a summary of the training and experience of the new monitor of the IND.

3. A commitment to amend the IND within 60 days to cover all changes in the IND resulting from new sponsorship and to provide for subsequent changes by amendments in accordance with the IND regulations. All changes in the IND from those described by the former sponsor, such as manufacturing facilities and controls, must be submitted in an information amendment.

4. A commitment to inform all active investigators of the change in sponsorship and to obtain from them updated forms FDA 1572 and commitments to you as the new sponsor.

5. A list of all active investigators or a statement that they are the same as currently listed in the IND, if that is the case.

6. Submission of any changes in protocols or other study parameters.

7. Assurance that a complete copy of the former sponsor's IND has been provided to you as the new sponsor.

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports [21 CFR 312.33].

In addition, you are responsible for any correspondence outstanding as of the effective date of the transfer.

If you have any questions, please contact:

Alisea Sermon, Pharm.D.
Regulatory Health Project Manager
(301) 594-5334

Sincerely yours,

Zelda McDonald
Acting Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation ODE I
Center for Drug Evaluation and Research

cc: Speedel Pharmaceuticals, Inc.
Attention: Mr. Frank LaSaracina
Managing Director
1661 Route 22 West
P.O. Box 6532
Bridgewater, NJ 08807

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Zelda McDonald
9/5/02 10:47:55 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 62,976

Speedel Pharma Ltd
Attention: Dimitrios Goundis, Ph.D.
Hirschgaesslein 11
4051 Basel
Switzerland

Dear Dr. Goundis:

Please refer to your Investigational New Drug Application (IND), dated July 19, 2001, submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Aliskiren hemifumarate (SPP 100B).

We have completed the clinical, chemistry, preclinical pharmacology, and biopharmaceutics reviews of your submission and have the following comments and recommendations:

1. Women practicing acceptable contraception should not be excluded from studies unless the use of Aliskiren hemifumarate in women will be contraindicated.

2. The drug interaction study should be conducted using the highest dose that will be marketed. In this case, the dose/dose range that will be studied in the clinical trials is not yet known, therefore, the dose of 150 mg that is proposed for this study could be too low to provide meaningful results.

These comments are not potential hold issues. The sponsor may proceed with the clinical studies.

If you have any questions, please call:

Ms. Sandra Birdsong
Regulatory Project Manager
301-594-5334.

Sincerely,

{See appended electronic signature page}

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Raymond Lipicky
8/29/01 03:26:39 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 62,976

Speedel Pharma Ltd
Attention: Dimitrios Goundis, Ph.D.
Hirschgaesslein 11
4051 Basel, Switzerland

Dear Dr. Goundis:

We acknowledge receipt of your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned: 62,976

Sponsor: Speedel Pharma Ltd

Name of Drug: Aliskiren hemifumarate (INN); SPP 100B (Code)

Date of Submission: July 19, 2001

Date of Receipt: July 23, 2001

Studies in humans may not be initiated until 30 days after the date of receipt shown above. If, on or before August 22, 2001 we identify deficiencies in the IND that require correction before human studies begin or that require restriction of human studies, we will notify you immediately that (1) clinical studies may not be initiated under this IND ("clinical hold") or that (2) certain restrictions apply to clinical studies under this IND ("partial clinical hold"). In the event of such notification, you must not initiate or you must restrict such studies until you have submitted information to correct the deficiencies, and we have notified you that the information you submitted is satisfactory.

It has not been our policy to object to a sponsor, upon receipt of this acknowledgement letter, either obtaining supplies of the investigational drug or shipping it to investigators listed in the IND. However, if the drug is shipped to investigators, they should be reminded that studies may not begin under the IND until 30 days after the IND receipt date or later if the IND is placed on clinical hold.

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports [21 CFR 312.33].

IND 62,976

Please forward all future communications concerning this IND in triplicate, identified by the above IND number, to either of the following addresses:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room
1451 Rockville Pike
Rockville, Maryland 20852

If you have any questions, please call me at (301) 594-5334.

Sincerely yours,

Sandra Birdsong
Regulatory Project Manager
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Frank LaSaracina
Speedel Pharmaceuticals Inc.
1661 Route 22 West
Bridgewater, NJ 08807

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sandra Birdsong
7/31/01 10:48:04 AM