MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 23, 2005

TO: HFD-530: Division File

FROM: HFD-530: Tanima Sinha, Regulatory Project Manager

SUBJECT: **Clinical Information Request**
NDA 21-814, (tipranavir) capsules

On Friday February 18, 2005, a clinical information request was sent to Boehringer Ingelheim Pharmaceuticals, Inc. via email on behalf of Dr. Melisse Baylor, a secondary clinical reviewer for this application. Below is the information that was requested.

> We are unable to determine the first ARV regimen for subjects in study 1182.51 and 1182.52 from the RM dataset due to the large number of blank rows in the RMSTDY column, the even higher number of blank rows in the RMENDY column, and the vague reasons for ARV meds in the RMREASON column (such as HIV).
>
> Please clearly label which ARVs were part of the OB regimen; one suggestion for doing this would be to use the term "optimized background" consistently in the RMREASON column. In addition, some ARVs were being used at enrollment and were continued after week 2. These should be identified as both prestudy regimen and OB.

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

/s/

Tanima Sinha
2/24/05 11:28:42 AM
CSO
clin request 2-18-05

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 18, 2005

TO: Division File, HFD-530

FROM: Tanima Sinha, Regulatory Project Manager

SUBJECT: **Clinical Pharmacology Information Request**
NDA 21-814, Tipranavir Capsules

On February 16, 2005, the following information request was sent via email to Boehringer-Ingelheim Pharmaceuticals Inc., on behalf of Dr. D. Zhang, the primary clinical pharmacology reviewer for this application. The contents follow:

Dear Nancy,

I hope that you are doing well. I have the following request from Dr. Zhang, the PK reviewer for your application.

Thanks,
Tanima Sinha
Regulatory Project Manager
Food And Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Drug Products
301-827-2335

-----Original Message-----
From: Zhang, Derek Yuanchao
Sent: Wednesday, February 16, 2005 10:03 AM
To: Sinha, Tanima
Cc: Zheng, Jenny J
Subject: NDA 21-814

Tanima,

Please ask BIPI to send us an electronic copy of the code (ctl file) for PPK analysis for Study 1182.52 alone. Thanks.

Derek

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

/s/

Tanima Sinha
2/24/05 11:02:59 AM
CSO
clin pharm info request 2-16-05

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 16, 2005

TO: HFD-530: Division File

FROM: HFD-530: Tanima Sinha, Regulatory Project Manager

SUBJECT: **Clinical Information Request**
NDA 21-814, Tipranavir capsules

On Monday February 14, 2005, a clinical information request was sent to Boehringer Ingelheim Pharmaceuticals, Inc. via email on behalf of Drs Gibbs, James and Baylor, the clinical reviewers for this application. Below is the information that was requested.

Questions from Dr. Gibbs:

Trials 1182.4, 1182.6 and 1182.51

1. Please provide results of autopsy on Patient # 0215/BI case # 2001-BP-01639/Trial #1182.6. Patient expired [ ]

2. Please provide the baseline hematology labs and post TPV labs on Pt #135. The subject arrested and died during Head CAT Scan on [ ] The Investigator reported the cause of death as "intracerebral hemorrhage" - (Clinical Narratives, Appendix 5, page 20 of 996). Did the CAT scan head reveal any lesions? Was an Autopsy performed? If so, please provide the autopsy report.

3. Pt #213 was hospitalized with Acute-on-Chronic Renal Failure.
   At what point of this patient's hospitalization were the ARV medications withheld?
   Your narrative summary states that "the patient was contacted to resume all medications at previous doses 16Feb01." How did the subject respond to this re-challenge with ARV medications?

4. Pt #1168: Case ID # 2001-BP-01871(0)
   Please provide baseline and in- study labs for this subject. Please provide further details of the subject's diagnosis of "Gastrointestinal Hemorrhage NOS" and "Renal Impairment NOS."

5. Pt #212: Case ID No. 2001-BP- 02598(1)
   Please provide dose of TPV that subject was started on 14th Jan 2000.
   Please provide baseline and in-study hematology labs.

6. The following cohorts were used in study 1182.4:
   - TPV 500 mg + RTV 100 mg bid
   - TPV 1250 mg + RTV 100 mg bid
   - SQV 400 mg + RTV 400 mg bid

   Please provide a numerical analysis of the following parameters by cohort in 1182.4, expressing the following specific parameters as change from baseline to week 24 weeks, namely:

   - Hb
   - Platelet count
   - Total WBC counts, neutrophil and lymphocyte count
   - BUN and creatinine
   - Liver function tests- GGT and triglyceride levels

7. Please provide information supporting the DSMB's decision to discontinue the TPV/r arm of the Study 1182.51.

Question from Dr. James:

8. In the original protocol for 1182.22 TPV is classified as a sulfonamide. There is no warning of the sulfonamide component in the current IB or proposed labeling. Please clarify your position on TPV as a sulfonamide and how you propose to instruct subjects with sulfa allergies on TPV use.

Question from Dr Baylor:

9. Since TPV is related to the sulfonamides, please provide any additional information on the adverse event of photosensitivity in study subject 2052 in study 1182.22.

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

/s/

Tanima Sinha
2/24/05 11:20:30 AM
CSO
clinical request 2-14-05

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 09, 2005

TO: Division File, HFD-530

FROM: Tanima Sinha, Regulatory Project Manager

SUBJECT: **Clinical-Stats Information Request**
NDA 21-814, Tipranavir Capsules

On February 08, 2005, an information request for sent via email to Boehringer-Ingelheim Pharmaceuticls, Inc. on behalf of Drs Bhore and Baylor, the statistical and secondary medical reviewer respectively. The contents of that email follow:

Good Morning Nancy,

I hope that you are doing well. I am back for the rest of the month.

I have the following requests from Dr. Bhore and Dr. Baylor.

From Dr. Bhore:

The following request is in reference to RESIST 1 (Study 1182.12) and RESIST 2 (Study 1182.48).

Regarding Discontinuations/Additions/Switches of Antiretrovirals on Study:

In the dataset requested on February 2, 2005, please add the following variables.
Pre-determined T-20 stratum (i.e., assigned T-20 or not assigned T-20)
Actual T-20 stratum (i.e., actually used T-20 or not actually used T-20)

From Dr. Baylor:

TPV study 1182.22:

Please ask BI if they measured temperatures when they checked vital signs in this study.

Question for BI re study 1182.51

Please provide the meaning for code #9 in DSTERM. Only codes 1-8 are listed in the CRF.

Can you tell us where CRF for Patient #2052 in study 1182.22 is?

Please provide a response for Dr. Baylor as soon as possible.

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

/s/

Tanima Sinha
2/24/05 01:23:39 PM
CSO
02-08-05 clin info request.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 7, 2005

TO: Division File, HFD-530

FROM: Tanima Sinha, Regulatory Project Manager

SUBJECT: **Clinical-Stats Information Request Clarification**
NDA 21-814, Tipranavir Capsules

On February 02, 2005, a clin-stats request was made to Boehringer Ingelheim, Pharmaceuticals, Inc., via email. Following that email communication, another request was generated to make some clarifications to the first request. Below outlines the clarifications made:

Please disregard request number 3 from the original email and replace it with the following:

3. The following two questions are regarding formats for two datasets in '\\2004-12-29\crt\datasets\analysis datasets\PK data\1182_0052'.

   a. In pk.xpt file, the formats for $ANALY1F, $PKQ1F, ACEA1F, SEX1F and YNIF were not found in 'DEFINE.pdf' (in the same sub-directory) or could not be loaded, respectively for variables ANALYTE, PKQ, RACEA, SEX and RANDEL. Please send these formats.

   b. In nonmem.xpt file, the 'date' is between 37381 and 37459. Therefore, if format Date9. is used, these dates will go beyond year 2062 (SAS day 0 is Jan. 1, 1960). Please explain and specify the format for the variable 'date'.

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

/s/

Tanima Sinha
2/24/05 01:18:54 PM
CSO
12-30-04 clin request.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 7, 2005

TO: Division File, HFD-530

FROM: Tanima Sinha, Regulatory Project Manager

SUBJECT: **Clinical Information Request**
NDA 21-814, Tipranavir Capsules

On January 31, 2005, a clinical information request was sent via email to Boehringer Ingelheim, Pharmaceuticals, Inc. on behalf of Dr. Rosemary Johann-Liang, the medical team leader for this application. The contents of that email follow:

I was not present at the teleconference that was held between the tipranavir FDA review team and BIPI last week (January 28th, 2005). It is my understanding that "optimization" period was briefly discussed. We will like to discuss this issue more in depth during this week's teleconference (February 2nd, Wednesday at 9:30 AM). In preparation for that teleconference, please populate the following Microsoft Word tables for each of the RESIST trials (one patient per row) and email (or fax) us prior to the teleconference. Please footnote for each table where in the raw CRT electronic datasets (from your re-submission) we can cross-check this data.

Table 1: RESIST ONE TRIAL – "Optimization (OTMZ) Period"

	Patient Unique ID#	Date Randomized (mo/date/yr)	Treatment Assignment (Include all drugs initially assigned)	Date Initial Drugs Started (mo/date/yr)	Optimization One Regimen Change (Include all changes)	Date OTMZ One	Optimization Two Regimen Change (Include all changes)	Date OTMZ Two	Optimization Three Regimen Change (Include all changes)	Date OTMZ Three (Add more Columns as needed for more changes)	Date OTMZ Period ENDS	FINAL Outcome Status of the Subject (Success or Failure)
1												
2												
3												
Etc.												

Table 2: RESIST TWO TRIAL – "Optimization (OTMZ) Period"

	Patient Unique ID#	Date Randomized (mo/date/yr)	Treatment Assignment (Include all drugs initially assigned)	Date Initial Drugs Started (mo/date/yr)	Optimization One Regimen Change (Include all changes)	Date OTMZ One	Optimization Two Regimen Change (Include all changes)	Date OTMZ Two	Optimization Three Regimen Change (Include all changes)	Date OTMZ Three (Add more Columns as needed for more changes)	Date OTMZ Period ENDS	FINAL Outcome Status of the Subject (Success or Failure)
1												
2												
3												
Etc.												

Appears This Way
On Original

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

/s/

Tanima Sinha
2/24/05 11:17:22 AM
CSO
clin info request 1-31-05

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-814
[ ]

2-4-05

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Nancy L. McKay, P.E.
Senior Associate Director, Drug Regulatory Affairs
900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368

Dear Ms. McKay:

Please refer to your December 21, 2004 new drug applications (NDAs) received December 22, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for tipranavir (TPV) capsules (NDA 21-814) [ ]

We acknowledge that these applications were originally submitted on October 22, 2004 and were consequently withdrawn and resubmitted in December 2004.

The following submissions refer to the first submission of the NDAs:

Oct. 27, 2004
Oct. 29, 2004
Nov. 01, 2004
Nov. 03, 2004
Nov. 12, 2004
Nov. 17, 2004
Nov. 18, 2004
Nov. 30, 2004
Dec. 03, 2004 (2)
Dec. 05, 2004
Dec. 06, 2004 (2)
Dec. 09, 2004
Dec. 17, 2004

The following submissions refer to the resubmission of the NDAs:

Dec. 29, 2004
Jan. 04, 2005
Jan. 12, 2005
Jan. 13, 2005
Jan. 25, 2005 (2)
Feb. 02, 2005
Feb. 03, 2005
Feb. 09, 2005
Feb. 10, 2005 (2)
Feb. 16, 2005
Feb. 22, 2005

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on February 22, 2005 in accordance with 21 CFR 314.101(a).

Your applications have been given priority review. The PDUFA user fee goal date is June 22, 2005.

However, in our filing review, we have identified the following potential review issues:

Clinical/Statistical Comments:

1. As you are aware, the FDA reviewers independently analyze datasets as part of the multi-disciplinary and comprehensive review of an NDA. The importance of the FDA reviewers' ability to independently verify the data submitted by the applicant is paramount, and thus reviewability of submitted datasets are essential to the integrity of the NDA review. The FDA clinical and statistical reviewers for your NDA 21-814 have already forwarded numerous queries and comments to you regarding the reviewability of your submitted datasets. We reference our multiple queries sent to you via email and/or facsimile on 11/17/04, 11/23/04, 11/30/04, 12/01/04, 12/02/2004, 12/06/04, 12/08/04, 12/28/04, 01/07/05, 01/11/05, 01/31/05, 02/02/05, 02/08/05, 02/14/05, 02/18/05 which all pertain to dataset reviewability issues. We are in receipt of your responses to our queries/comments and your multiple revised submissions with the latest revised datasets being submitted on February 16, 2005. These subsequently submitted, format-revised and definition-clarified datasets are currently under review. We will continue to forward you our queries/comments regarding the datasets and will expect a timely response to facilitate this priority review of your application. Please keep in mind that periodically, we will not only request to review raw datasets, but also selective source data to clarify, verify, and expand upon the information in the datasets.

2. Starting with the FDA team's realization that deaths of subjects in the TPV pre-approval clinical trials were not being reported in an expedited manner (November 2003), there has been an extensive dialogue between FDA and the members of BIPI regarding deaths of subjects on study. Inconsistencies and missing information with dates of reports, dates of treatments, dates of deaths, reasons for deaths, follow-up information, as well as uncertain attribution of drug-relatedness have contributed to this extensive dialogue. We reference our queries and comments sent to you via email and/or facsimile on 10/20/04 and 11/05/2004, as well as the minutes from the face-to-face meeting between FDA and BIPI on 11/22/2004. We are in receipt of your responses to our queries/comments which include clarifications regarding inconsistencies, retrieval of missing information from source data, and submission of individual case report files for each fatal case. We have also received your recent submission which updates subjects who died on TPV clinical trials as part of your 2-month safety report. In taking a first look at the recent death cases, we have the following additional comments at this time.

a. There appear to be 8 new deaths in Resist 1; 2 new deaths in Resist 2 (1 was approximately 63 days after discontinuing TPV, so in actuality only 1 on study death for Resist 2); and 3 new deaths on the naive trial, 1182.33 since the June 11, 2004 database cutoff through December 31, 2004. TDF was a background ARV in 10 of the 13 deaths. Renal failure was a part of the clinical picture in 6 of the 13 deaths.
    1. Please conduct a safety analyses examining TDF + TPV given concurrently in your controlled TPV trials.
    2. Please examine possible safety issues with the renal system as follows:

        - Perform the following survival analyses using the Kaplan-Meier method on all subjects in the two RESIST trials through time of safety cutoff date: Time to confirmed increase in serum creatinine >=0.5 mg/dL from baseline (confirmed by laboratory values at two consecutive visits). Please compare and contrast between subjects on TPV vs. control arms and all subjects on TDF + TPV vs. all subjects on no TDF + TPV.

b. In your February 22, 2005 submission you state that not all clinical report forms (CRFs) for the fatal cases were included. These CRFs should be submitted to FDA for review at the earliest possible date. Please provide an estimate of when the missing CRFs will be submitted for our review.

3. Extensive drug interactions between tipranavir and other concomitant medications including multiple antiretrovirals have been determined via the review of your pharmacokinetic studies. Please see comments from FDA's clinical pharmacology reviewer included in this letter. In light of these drug interaction issues, we recommend that you perform the following analyses in your RESIST trials.

    a. Please perform subgroup analyses on the primary efficacy endpoint of treatment response at Week 24 for RESIST 1 and RESIST 2 trials for the following subgroups. Use the Intent-to-Treat population (i.e., your FASS24 population) data for the analyses.

    Background antiretroviral regimen containing:
        1. abacavir (ABC) or no abacavir (ABC)
        2. zidovudine (ZDV) or no zidovudine (ZDV)
        3. NNRTI or no NNRTI
        4. additional non-study PI added (i.e., dual-boosted PI) or no additional non-study PI (i.e., no dual-boosted PI). We recognize that subjects on dual-boosted PI during study will be considered as non-responders by definition.

    Present the above subgroup analyses in the following two formats
        1. As shown in Table 3.2.1:1 in the Summary of Clinical Efficacy for the ITT population (FASS24)
        2. As shown in Table 3.2.1:3 in the Summary of Clinical Efficacy for the ITT population (FASS24)

4. Due to the nature of the study design in your Phase 3 pivotal trials (i.e. open-label study in a salvage population), introduction of systemic bias at all levels from the investigators to subjects is inevitable. Our concern regarding bias in these studies was accentuated when our initial review of your application revealed the post randomization events during the "optimization period" as well as our difficulties in assessing background switch drug regimens via your datasets. We reference our queries/comments which were forwarded to you via email and/or facsimile on 01/07/05, 01/11/05, 01/31/05, 02/02/05, and 02/18/05. We are in receipt of your responses to our queries/comments including revised datasets. We have also held multiple teleconferences with you to clarify some of these issues that are currently under review by the Division. We recommend that as we are undergoing our review, you also re-examine the data for possible sources of systemic bias. In particular, we ask that you verify all subjects who deviated from protocol conduct/specifications were captured using your pre-specified definitions for protocol violation.

5. You state in your cover letter for the 27-volume two month safety update submission on February 22, 2005 that a revised proposed package insert will be submitted to the FDA shortly. Changes to the proposed package insert will include upgrading hepatic toxicity from the Precautions section to WARNINGS. Your safety analyses that provide the rationale for this change are under review by the Division. Furthermore, we recommend that as you revise your proposed package insert, you further consider the following query that was forwarded to you on 02/14/05: "In the original protocol for 1182.22, TPV is classified as a sulfonamide. There is no warning of the sulfonamide component in the current investigator's brochure or proposed labeling. Please clarify your position on TPV as a sulfonamide and how you propose to instruct subjects with sulfa allergies on TPV use." We are in receipt of your initial response to this query which you submitted on 02/28/05. We recommend further dialogue regarding this matter before the finalization of your revised proposed package insert. Also, given the extensive drug-interaction issues with TPV, we recommend that you dialogue with our reviewers regarding the Clinical Pharmacology section of your proposed package insert.

6. The safety findings of study 1182.22 are concerning. This study enrolled 51 healthy females who received at least one dose of TPV. Nineteen subjects (37%) prematurely discontinued due to adverse events and the study terminated early due to a concern about possible serum sickness. Since your safety database thus far contains a low percentage of females, it is difficult to determine what the concerning safety signals of 1182.22 in healthy young females translate to in the HIV-infected females of varying immunodeficiency. We recommend that you

   a. propose an analysis plan that examines gender-related safety differences as thoroughly as possible both from the controlled trials and from your whole current TPV safety database.

   b. take steps to ensure that female subjects are enrolled into the current treatment naïve trial (please discuss with the Division what these steps will be).

Pharmacology/Toxicology Comment:

7. Please include information on cell viability in the final report on the Sheep Red Blood Cell Plaque Forming Assay study to determine the potential for tipranavir to cause immune suppression.

Clinical Pharmacology Comments:

8. Based on your *in vitro* drug interaction assessment (Report # U03-3576), I/K_i ratios are much greater than 1 for CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. Note that for the calculation of I/Ki, we use *in vivo* Cmax (bound plus unbound) to represent inhibitor concentrations (I). Follow-up *in vivo* evaluations to determine the drug interaction potential with CYP1A2, CYP2C9, CYP2C19 and CYP2D6 drugs are needed. The label will describe the absence of such information. Please provide us with your interpretation of the significance of the *in vitro* findings and describe your plans for *in vivo* evaluations.

9. Based on cross study comparisons, multiple doses of efavirenz administration (600 mg QD) decreased the steady-state tipranavir exposure by about 30-40% compared to tipranavir/ritonavir alone (at either 500/100 or 750/200 mg dose combinations). The current proposed label does not address the potential significance of this interaction. Please update the wording in the label to provide useful instructions to health care providers. Provide your plans for further evaluation of this interaction.

10. Further study may be needed to fully characterize the extent of the interaction between didanosine and tipranavir/ritonavir at the proposed dose level, 500 mg/200 mg, due to the insufficient number of patients in the study conducted. The need for further evaluation will be considered during our review.

11. Study 1182.44 evaluated the effect of single dose rifabutin on the steady-state PK of tipranavir/ritonavir. Since rifabutin is also a CYP3A inducer, the multiple dose administration of rifabutin might shift the balance of induction and inhibition of CYP3A towards more induction, and thus reduce the tipranavir exposure. Please provide us with your interpretation of this potential interaction. Also, indicate whether you plan further evaluations of the interaction between tipranavir/ritonavir and multiple doses of rifabutin.

12. Please update the drug metabolism and drug interaction information in your proposed label. You can refer to the latest Kaletra and Reyataz labels for the both content and format. Areas to address include the following:

    a. Update Table 1 to include the effects of co-administered drugs on tipranavir exposure, for all drugs evaluated. If the comparison is based on a cross study comparison, that fact should be noted clearly in the table.

    b. Update Table 10, to include a more complete list of potential interactions. The table needs to include useful information regarding dosing and clinical significance.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, please contact Tanima Sinha, M.S., Regulatory Project Manager, at (301) 827-2335

Sincerely yours,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV
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/

Debra Birnkrant
3/4/05 03:50:41 PM
NDA 21-822, 21-814

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 2, 2005

TO: Division File, HFD-530

FROM: Monica Zeballos, Pharm.D. on behalf of Tanima Sinha, M.S., Regulatory Project Manager

SUBJECT: Clinical/Statistics Information Request
NDA 21-814, Tipranavir

On Wednesday, February 2, 2005, a clinical/statistical information request was sent to Boerhinger Ingelheim, Pharmaceuticals, Inc. via email regarding their NDA 21-814 for tipranavir. The request was sent on behalf of Dr. Kim Struble, the medical reviewer, Dr Melisse Baylor, the medical reviewer, Dr. R. Bhore, the primary statistical reviewer and Dr Susan Zhou, statistical reviewer for this application. Below is the information that was requested.

1. Please clarify why you classified the following subjects responders. These subjects do not appear to have two consecutive 1 log decreases in HIV RNA.

PT ID	Wk 8 change	Wk 16 change	Wk 24 change
Study 48			
1041	-1.8352769	0.34697024	-2.0282127
1245	-1.1608897	-0.7209138	-1.3881669
3151	-1.010991	-0.6486007	-1.0163661
3187	-1.1846807	-0.9478441	-1.1949919
3274	-1.0543168	-0.7697907	-1.1616309
4082	-1.8531893	-0.9479577	-1.0001032
4291	.	-0.7042988	-1.6780143
Study 12			
1194	-1.162354	-0.9699694	-1.1923913
1702	-2.3091481	-0.6303423	-2.71867
1717	.	-0.944017	-1.1428617
1931	-0.2172624	-0.7796467	-1.1859108
1960	-1.6744018	0.15518572	-1.413489
2121	-1.1622839	-0.8612539	-1.1622839
3021	-1.8090668	-0.6941562	-1.0226698

3038	-1.5828072	-0.9207183	-1.5495259
3120	-1.4873404	-0.9872048	-1.4873404

2. In addition you classified the following subjects as D/C Before Achieve Viral suppression; however it appears that all these subjects had a week 24 value. Please provide the discontinuation date and clarification regarding the classification.

   PT ID #'s 4092, 6008, 1405, 1597 1924

3. The following two questions are regarding formats for two datasets in '\\2004-12-29\crt\datasets\analysis datasets\PK data\1182_0052'.

   a. In pk.xpt file, the formats for $ANALY1F, $PKQ1F, ACEA1F, SEX1F and YNIF were not found in 'DEFINE.pdf' (in the same sub-directory) or could not be loaded, respectively for variables ANALYTE, PKQ, RACEA, SEX and RANDEL. Please send these formats.

   b. In nonmem.xpt file, the 'date' is between 37381 and 37459. Therefore, if format Date9. is used, these dates will go beyond year 2062 (SAS day 0 is Jan. 1, 1960). Please explain and specify the format for the variable 'date'.

Statistical Queries on APTIVUS (tipranavir) NDA 21-814, N000.

The following Statistical comments/questions refer to RESIST 1 (Study 1182.12) and RESIST 2 (Study 1182.48).

Questions regarding Optimized Background Regimen

4. Were the background antiretrovirals (i.e., background regimen) determined prior to randomization for each patient?
5. If yes, which dataset(s) has(/have) the information on the pre-determined background regimen for each patient.
6. If yes to question 1, was the planned background regimen actually started for each patient at the start of the randomized protease inhibitor (PI)?
7. If no to question 3, how many of the patients in the RESIST 1 and RESIST 2 trials had a delayed start?
8. Please provide this information by treatment group and provide summary statistics on the median time to start of the optimized background regimen (OBR) in both groups.
9. Please provide us references within in the Protocol(s) and Statistical Analysis Plan (s), if any, on definition(s) of optimized background regimen.

Regarding Discontinuations/Additions/Switches of Antiretrovirals on Study:

10. Please provide us the following dataset with the following variables. This dataset may have multiple records per patient in the chronological order that drugs were discontinued, added, or switched.

- Study ID
- Patient ID
- Treatment Group
- PI Stratum
- Study Start Date
- Pre-determined Optimized Background Regimen
- Actual Optimized Background Regimen
- Start Date of the Optimized Background Regimen
- Study Day of the start of Optimized Background Regimen
- Identify whether the Protease Inhibitor (PI) that patient was randomized to discontinued or added (code as: discontinued, or added)
- Name of PI discontinued or added
- Date PI was discontinued or added
- Study day PI was discontinued or added
- Reason PI was discontinued or added
- Identify whether non-PI ARV was discontinued or added (code as: discontinued, or added)
- Name of non-PI ARV discontinued or added
- Date non-PI ARV discontinued or added
- Study day non-PI ARV was discontinued or added
- Reason non-PI ARV was discontinued or added

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

/s/

Monica Zeballos
2/7/05 10:04:28 AM
CSO

Monica Zeballos
2/7/05 10:10:14 AM
CSO

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 12, 2005

TO: Division File, HFD-530

FROM: Tanima Sinha, Regulatory Project Manager

SUBJECT: **Statistical Information Request Follow Up**
NDA 21-814, tipranavir capsules

The following email was sent to boerhinger Ingelheim Pharmaceuticals, Inc. on behalf of Dr. Bhore, the primary statistician for this application.

Good Morning Nancy and Pam,

I hope that both of you are doing well. I am forwarding a message from Dr. Bhore regarding information that was previous requested by her, but we don't seem to have a response to it.

"As requested at one of our teleconferences, please provide us a table showing the database lock dates and length of follow-up of patients corresponding to each of the electronic data submission dates for tipranavir NDA 21-814 that contained efficacy data. The submission dates of efficacy data were 21-Oct-2004, 24-Nov-2004, 05-Dec-2004, 09-Dec-2004, and 29-Dec-2004. During our review we have observed some examples of patient records across these submissions with different lengths of follow-up data. If the requested information has already been provided to us, please give us the reference."

Please let me know when this information will be submitted to the NDA. If you have any questions, please contact me at 301-827-2335. I will be in the office until 11:30 this morning.

Thank you,
Tanima Sinha
Regulatory Project Manager
Division of Antiviral Drug Product
Center for Drug Evaluation and Research
301-827-2335
sinhat@cder.fda.gov

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

/s/

Tanima Sinha
2/24/05 11:31:50 AM
CSO
1-11-05 info request

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 07, 2005

TO: Division File, HFD-530

FROM: Tanima Sinha, Regulatory Project Manager

SUBJECT: **Statistical Information Request**
NDA 21-814, tipranavir capsules

On January 07, 2005, the following statistical information request was sent via email to Boerhinger Ingelheim, Pharmaceuticals, Inc. on behalf of Dr. Bhore, the primary statistical reviewer for this application.

The following Statistical comments/questions refer to the data for RESIST 1 (Study 1182.12) and RESIST 2 (Study 1182.48).

1. Please refer to your data file SM.XPT called Baseline Antiretrovirals. This file name is a misnomer and unclear to us because this data file does not give the baseline optimized background antiretroviral regimen (ARV) for a patient at Day 0 (start of study). Instead this file provides the names of background drugs taken by the patient prior to baseline and prior to optimizing the background regimen.

2. Please refer to your "raw" data file called RM.XPT (Antiretrovirals on Study) for Studies 1182.12 (RESIST 1) and 1182.48 (RESIST 2).

   In particular, consider the data for Patient ID 1182_0012/001001. This patient was randomized to the TPV/RTV treatment group and has received the additional background drugs enfuvirtide (ENF) + lamivudine (3TC) + nevirapine (NVP) + tenofovir (TDF). However, your patient master file shows that the background ARV for this patient was ENF + 3TC + TDF. The dose of nevirapine was apparently tapered. Was nevirapine (NVP) removed from this patient's background at Day 0 or dropped from background later?

   With the vertical file structure of RM.XPT file, it is extremely challenging to find out what were the background ARVs for a patient at start of study. How does one identify which drugs form the optimized background antiretroviral (ARV) regimen for a given patient at the start of study (i.e., at baseline)?

3. For each patient, please help us identify which drugs were added/switched to/from a patient's regimen and at what time point during their treatment in the study.

   Your raw data file RM.XPT does not clearly identify this, neither does your master patient file submitted on 09-December-2004 specify the switching mechanism for patients. Again, the vertical file structure of your raw data file RM.XPT make it extremely challenging and it may not even be possible to write a statistical program identifying the optimized background ARV regimen of patients, adding and switching of ARV drugs, if any, during the study. Provide us a statistical program for this data file, if you have one.

4. What does the variable VISITNUM taking values 4 and 7 mean in the context of the above questions? Visit numbers 4 and 7 represent Weeks 2 and 16, respectively, in RESIST 1 and RESIST 2 studies.

5. Please give us reference to any other raw data file(s) that address the question of identifying the background ARV drugs and the ARV drugs that were added/switched during the study.

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

/s/

Tanima Sinha
2/24/05 12:09:49 PM
CSO
1-7-05 stats request.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 30, 2004

TO: Division File, HFD-530

FROM: Tanima Sinha, Regulatory Project Manager

SUBJECT: **Clinical Information Follow Up.**
NDA 21-814, tipranavir capsules

On December 30, 2004, Boehringer-Ingelheim Pharmaceucials, Inc. was sent via email the following request on behalf of Dr. James, the primary medical reviewer for this application. The contents follow:

Good Morning Nancy and Pam

Happy New Year. Nancy... I hope that you are feeling better. :-)

I am forward more comments from Dr. James regarding your responses... her comments are in 'burgundy' below. If you have problems finding them because the color format didn't forward, please let me know and I can further clarify.

Tanima Sinha

==========

The definition for SMREAS is 'reason'. What exactly does reason stand for? Do you mean what happened with each of the drugs i.e. continued as part of on study treatment versus discontinued.

RESPONSE: Reason is taken from Baseline ARV Medications (All PI and Non-PI) CRF page (page 25 in 1182.12) from the list of values under "Action Taken with ARV Medication". Four choices are provided on the CRF for the investigator to choose from: (1) Drug continued into treatment period, (2) Optimization of background therapy upon randomization, (3) Switch to study PI upon randomization and (4) Other. The "Other" category included any free text comments by the site. The field was to be completed for all ARVs, thus in response to the question of what is meant, it was intended to capture what happened to each of the drugs in the screening regimen with respect to continuation as part of the study regimen. Specifically, (1) captured that the given ARV was continued, (2) captured that the drug was discontinued as part of optimization, (3) specifies switch of the screening PI to the study PI and (4) gave provision for capturing details, i.e. dose modification, however, based on the free text entries provided, some investigators chose to record discontinuation using this code.

FDA Comment: Thanks for the explanation. For future reference, it is most helpful and appreciated if the column definition and the define.pdf file state exactly what it is you are coding. If the column definition said "Action Taken with ARV Medication" and the define.pdf

had numbers 1-4 above spelled out as they are above I would not have had to query you about this.

What does optimization refer to; does it mean the drug was continued as part of the optimized background?

RESPONSE: The optimization code captured that the ARV on the record with a reason of "optimization" was part of the screening regimen but was discontinued for the reason that it was changed and the background regimen was optimized for the study.

If 'cont into treatment' is written under SMREAS can I assume that the drug was continued once the subject was on study?

RESPONSE: We did not utilize this field this way, so, although in almost every case this would most likely be true, to answer this question we would have to do a cross check against the dosing drug records for baseline (SM) and on-study (now RM in response to FDA requests) similar to what you are trying to do (please see response to 6 below).

We did the following on this topic: First we identified the comparator PI (i.e. we did not attempt to address this question for all drugs). Then only for that drug, we cross checked against SM to check for the presence of any drug records for that drug. Because the SM page was intended to only cover the time of the screening period, which is not long, we only checked for the presence of the records and not the dates on the records.

The result of this is provided in the DSRAND datasets in the variable ONAPI (Ongoing Actual PI).

Does SMONGO also mean that the ARV is 'ongoing' while on study

RESPONSE: Unfortunately No. The monitoring manual instructs, in reference to end dates in SM, that "The end date must not be left blank. All ARVs that are continuing into the study treatment must have "cont" entered; otherwise an end date must be entered." The logic used to derive SMONGO was dependent upon this instruction being followed. From your examples below, it is clear that in some cases (e.g. 1182.12, Patient 1736), an end date was written in on the SM page, and the same date was entered as a start date on the AM page (now referred to as the RM dataset in response to FDA requests), without any change in dose. We did not utilize SMONGO in the manner you are attempting to utilize it and did not see this contradiction.

If the two previous bullets are true then why do subjects 4247, 1801, 9318, and 9048 in 1182.48 and subjects 1736, 2161, 2208, 3013, 3042, 3044, 3046, 3049, 3063, 3066, 3081, 3113, 3122, 3196 have 'cont into treatment' under SMREAS but N for no under SMONGO.

RESPONSE: See bullet 4 above. One way this can happen is that CRF shows an end date for the drug on the SM page and the same date (or even the next day) is recorded on the AM page as a start date. Hypothetically, another possible way would be that the reason recorded by the investigator was incorrect, but that does not appear to be the explanation for the cases we have been able to check so far.

FDA comment/question: It appears that with only a couple of exceptions investigators put end dates of 1 day before or after the start of the trial. It is unlikely that these subjects actually had their PI interrupted one day prior or after randomization and then restarted, but please verify. In 2 cases (subject 9048 and 1801) in 1182.48 the end dates are 11 days after and 1,610 days before the start of the trial respectively. Please look into what actually occurred with these subjects.

The comment under SMONGO cannot be correct. Please fix it.

RESPONSE: The current SMONGO does not look at therapy records across the baseline and on-study therapy records to check whether the drug is ongoing in the way Dr. James would like to use it. We have been experimenting with algorithms to do this last evening and this morning. At the moment we can not say for certain if an algorithm will resolve every case Dr. James has highlighted, but along with the algorithm and a new SMONGO flag, we will identify any inconsistencies between the reason stated and results of the algorithm so they can be examined further individually. We estimate that this new flag can be submitted early next week at the latest. In order to avoid delaying Dr. James, as soon as it is finished, we could provide the flag by e-mail slightly earlier if that is desired. At the moment we think we should do this for 1182.12, 1182.48 and possibly 1182.51

Appears This Way
On Original

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

/s/

Tanima Sinha
2/24/05 01:05:23 PM
CSO
12-30-04 clin request.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 28, 2004

TO: Division File, HFD-530

FROM: Tanima Sinha, Regulatory Project Manager

SUBJECT: **Clinical Information Request (2)**
NDA 21-814, tipranavir capsules

On December 28, 2004, another clinical information request was made to Boehringer Ingelheim Pharmaceuticals, Inc. via email on behalf of Dr. James, the primary medical reviewer for this application. The contents follow:

I have another request from Dr. James. Please find the information requested below. Please provide this information by Wednesday morning.

Thank you,
Tanima Sinha
Regulatory Project Manager
Food And Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Drug Products
301-827-2335

As I understand it the SM dataset provides the baseline antiretrovirals. In trying to determine which PIs were continued from baseline I have encountered a few problems.

- The definition for SMREAS is 'reason'. What exactly does reason stand for? Do you mean what happened with each of the drugs i.e. continued as part of on study treatment versus discontinued.
- What does optimization refer to; does it mean the drug was continued as part of the optimized background?
- If 'cont into treatment' is written under SMREAS can I assume that the drug was continued once the subject was on study?
- Does SMONGO also mean that the ARV is 'ongoing' while on study
- If the two previous bullets are true then why do subjects 4247, 1801, 9318, and 9048 in 1182.48 and subjects 1736, 2161, 2208, 3013, 3042, 3044, 3046, 3049, 3063, 3066, 3081, 3113, 3122, 3196 have 'cont into treatment' under SMREAS but N for no under SMONGO.

The comment under SMONGO cannot be correct. Please fix it.

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

/s/

Tanima Sinha
2/24/05 12:46:09 PM
CSO
12-28-04 info request, (2)