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

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: August 30, 2007

To: Robert A. Fromtling, Ph.D., Director, Worldwide Regulatory Affairs

Applicant: Merck & Co., Inc.

Address: P.O. Box 2000 (RY 33-208)
126 East Lincoln Avenue
Rahway, NJ 07065-0900

From: Sung Rhee, Ph.D., Microbiology Reviewer, Division of Antiviral Products (DAVP)
Sarah Connelly, M.D., Medical Reviewer, DAVP
Ita Yuen, Ph.D., Pharmacology/Toxicology Reviewer, DAVP
Monica Zeballos, Pharm.D., Sr. Regulatory Project Manager, DAVP

Concur: Kendall Marcus, M.D., Medical Team Leader, DAVP
Jules O'Rear, Ph.D., Microbiology Team Leader, DAVP
Hanan, Ghantous, Ph.D., D.A.B.T., Acting Pharmacology/Toxicology Team Leader, DAVP

NDA: 22-145

Drug: Raltegravir potassium (formerly MK-0518)

Subject: Labeling recommendations # 3 for PI and PPI for NDA 22-145

The following labeling comments are being conveyed on behalf of the Review Team, the Division of Surveillance, Research, and Communication Support (DSRCS), Division of Drug Marketing, Advertising, and Communications (DDMAC), and the Interdisciplinary Review Team (IRT) for QT studies, and are directed towards your April 13, 2007, June 15, 2007, and July 27, 2007 submissions for this NDA. Reference is made to our labeling comments No. 1 and No. 2 sent to you on July 20, 2007 and July 31, 2007, respectively via facsimile correspondence.

Please address the identified deficiencies/issues/recommendations and re-submit labeling by September 6, 2007. This updated version of labeling will be used for further labeling discussions. Please find enclosed an annotated version of the package insert (PI) and an annotated and clear version of the patient package information (PPI).

33 Page(s) Withheld

_____ Trade Secret / Confidential

X Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 3

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/s/

Monica Zeballos
8/30/2007 04:24:19 PM
CSO

Kendall Marcus
9/7/2007 12:16:23 PM
MEDICAL OFFICER

Attachment A

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: November 9, 2006

To: Robert A. Fromtling, Ph.D., Director, Worldwide Regulatory Affairs

Address: P.O. Box 2000 (RY 33-208)
126 East Lincoln Avenue
Rahway, NJ 07065-0900

From: Monica Zeballos, Pharm.D., Regulatory Project Manager

Through: Sarah Connelly, M.D., Medical Reviewer, DAVP
Sung Rhee, Ph.D., Microbiology Reviewer, DAVP
Suresh Pagay, Ph.D., Chemistry Reviewer, DPA2, ONDQA
Ita Yuen, Ph.D., Pharmacology/Toxicology Reviewer, DAVP
Derek Zhang, Ph.D., Clinical Pharmacology Reviewer, OCP
Karen Qi, Ph.D., Statistical Reviewer, OB, OTS

Concur: Kendall Marcus, M.D., Medical Team Leader, DAVP
Julian O'Rear, Ph.D., Microbiology Team Leader, DAVP
Norman Schmuff, Ph.D., Branch Chief, DPA2, ONDQA
Stephen P. Miller, Ph.D., PAL, DPA2, ONDQA
James Farrelly, Ph.D., Pharmacology/Toxicology Team Leader, DAVP
Kellie Reynolds, Pharm.D., Clinical Pharmacology Team Leader, OCP
Fraser Smith, Ph.D., Acting Statistical Team Leader, OB, OTS

IND: 69,928

Drug: MK-0518 (formerly L-000900612)

Subject: Division's preliminary responses and additional comments regarding BP (SN254)

Attached are the FDA preliminary responses to the questions that you posed in your submissions dated June 26, 2006 (SN254). During our upcoming type B (Pre-NDA) teleconference meeting with you on December 1, 2006 we will be prepared to clarify any questions you have regarding our responses. However, please note that if there are any major changes to your development plan (based upon our responses herein), we will not be prepared to discuss, nor reach agreement on, such changes at the December 1, 2006 meeting. Any modifications to the development plan that you would like to discuss with the FDA should be submitted as a new meeting request.

Quality

Drug substance and drug product information will be organized as outlined in the Table of Contents presented under Tab 5, A. Quality Module 3 TOC.

1.MR L believes that the proposed contents of the chemistry, manufacturing, and controls included in the planned NDA will be adequate to support the commercial use of MK-0518. Does the Agency concur?

FDA Response: We concur that the CTD format for Module 3, plus an appropriate Quality Overall Summary, Module 2, should support the evaluation of quality for MK-0518. In addition, we have the following comments:

1.Pleas e provide appropriate information on the manufacturing site, process, the equipments used, and the batch sizes for manufacturing the primary stability batches of the drug substance and the drug product supporting the proposed shelf life.

2.Pleas e provide similar information for manufacturing the commercial size batches.

Nonclinical Study Reports

The list of nonclinical pharmacology and toxicology studies will be organized as outlined in the Table of Contents presented under Tab 5, B. Nonclinical Pharmacology and Toxicology Module 4 TOC.

2.MR L believes that the proposed contents of the nonclinical pharmacology and toxicology module included in the planned NDA will be adequate to support the commercial use of MK-0518. Does the Agency concur?

FDA Response: Yes

Clinical Pharmacology

The clinical pharmacology development program was discussed and agreed on a t the End-of-Phase I and End-of-Phase II meetings and has proceeded as planned. The complete Phase I Clinical Study Report (CSR) for Protocol 002 is included in this BP to provide the Agency with a sample Phase I CSR demonstrating format and content.

3.MR L believes that the clinical pharmacology development program, as described within this BP and discussed at the End-of-Phase I and II meetings is adequate to support a NDA filing for MK-0518. Does the Agency agree?

FDA Response: We agree that your planned clinical pharmacology information is adequate to support the NDA filing. We have the following comments:

3.Pleas e provide an update on the current status of UGT1A1 polymorphism study (Protocol 013) and the population PK model development.

4.Pleas e provide an update on the number of females enrolled in your PK studies.

Clinical

The Table of Contents for the Phase II CSR for Protocol 005 accompanied by sample efficacy and safety tables and figures also are included in this BP to provide the Agency with an example of the format and contents of a pivotal CSR.

4.MR L believes that the clinical development program, as described within this BP and discussed at the End-of-Phase II meeting and the Type C planning meeting is adequate to support a NDA filing for MK-0518 for the indication proposed. Does the Agency agree?

FDA Response: Yes

5.MR L believes that the format of the sample Phase I CSR and the prototype Phase II CSR will be acceptable to support the review of the NDA. Does the Agency agree?

FDA Response: Yes, however, we have the following comments with regard to the ongoing development program of MK-0518:

6.Th e 24-week data submitted from Protocols 004 and 005 demonstrate a robust virologic response to MK-0518. In addition, the summarized safety data from the Phase II studies presently demonstrate an acceptable safety profile. The 24-week data were not available at the time of the End-of-Phase II meeting, and upon review of the Phase II data, the Division requests reevaluation of your

7.Pleas e submit data on both race and gender for all Phase I, II, and III studies including Protocol 023 (Treatment IND ——, and Phase III Protocol 021(treatment-naïve study).

8.Pleas e provide an update on the current enrollment in Protocol 023 (Treatment IND ——, and Protocol 021.

9.Pleas e provide an update on Protocol 026 (MK-0518 and TMC-125). The Division requests data from this trial be included in the NDA submission.

10. During the End-of-Phase II meeting, inclusion of information on 'all cause mortality' in the Phase III 48 week CSRs was agreed upon. Please submit this inclusion as a protocol amendment to Protocols 018 and 019.

11. Please submit a sample dataset after you submit Module 3 but no later than January 31, 2007.

12. Please ensure that all dates in the datasets are submitted in numeric format, not in character format.

13. Please ensure that the corresponding study day from randomization is submitted.

Statistics

The Statistical Analysis Plan (SAP) for Phase III Protocols 018 and 019 has been provided to the Agency earlier, but is presented in this BP as well. The SAP conforms to prior agreements reached between MRL and the Agency and established principles of clinical trials analysis.

FDA Response: At the Type C planning meeting held on August 9, 2006, the Agency agreed that MRL would submit the NDA based on 100% of the Week 16 data from the two Phase III studies (PN018 and 019) and partial (~ 60%) Week 24 data to support accelerated approval. More specifically, Week 16 will be the primary timepoint. However, the SAP in this package is not updated and is still based on the original protocol in which Week 24 is the primary timepoint, and, therefore, not acceptable. We would like to remind you that the Week 16 data should be analyzed separately for the primary analysis in the two studies. Also, please let us know the Week 36 results when the primary analysis is done.

We also acknowledge receipt of your October 2, 2006 submission (SN251) in response to our comment 4 for the background package Question 6 provided in our August 7, 2006 facsimile correspondence. However, we have the following comment:

14. Please ensure that the annotated Case Report Forms (CRFs) are submitted and the names of the variables in the annotated CRFs are the same as those in the raw datasets as stripped from your official database.

Additional comments

15. **Please confirm that you will comply with the implementation of the Physician's Labeling Rule (PLR) [21 CFR 201.56, 201.57] and the Structured Product Labeling (SPL) requirements (http://www.fda.gov/oc/datacouncil/spl.html) when you file the original NDA for MK-0518. For additional information, please refer to the FDA Guidance for Industry on:**

    - ***Providing Regulatory Submissions in Electronic Format — Content of Labeling*** **(April 2005)**
    - **Draft-** ***Labeling for Human Prescription Drug and Biological Products — Implementing the New Content and Format Requirements*** **(January 2006)**

16. **We acknowledge receipt of your September 8, 2006 submission (SN239) and September 26, 2006 submission (SN247) in response to our microbiology comment/responses provided to you on August 8, 2006 by facsimile correspondence regarding the background package (SN194). However, we have the following microbiology comments:**

    a. **For the screening genotypic resistance data, please provide the number of resistance-associated substitutions for NNRTIs, NRTIs, and PIs in individual patients in a baseline resistance analysis table, separately from the Monogram electronic data deliveries. We do understand that you may have to use a different list of resistance-associated substitutions from that used by Monogram to establish genotypic resistance.**

    b. **Please clarify if the PSS algorithm employed was based upon an all or none scoring system, *i.e.,* 0 or 1, or, used a system to indicate some activity, *i.e.,* 0, ½, and 1.**

    c. **Please include in your NDA submission cellular cytotoxicity study reports of MK-0518.**

    d. **Please provide additional information on 'virologic failure', such as null-response or relapse, in your resistance analysis tables.**

    e. **Please submit the resistance data in the HIV resistance template format [please refer to the FDA Guidance for Industry on *Guidance on Antiviral Product Development – Conducting and Submitting Virology Studies to the Agency* (June 2006)]. We recommend that you presubmit the 1st dataset when it is available.**

    f. **Please determine for the failure isolates, the average number of amino acid changes in the MK-0518 binding domain of integrase above background.**

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at (301) 796-0840, if you have any questions regarding the contents of this transmission.

_____

Monica Zeballos, Pharm.D.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products

Attachment B

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: November 21, 2006

To: Robert A. Fromtling, Ph.D., Director, Worldwide Regulatory Affairs

Address: P.O. Box 2000 (RY 33-208)
126 East Lincoln Avenue
Rahway, NJ 07065-0900

From: Monica Zeballos, Pharm.D., Regulatory Project Manager

Through: Sarah Connelly, M.D., Medical Reviewer, DAVP
Karen Qi, Ph.D., Statistical Reviewer, OB, OTS

Concur: Kendall Marcus, M.D., Medical Team Leader, DAVP
Fraser Smith, Ph.D., Acting Statistical Team Leader, OB, OTS

IND: 69,928

Drug: MK-0518 (formerly L-000900612)

Subject: Division's clarifying responses regarding comments sent on November 9, 2006 and new comments regarding the revised SAP (SN283)

The following clarifying responses and new comments are being conveyed on behalf of the Review Team, and are directed towards your clarifying questions posted on November 16, 2006 and your November 10, 2006 submission (SN283), which included a revised Statistical Analysis Plan (SAP). Please refer to the FDA preliminary responses to the questions that you posed in your submission dated June 26, 2006 (SN254) sent to you via fax on November 9, 2006.

Clarifying responses italicized for FDA comments sent to Merck via fax on November 9, 2006

11. Please submit a sample dataset after you submit Module 3 but no later than January 31, 2007.

12. Please ensure that all dates in the datasets are submitted in numeric format, not in character format.

13. Please ensure that the corresponding study day from randomization is submitted.

FDA clarification for comments 11, 12, and 13: These comments are in reference to the Case Report Tabulations. Please submit sample derived analysis datasets in addition to the Case Report Tabulations (raw data).

Statistics

FDA Response: At the Type C planning meeting held on August 9, 2006, the Agency agreed that MRL would submit the NDA based on 100% of the Week 16 data from the two Phase III studies (PN018 and 019) and partial (~ 60%) Week 24 data to support accelerated approval. More specifically, Week 16 will be the primary timepoint. However, the SAP in this package is not updated and is still based on the original protocol in which Week 24 is the primary timepoint, and, therefore, not acceptable. We would like to remind you that the Week 16 data should be analyzed separately for the primary analysis in the two studies. Also, please let us know the Week 36 results when the primary analysis is done.

FDA clarification: Yes, Week 36 was an error. Please refer to our new statistical comment number 6 below pertaining to the SAP requesting Week 32 results.

New FDA comments for the revised SAP submitted unofficially via email on November 8, 2006 and officially on November 10, 2006 (SN283)

Clinical

1. The revised SAP states t he primary analysis will be performed at Week 16 when "approximately" all subjects have completed Week 16. Please clarify this statement to reflect that 100% of subjects will have completed Week 16 or discontinued at this time of analysis.

Statistics

2. The primar y efficacy analysis should use the Non-Completer=Failure (NC=F) approach rather than the more subjective Treatment-Related Discontinuation=Failure (TRD=F) approach. However the TRD=F approach would be useful in sensitivity analyses to assess how robust the primary analysis is to missing data. As you pointed out, in a well conducted trial, where non-treatment related discontinuations including withdrawals, losses to follow-up, missing data and other deviations in the protocol are minimized, non-treatment related discontinuations rates are low and the TRD=F approach should be similar to using NC=F.

3. You propose to use logistic regression analysis with five covariates in the primary analysis, which may result in small strata. The stratified Cochran-Mantel-Haenszel (CMH) chi-square statistics tends to be more robust to small strata than the logistic regression. Therefore, we recommend use of the stratified CMH test for the primary analysis.

4. Note that different alpha allocations are possible for analyses of individual studies and a meta-analysis (For more details, please refer to Lu and Huque, Biometrical Journal 2001, 7:909-923). The role of the meta-analysis of the two Phase III studies (Protocols 018 and 019) should only be for increasing the precision of the estimated treatment effect, as specified in the new version of the protocols and the and SAP. The meta-analysis should not be used to make efficacy claims.

5. We prefer that you perform a test for treatment by study interaction at the 0.20 (rather than 0.10) level of significance, A 0.10 significance level for the treatment by study interaction test will not be powerful enough to detect a qualitative interaction and will even have less power to detect a quantitative interaction.

6. In addition to Week 24 analyses, we would also like to see analyses of Week 32 data at the time the primary analysis is performed. For Week 24 analysis, all patients who could have completed the 24-week visit should be included in the denominator. Similarly for Week 32 analysis, all patients who could have completed the 32-week visit should be included in the denominator. For your NDA submission, all data before or at database lock, including the data beyond Week 16, should be submitted.

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/s/

Debra Birnkrant
8/3/2007 12:54:05 PM
IND 69,928

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

FACSIMILE TRANSMITTAL SHEET

DATE: August 9, 2007

To: Robert A. Fromtling, Ph.D., Director, Worldwide Regulatory Affairs	**From:** Monica Zeballos, Pharm.D. Senior Regulatory Project Manager
Company: Merck & Co., Inc.	Division of Antiviral Products
Fax number: 732 594-5235	**Fax number:** 301 796-9883
Phone number: 732 594-4809	**Phone number:** 301 796-0840

Subject: CMC replies towards Merck's July 27, 2007 responses

Total no. of pages including cover: 3

Comments: see next page

Document to be mailed: No

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: August 9, 2007

To: Robert A. Fromtling, Ph.D., Director, Worldwide Regulatory Affairs

Applicant: Merck & Co., Inc.

Address: P.O. Box 2000 (RY 33-208)
126 East Lincoln Avenue
Rahway, NJ 07065-0900

From: Monica Zeballos, Pharm.D., Senior Regulatory Project Manager
Division of Antiviral Products

Through: George Lunn, Ph.D., Chemistry Reviewer, DPA2, ONDQA

Concur: Norman Schmuff, Ph.D., Branch Chief, DPA2, ONDQA

NDA: 22-145

Drug: Raltegravir potassium (MK-0518)

Subject: CMC replies towards Merck's July 27, 2007 responses

The following replies are being conveyed on behalf of the Chemistry Review Team, and are directed towards your July 27, 2007 amendment to NDA 22-145 submitted in response to our July 5, 2007, facsimile correspondence, which included 29 CMC queries.

1.

2.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at (301) 796-0840, if you have any questions regarding the contents of this transmission.

Monica Zeballos

Monica Zeballos, Pharm.D.
Senior Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

FACSIMILE TRANSMITTAL SHEET

DATE: July 31, 2007

To: Robert A. Fromtling, Ph.D., Director, Worldwide Regulatory Affairs	**From:** Monica Zeballos, Pharm.D. Senior Regulatory Project Manager
Company: Merck & Co., Inc.	Division of Antiviral Products
Fax number: 732 594-5235	**Fax number:** 301 796-9883
Phone number: 732 594-4809	**Phone number:** 301 796-0840

Subject: Comments regarding final trade name review including labeling recommendations No. 2

Total no. of pages including cover: 3

Comments: see next page

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Document to be mailed: No

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

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: July 31, 2007

To: Robert A. Fromtling, Ph.D., Director, Worldwide Regulatory Affairs

Applicant: Merck & Co., Inc.

Address: P.O. Box 2000 (RY 33-208)
126 East Lincoln Avenue
Rahway, NJ 07065-0900

From: Monica Zeballos, Pharm.D., Senior Regulatory Project Manager,
Division of Antiviral Products (DAVP)

Through: Sarah Connelly, M.D., Medical Reviewer, DAVP
George Lunn, Ph.D., Chemistry Reviewer, DPA2, ONDQA

Concur: Debbie Birnkrant, M.D., Director, DAVP
Kendall Marcus, M.D., Medical Team Leader
Norman Schmuff, Ph.D., Branch Chief, DPA2, ONDQA

Applications: NDA 22-145/ IND 69,928

Drug: Raltegravir Potassium (formerly MK-0518)

Subject: Comments regarding final trade name review including labeling recommendations No. 2

The following comments are in reference to your February 13, 2007, IND submission (SN396) for trade name consult and the final trade name review for NDA 22-145.

1. The Division of Drug Marketing, Advertising, and Communications (DDMAC) finds the proprietary name "Isentress" acceptable from a promotional perspective.

2. The Division of Medication Errors and Technical Support (DMETS) has no objections to the use of the proprietary name "Isentress". DMETS considers this a final review. However, if approval of the application is delayed beyond 90 days from the signature date of this review (July 20, 2007), then the name and its labels and labeling must be re-evaluated. DMETS recommends implementation of the container label and labeling revisions outlined below in order to minimize potential user error.

1 Page(s) Withheld

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X Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 4

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/s/

Monica Zeballos
7/31/2007 06:50:38 PM
CSO

Kendall Marcus
8/3/2007 12:18:44 PM
MEDICAL OFFICER

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

FACSIMILE TRANSMITTAL SHEET

DATE: July 20, 2007

To: Robert A. Fromtling, Ph.D., Director, Worldwide Regulatory Affairs	**From:** Monica Zeballos, Pharm.D. Senior Regulatory Project Manager
Company: Merck & Co., Inc.	Division of Antiviral Products
Fax number: 732 594-5235	**Fax number:** 301 796-9883
Phone number: 732 594-4809	**Phone number:** 301 796-0840

Subject: Labeling recommendations # 1 for NDA 22-145

Total no. of pages including cover: 6

Comments: see next page

[redacted]

Document to be mailed: No

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: July 20, 2007

To: Robert A. Fromtling, Ph.D., Director, Worldwide Regulatory Affairs

Sponsor: Merck & Co., Inc.

Address: P.O. Box 2000 (RY 33-208)
126 East Lincoln Avenue
Rahway, NJ 07065-0900

From: Monica Zeballos, Pharm.D., Senior Regulatory Project Manager

Through: Monica Zeballos, Pharm.D., Senior Regulatory Project Manager

Concur: Kendall Marcus, M.D., Medical Team Leader
Sarah Connelly, M.D., Medical Reviewer

NDA: 22-145

Drug: Raltegravir potassium (formerly MK-0518)

Subject: Labeling recommendations # 1 for NDA 22-145

The following labeling comments are being conveyed on behalf of the Review Team, and are directed towards your April 13, 2007 and June 15, 2007 submissions for this NDA. Please address the identified deficiencies/issues and re-submit labeling by July 27, 2007. This updated version of labeling will be used for further labeling discussions.

These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions.

GENERAL COMMENTS

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X Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 5

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/s/

Monica Zeballos
7/24/2007 03:51:14 PM
CSO

Kendall Marcus
7/27/2007 01:22:39 PM
MEDICAL OFFICER

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Antiviral Products

Application Number: NDA 22-145

Name of Drug: Isentress™ (raltegravir potassium) 400 mg tablets

Applicant: Merck & Co., Inc.

Material Reviewed:

Submission Date(s): April 13, 2007 and June 15, 2007

Receipt Date(s): April 13, 2007 and June 15, 2007

Submission Date of Structure Product Labeling (SPL): April 13, 2007 and June 2007

Type of Labeling Reviewed: WORD

Background and Summary

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Review

Please address the identified deficiencies/issues and re-submit labeling by July 27, 2007. This updated version of labeling will be used for further labeling discussions.

GENERAL COMMENTS

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4 Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 6

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/s/

Monica Zeballos
7/24/2007 03:54:27 PM
CSO

Kendall Marcus
7/27/2007 01:36:17 PM
MEDICAL OFFICER

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

FACSIMILE TRANSMITTAL SHEET

DATE: July 5, 2007

To: Robert A. Fromtling, Ph.D., Director, Worldwide Regulatory Affairs	**From:** Monica Zeballos, Pharm.D. Senior Regulatory Project Manager
Company: Merck & Co., Inc.	Division of Antiviral Products
Fax number: 732 594-5235	**Fax number:** 301 796-9883
Phone number: 732 594-4809	**Phone number:** 301 796-0840

Subject: CMC Information Request for NDA 22-145

Total no. of pages including cover: 5

Comments: see next page

[redacted]

Document to be mailed: No

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: July 5, 2007

To: Robert A. Fromtling, Ph.D., Director, Worldwide Regulatory Affairs

Applicant: Merck & Co., Inc.

Address: P.O. Box 2000 (RY 33-208)
126 East Lincoln Avenue
Rahway, NJ 07065-0900

From: Monica Zeballos, Pharm.D., Senior Regulatory Project Manager, DAVP

Through: George Lunn, Ph.D., Chemistry Reviewer, DPA2, ONDQA

Concur: Norman Schmuff, Ph.D., Branch Chief, DPA2, ONDQA

NDA: 22-145

Drug: Raltegravir potassium (MK-0518)

Subject: CMC Information Request

Please address the following Chemistry, Manufacturing, and Controls (CMC) comments and recommendations that are related to NDA 22-145 for raltegravir potassium (MK-0518):

1.

2. In section 3.2.S.2.6.2 you describe a number of [redacted] batches and drug substance batches. In a tabular fashion please indicate, for each batch referenced in section 2.6.2, the processing parameters that were varied and the analytical characteristics of the resulting batches. Processing parameters that remain constant for all batches do not need to be described. Please also indicate the relationship between the various coupling batches and drug substance batches.

3.

3 Page(s) Withheld

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_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 8

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/s/

Monica Zeballos
7/5/2007 01:54:44 PM
CSO

Norman Schmuff
7/5/2007 03:53:14 PM
CHEMIST

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

FACSIMILE TRANSMITTAL SHEET

DATE: June 26, 2007

To: Robert A. Fromtling, Ph.D., Director, Worldwide Regulatory Affairs	**From:** Monica Zeballos, Pharm.D. Senior Regulatory Project Manager
Company: Merck & Co., Inc.	Division of Antiviral Products
Fax number: 732 594-5235	**Fax number:** 301 796-9883
Phone number: 732 594-4809	**Phone number:** 301 796-0840

Subject: Filing letter for NDA 22-145 with no issues identified with one comment.

Total no. of pages including cover: 3

Comments: see next page

Document to be mailed: YES

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-145

Merck & Co., Inc.
Attention: Robert A. Fromtling, Ph.D.
Director, Worldwide Regulatory Affairs
126 E. Lincoln Avenue
P.O. Box 2000, RY33-208
Rahway, NJ 07065-0900

Dear Dr. Fromtling:

Please refer to your April 13, 2007, new drug application (NDA) 22-145 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Isentress™ (raltegravir potassium) Oral Tablets 400 mg.

We also refer to your submissions dated:

January 12, 2007	February 27, 2007
January 31, 2007	March 15, 2007

We completed our filing review and 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 June 26, 2007, in accordance with 21 CFR 314.101(a). This NDA will receive a priority (6-month) review with an action date of October 13, 2007.

At this time, we have not identified any potential filing 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. However, we have the following comment:

Pharmacology/Toxicology

1. Please provide updated information on the status, mortality rate, and tumor findings on the ongoing carcinogenicity studies in rats and mice.

We note that you submitted labeling compliant with the Structured Product Labeling (SPL) requirements and the Physician's Labeling Rule (PLR) format. We will have labeling comments and recommendations for you soon.

If you have any questions, call Monica Zeballos, Pharm.D., Senior Regulatory Project Manager, at (301) 796-0840.

Sincerely yours,

{See appended electronic signature page}

Debra B. Birnkrant, M.D.
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

Debra Birnkrant
6/26/2007 02:34:00 PM
NDA 22-145

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-145

NDA ACKNOWLEDGMENT

Merck & Co., Inc.
Attention: Robert A. Fromtling, Ph.D.
Director, Worldwide Regulatory Affairs
126 E. Lincoln Avenue
P.O. Box 2000, RY33-208
Rahway, NJ 07065-0900

Dear Dr. Fromtling:

We have received your new drug application (NDA) 22-145 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Isentress™ (raltegravir potassium) Oral Tablets 400 mg
Review Priority Classification:	Priority (P)
Date of Application:	April 13, 2007
Date of Receipt:	April 13, 2007
Our Reference Number:	NDA 22-145

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 26, 2007, in accordance with 21 CFR 314.101(a). If we file the application, the user fee goal date will be October 13, 2007.

We will review this application under the provisions of 21 CFR 314 Subpart H (accelerated approval). Before approval of this application, you must submit copies of all promotional materials, including promotional labeling as well as advertisements, to be used within 120 days after approval.

Under 21 CFR 314.102(c), you may request a meeting with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We acknowledge receipt of your request for a deferral of pediatric studies for this application. Once the application has been filed, we will notify you whether we have deferred the pediatric study requirement for this application.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call Monica Zeballos, Pharm.D., Regulatory Project Manager, at (301) 796-0840.

Sincerely yours,

{See appended electronic signature page}

Victoria Tyson-Medlock
Acting Chief, Project Management Staff
Division of Antiviral Products
Office Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

Victoria TysonMedlock
5/11/2007 10:46:31 AM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

FACSIMILE TRANSMITTAL SHEET

DATE: May 7, 2007

To: Robert A. Fromtling, Ph.D., Director, Worldwide Regulatory Affairs	**From:** Monica Zeballos, Pharm.D. Senior Regulatory Project Manager
Company: Merck & Co., Inc.	Division of Antiviral Products
Fax number: 732 594-5235	**Fax number:** 301 796-9883
Phone number: 732 594-4809	**Phone number:** 301 796-0840

Subject: Clinical comments for NDA 22-145 in reference to IND 69,928 (SN414)

Total no. of pages including cover: 3

Comments: see next page

[redacted]

Document to be mailed: No

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

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: May 7, 2007

To: Robert A. Fromtling, Ph.D., Director, Worldwide Regulatory Affairs

Sponsor: Merck & Co., Inc.

Address: P.O. Box 2000 (RY 33-208)
126 East Lincoln Avenue
Rahway, NJ 07065-0900

From: Monica Zeballos, Pharm.D., Regulatory Project Manager

Concur: Kendall Marcus, M.D., Medical Team Leader

NDA: 22-145

Drug: Raltegravir Potassium (formerly MK-0518)

Subject: Clinical comment for NDA 22-145 in reference to IND 69,928 (SN414)

The following comment is being conveyed on behalf of the Review Team, and is directed towards your NDA 22-145.

1. Please refer to IND 69,928 (SN414) dated February 23, 2007. We note the following discrepancies between study site data in this submission and the datasets provided with NDA 22-145. Please provide us with an explanation for these discrepancies by Friday, May 11, 2007.

Study 005

1) SN414 lists 15 subjects randomized at study site 0030. Datasets indicate 24 enrolled at this site.
2) SN414 lists a study site 0038 with principal investigator Daniel Vittecoq randomizing 9 subjects. This study site does not exist in the datasets.
3) Study sites 11 and 35 have discrepancies in the listed principal investigators.

Study 018

No discrepancies are noted.

Study 019

1) Discrepancies between SN414 and the datasets are noted in the numbers of subjects randomized at the following sites: 0003, 0004, 0006, 0008, 0009, 0010, 0011, 0013, 0015, 0016, 0017, and 0018.
2) In SN414 study site 001 with principal investigator Ralph Liporace randomized 6 subjects. In the datasets, Ralph Liporace is the principal investigator at study site 0019 and randomized 4 subjects.
3) A discrepancy in principal investigator is noted for study site 0009.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at (301) 796-0840, if you have any questions regarding the contents of this transmission.

Monica Zeballos, Pharm.D.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products

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/s/

Monica Zeballos
5/7/2007 03:44:36 PM
CSO

Kendall Marcus
5/10/2007 02:32:31 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: Division of Drug Marketing, Advertising, and Communication (DDMAC)
Office of Medical Policy
Attention: Lynn Panholzer

FROM: Monica Zeballos, Pharm.D., Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Phone (301)796-0840

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
April 23, 2007		22-145	New NDA with all labeling in electronic CTD format	April 13, 2007

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Raltegravir Potassium (MK-0518) Proposed trade name: Isentress	ASAP (This will go to Advisory Committee on Sept. 5, 2007)	7030210 Antiviral/systemic/ HIV/ integrase inhibitor	**July 23, 2007**

NAME OF FIRM: Merck & Co., Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: **This is a new NDA with a 6-month review clock submitted in a rolling review fashion (5 pieces). The PI is compliant with the PLR and SPL requirements. Please review all labeling submitted on April 13, 2007 and can be found on the EDR (http://cdernet/edr/) or using the following link: \\CDSESUB1\EVSPROD\NDA022145\022145.enx (make sure you copy and paste either links in the internet explorer address box). The PDUFA action date is October 12, 2007 and the Advisory Committee meeting on Sept. 5, 2007. Please contact Monica Zeballos if you have any questions regarding this NDA. Note: this NDA is completely electronic and in eCTD format, thus it is recommended to use the Global Submit (GS) review tool.**

A request for consultation for the trade name review of "Isentress" was submitted to OSE/DMETS on March 5, 2007 for the reference IND 69,928.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Monica Zeballos	

	☒ MAIL (DFS) ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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Monica Zeballos
4/25/2007 11:57:57 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: Dision of Cardiovascular and Renal Products
OND/Office of Drug Evaluation I
Attention: Devi Kozeli

FROM: Monica Zeballos, Pharm.D., Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Phone (301)796-0840

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
April 23, 2007		22-145	Clinical Study Report synopsis for QT protocol in electronic CTD format	April 13, 2007

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Raltegravir Potassium (MK-0518) Proposed trade name: Isentress	ASAP (This will go to Advisory Committee on Sept. 5, 2007)	7030210 Antiviral/systemic/ HIV/ integrase inhibitor	**June 11, 2007**

NAME OF FIRM: Merck & Co., Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
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- ☐ RESUBMISSION
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- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: **This is a new NDA with a 6-month review clock submitted in a rolling review fashion (5 pieces). Please review the Clinical Study Report synopsis for the QT Protocol 024 submitted on April 13, 2007 and can be found on the EDR (http://cdernet/edr/) or using the following link: \\CDSESUB1\EVSPROD\NDA022145\022145.enx (make sure you copy and paste either links in the internet explorer address box). The PDUFA action date is October 12, 2007 and the Advisory Committee meeting on Sept. 5, 2007. Please contact Monica Zeballos if you have any questions regarding this NDA. Note: this NDA is completely electronic and in eCTD format, thus it is recommended to use the Global Submit (GS) review tool.**

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
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/s/

Monica Zeballos
4/23/2007 05:59:24 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 69,928

Merck & Co., Inc.
Attention: Robert A. Fromtling, Ph.D.
Director, Worldwide Regulatory Affairs
126 E. Lincoln Avenue
P.O. Box 2000, RY33-208
Rahway, NJ 07065-0900

Dear Dr. Fromtling:

Please refer to your Investigational New Drug Application (IND) 69,928 submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MK-0518 (formerly L-000900612).

We also refer to the teleconference meeting between representatives of your firm and the FDA on December 1, 2006. The purpose of this Type B teleconference meeting was to discuss and gain concurrence on the issues pertaining to the planned April 2007 filing of the original NDA for MK-0518.

The official minutes of the teleconference meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Monica Zeballos, Pharm.D., Senior Regulatory Project Manager, at (301) 796-0840.

Sincerely yours,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure

RECORD OF FDA/INDUSTRY MEETING

Date of Meeting: **December 1, 2006**

IND: **69,928**

Drug: **MK-0518 (formerly L-000900612) integrase inhibitor**

Sponsor: **Merck & Co., Inc.**

Indication: **Treatment of HIV-1 infection**

Type of Meeting: **Type B (Pre-NDA) teleconference meeting**

FDA Participants: (Title, Division/Office)

Jeffrey Murray, M.D., M.P.H., Acting Deputy Director, Office of Antimicrobial Products (OAP)
Debra Birnkrant, M.D., Division Director, Division of Antiviral Products (DAVP)
Katherine Laessig, M.D., Acting Deputy Director, DAVP
Kendall Marcus, M.D., Medical Team Leader, DAVP
Sarah Connelly, M.D. Medical Reviewer, DAVP
Kellie Reynolds, Pharm.D., Clinical Pharmacology Team Leader, Division of Clinical Pharmacology 4 (DCP4), Office of Clinical Pharmacology (OCP), Office of Translational Sciences (OTS)
Derek Zhang, Ph.D., Clinical Pharmacology Reviewer, DCP4, OCP, OTS
Ita Yuen, Ph.D., Pharmacology/Toxicology Reviewer, DAVP
Jules O'Rear, Ph.D., Microbiology Team Leader, DAVP
Sung Rhee, Ph.D., Microbiology Reviewer, DAVP
Greg Soon, Ph.D., Statistical Team Leader, Division of Biometrics 4 (DB4), Office of Biostatistics (OB), Office of Translational Sciences (OTS)
Fraser Smith, Ph.D., Acting Statistical Team Leader, DB4, OB, OTS
Karen Qi, Ph.D., Statistical Reviewer, DB4, OB, OTS
Suresh Pagay, Ph.D., Chemistry Reviewer, Division of Pre-Marketing Assessment 2 (DPA2), Office of New Drug Quality Assessment (ONDQA)
Virginia Behr, B.S., Chief, Project Management Staff, DAVP
John O'Malley, Specialist, Information Technology
Monica Zeballos, Pharm.D., Senior Regulatory Project Manager, DAVP

Merck Research Laboratories (MRL) Participants:

Bach-Yen T. Nguyen, M.D., Senior Director, Clinical Research
Robin D. Isaacs, M.D., Executive Director, Clinical Research
Robert Fromtling, Ph.D., Director, Worldwide Regulatory Affairs
Ercem Atillasoy, M.D., Senior Director, Regulatory Affairs
Michael L. Nessly, M.S., Director, Scientific Staff Statistics
Joshua Chen, Ph.D., Associate Director, Scientific Staff Statistics
Marian Iwamoto, M.D., Ph.D., Director, Clinical Pharmacology
Pamela M. Iori, M.S., Senior Regulatory Coordinator, Worldwide Regulatory Coordination
Ramon K. Kemp, D.V.M., Ph.D., Director, Preclinical Safety Assessment
John A. Wagner, M.D., Ph.D., Executive Director, Clinical Pharmacology
Dawn Morrow, A.S., Senior ESIAS Associate, Worldwide Regulatory Operations
Mike Miller, Ph.D., Director, Antiviral Research
Hedy Teppler, M.D., Senior Director, Clinical Research
Larissa Wenning, Ph.D., Senior Investigator, Clinical Drug Metabolism
Keith D. Chirgwin, M.D., Executive Director, Worldwide Regulatory Group Lead
Vinaya Kapoor, Ph.D., Senior Regulatory Scientist, RAS CMC

BACKGROUND:

MRL requested this Type B (Pre-NDA) teleconference meeting on September 5, 2006 (SN234). The meeting background package (BP) was submitted on October 6, 2006 (SN254). This teleconference meeting was originally scheduled for November 13, 2006, but because the BP did not include the required amended Phase III studies (Protocol 018 & 019) and Statistical Analysis Plan (SAP), it was rescheduled for December 1, 2006. The amended Protocol 019, SAP, and Protocol 018 were submitted by electronic mail correspondence on November 7, November 8, and November 13, 2006 respectively, and officially on November 10, 2006 [Protocol 019 (SN284), SAP (SN283)] and January 3, 2007 [Protocol 019 (SN333)]. The following communications between MRL and the Division included:

- On November 9, 2006, DAVP sent preliminary responses and additional comments (1-16) to MRL by telephone facsimile correspondence, in reply to the BP questions (see Attachment A).
- On November 16, 2006, MRL requested clarification of DAVP's November 9, 2006 additional comments including the statistical comment requesting Week 36 results.
- On November 21, 2006, DAVP replied to MRL's November 16, 2006 request for clarification by electronic mail correspondence.
- On November 21, 2006, DAVP sent comments regarding the revised SAP submitted unofficially by electronic mail correspondence on November 8, 2006 and officially on November 10, 2006 (see Attachment B).
- On November 29, 2006, MRL provided DAVP with responses to the November 9 preliminary responses and additional comments (1-16) and to the November 21

comments (regarding MRL's revised SAP) by electronic mail correspondence (see official submission SN300).

OBJECTIVE:

To gain Agency concurrence with the proposed content and format of the planned NDA

DISCUSSION:

Introduction

Monica Zeballos from FDA made opening remarks and participants' introduction was conducted. The meeting agenda was announced as follows:

1. Further discussion of Nov 21 FDA comments (1-6)
2. MR L will recap agreements reached/key items/action items captured during item 1 (Dr. Fromtling).
3. Further discussion of Nov 9 FDA microbiology comment 16a-f
4. MR L will recap agreements reached/key items/action items captured during item 3 (Dr. Fromtling).
5. Discussion of Nov 9 FD A preliminary responses and MLR's responses to Nov 9 FDA comments (1-15)
6. MR L will recap key items/action items captured during item 5 (Dr. Fromtling).

Questions

On November 9, 2006, DAVP sent preliminary responses and additional comments (1-16) to MRL by telephone facsimile correspondence in response to the following questions (see Attachment A for the complete version of the submitted questions). MRL's submission questions are listed first, followed by DAVP's responses in bold. MRL's responses to DAVP's November 9 preliminary responses/additional comments (1-16) or November 21 comments (regarding MRL's revised SAP) are located below DAVP's initial preliminary responses in *italic*. Additional comments, if any, from the December 1, 2006, Pre-NDA teleconference meeting are located below MRL's initial responses in **bold**.

Quality

1. MRL believes that the proposed contents of the chemistry, manufacturing, and controls included in the planned NDA will be adequate to support the commercial use of MK-0518. Does the Agency concur?

FDA Preliminary Response sent on Nov 9: We concur that the CTD format for Module 3, plus an appropriate Quality Overall Summary, Module 2, should support the evaluation of quality for MK-0518. In addition, we have the following comments:

1. **Please provide appropriate information on the manufacturing site, process, the equipments used, and the batch sizes for manufacturing the primary stability batches of the drug substance and the drug product supporting the proposed shelf life.**

2. **Please provide similar information for manufacturing the commercial size batches.**

MRL Response to Comments 1 & 2 received on Nov 29: The requested information will be provided as part of the forthcoming NDA. Module 3 and Module 2.3 will be sent to the FDA on January 18, 2007 as part of the agreed roll-out. Specifically, the Drug Substance information on the primary stability batches and the commercial scale process will be included in 3.2.S.7 and 3.2.S.2 respectively. The scale-up and optimization of the process used in the primary stability batches to the commercial scale process will be described in 3.2.S.2.6. Batch analysis information for all drug substance batches will be included in 3.2.S.4.4. The requested Drug Product information on the primary stability batches and the commercial scale process will be included in 3.2.P.8.1. Additionally, the scale-up and optimization of the process to commercial scale will be described in 3.2.P.2. Batch analysis information for all drug product batches will be included in 3.2.P.5.4.

December 1: DAVP stated that MRL's responses to chemistry comments 1 and 2 are acceptable. DAVP questioned whether the facilities would be ready for inspection in January 2007. MRL responded that the facilities will be ready for inspection at the time of submission of the last reviewable component of the NDA (April 2007). MRL reminded DAVP that this topic was discussed and agreed to at the August 9, 2006 Type C (NDA Roll-Out Planning) meeting.

Clinical Pharmacology

3. MRL believes that the clinical pharmacology development program, as described within this BP and discussed at the End-of-Phase I and II meetings is adequate to support a NDA filing for MK-0518. Does the Agency agree?

FDA Preliminary Response sent on Nov 9: We agree that your planned clinical pharmacology information is adequate to support the NDA filing. We have the following comments.

3. **Please provide an update on the current status of UGT1A1 polymorphism study (Protocol 013) and the population PK model development.**

*MRL Response to Comment 3 received on Nov 29: Protocol 013 is presently ongoing. To date, 11 UGT1A1*28/*28 and 7 UGT1A1*1/*1 subjects have been enrolled. An interim analysis was performed earlier to inform whether archived DNA samples in the clinical program should be genotyped for UGT1A1 polymorphisms. Preliminary data from the interim analysis are attached. In summary, in subjects administered 400-mg MK-0518, the estimated GMR for MK-0518 $AUC_{0-\infty}$ is 0.94 with a corresponding 90%*

confidence interval of (0.36, 2.49). Subsequently, this study will be amended to recruit additional subjects as the original estimate of variance had to be adjusted upward.

Merck remains committed to characterizing the pharmacokinetics of MK-0518 in a patient population, to examining the effect of various covariates (e.g., age, race, gender) and concomitant medications on MK-0518 pharmacokinetics, and to exploring possible PK/PD relationships. To this end, a population pharmacokinetic analysis of data from the 24-week blinded treatment periods of the two Phase II studies (P004 and P005) is ongoing. This analysis has been contracted out to ~~[redacted]~~ *and personnel from Merck are working closely with* ~~[redacted]~~ *to aid completion of the analysis under very tight timelines so that results can be included in the NDA. Pending completion of the Phase II modeling, we also plan to contract with* ~~[redacted]~~ *to apply the population PK model developed based on the Phase II data to a subset of the Phase III PK data (whatever data are available from P018 and P019 by the cut-off date) in an interim analysis to generate preliminary Bayesian estimates of PK parameters for patients in the Phase III studies. The goal is again to characterize the pharmacokinetics of MK-0518 in this patient population and to explore possible PK/PD relationships, and to include this limited interim Phase III analysis in the NDA.*

MK-0518 Protocol 013 (UGT1A1 Study) Interim Analyses

Executive Summary

In subjects administered 400-mg MK-0518, the estimated GMR for MK-0518 $AUC_{0-\infty}$ is 0.94 with a corresponding 90% confidence interval of (0.36, 2.49). The estimated GMR for MK-0518 $C_{12\,hr}$ is 2.51 with a corresponding 90% confidence interval of (0.81, 7.82).

Study Design

*MK-0518 Protocol 013 is being conducted to assess the pharmacokinetics of a single oral dose of MK-0518 in healthy subjects who have either the UGT1A1*1/*1 or UGT1A1*28/*28 genotype. A total of twenty-four healthy subjects are to receive, in a fasted state, a 400-mg single oral dose of MK-0518 in an open-labeled fashion. Of the 24 healthy subjects included in this study, half must have a genotype for UGT1A1*1/*1 and the other half must have a genotype for UGT1A1*28/*28.*

Table 1

Study Design

Healthy Subjects	*Treatment*
*UGT1A1*1/*1 (n=12)*	*400-mg MK-0518*
*UGT1A1*28/*28 (n=12)*	*400-mg MK-0518*

Subject and Data Accounting

*At the time of this interim analysis, seven UGT1A1*28/*28 subjects and four UGT1A1*1/*1 subjects have completed.*

Reasons for Conducting Interim Analysis

*This interim analysis is being conducted to alert the MK-0518 development team as to the likelihood of pharmacokinetic issues with respect to the administration of MK-0518 to subjects with the UGT1A1*28/*28 genotype.*

Statistical Methods

Analysis Overview

Under the assumption that $AUC_{0-\infty}$, C_{max}, and $C_{12\ hr}$ are lognormally distributed, all of the following analysis were conducted on the natural log scale and the results were back-transformed prior to reporting. All confidence intervals for the following analyses were based on a two-sample t-test.

Primary Analysis

*The primary pharmacokinetic hypothesis states that MK-0518 $AUC_{0-\infty}$ following a single 400-mg oral dose in subjects with UGT1A1*28/*28 is similar to that obtained in subjects with UGT1A1*1/*1. That is, the MK-0518 $AUC_{0-\infty}$ geometric mean ratio (with UGT1A1*28/*28 / with UGT1A1*1/*1) is contained within the interval (0.50, 2.00). This hypothesis is to be supported if the 90% confidence interval for the geometric mean ratio (GMR) is contained within the interval (0.50, 2.00).*

Exploratory Analyses

*Ninety-five percent confidence intervals were constructed for the geometric means of MK-0518 $AUC_{0-\infty}$, C_{max}, and $C_{12\ hr}$ by genotype, and 90% confidence intervals were also constructed for the geometric mean ratios (with UGT1A1*28/*28 / with UGT1A1*1/*1) of MK-0518 C_{max} and $C_{12\ hr}$.*

Results

Primary Analysis (MK-0518 $AUC_{0-\infty}$)

The computed 95% confidence intervals for MK-0518 $AUC_{0-\infty}$ are presented for each genotype in Table 2, as is the 90% confidence interval for the GMR. The estimated GMR for MK-0518 $AUC_{0-\infty}$ is 0.94 with a corresponding 90% confidence interval of (0.36, 2.49). Though the point estimate for the GMR is relatively close to 1.0, it is noted that the confidence interval is quite wide, due to the large variability.

The individual $AUC_{0-\infty}$ values are displayed by genotype in Figure 1.

Exploratory Analysis (MK-0518 C_{max} and $C_{12\,hr}$)

*Analyses for MK-0518 C_{max} and $C_{12\,hr}$ are also presented in Table 2. MK-0518 $C_{12\,hr}$ has an estimated GMR of 2.51 and a corresponding 90% confidence interval of (0.81, 7.82). The individual $C_{12\,hr}$ values are displayed by genotype in Figure 3, where it is shown that roughly half of the UGT1A1*28/*28 subjects had trough values at or above 200 nM.*

The individual C_{max} values are displayed by genotype in Figure 2.

Table 2

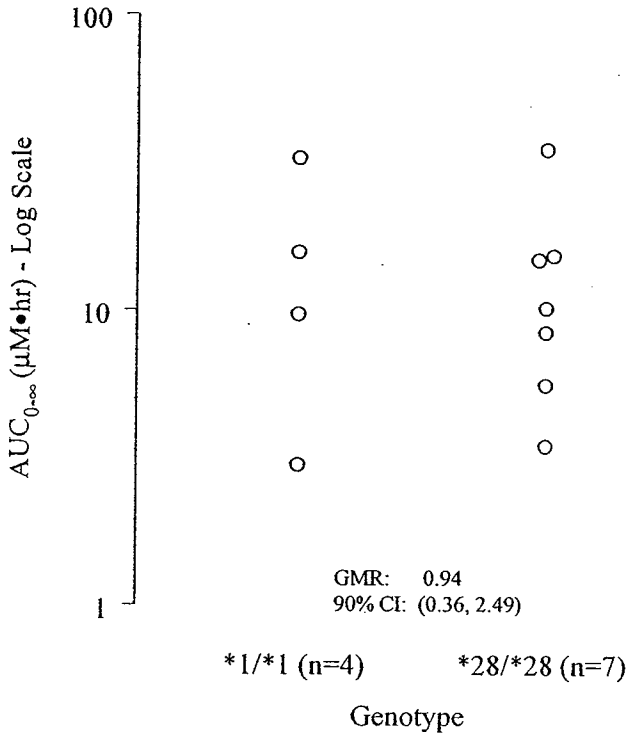
Comparison of MK-0518 Plasma Pharmacokinetic Parameter Values for Subjects Administered a Single Oral Dose of 400-mg MK-0518

	Genotype *28 / *28			Genotype *1 / *1			(*28 / *28) / (*1 / *1)	
Pharmacokinetic Parameter	N	Geometric Mean	95% CI for Geometric Mean	N	Geometric Mean	95% CI for Geometric Mean	GMR	90% CI for GMR
$AUC_{0-\infty}$ (μM•hr) †	7	10.43	(5.06, 21.47)	4	11.04	(4.25, 28.72)	0.94	(0.36, 2.49)
C_{max} (μM) †	7	2.64	(0.99, 7.04)	4	2.57	(0.70, 9.41)	1.03	(0.27, 3.84)
$C_{12\,hr}$ (nM) †	7	202.4	(86.8, 471.6)	4	80.7	(26.3, 247.0)	2.51	(0.81, 7.82)

† Geometric mean computed from least squares estimate from an ANOVA performed on the natural-log transformed values.
CI=Confidence interval; GMR=Geometric mean ratio

Figure 1

*Individual MK-0518 $AUC_{0-\infty}$ (μM•hr) Values Following Single Oral Dose of 400-mg MK-0518 in Subjects with UGT1A1*1/*1 or UGT1A1*28/*28, Fasted*



Appears This Way
On Original

Figure 2

*Individual MK-0518 C_{max} (μM) Values Following Single Oral Dose of 4000-mg MK-0518 in Subjects with UGT1A1*1/*1 or UGT1A1*28/*28, Fasted*

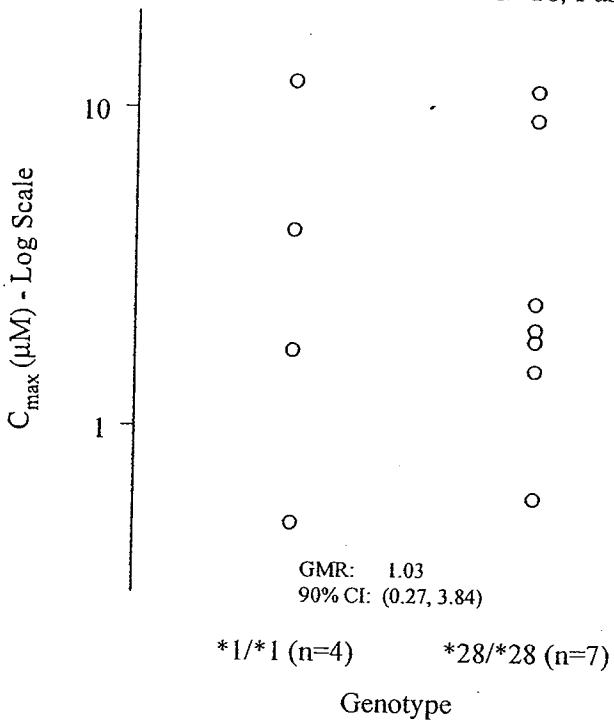
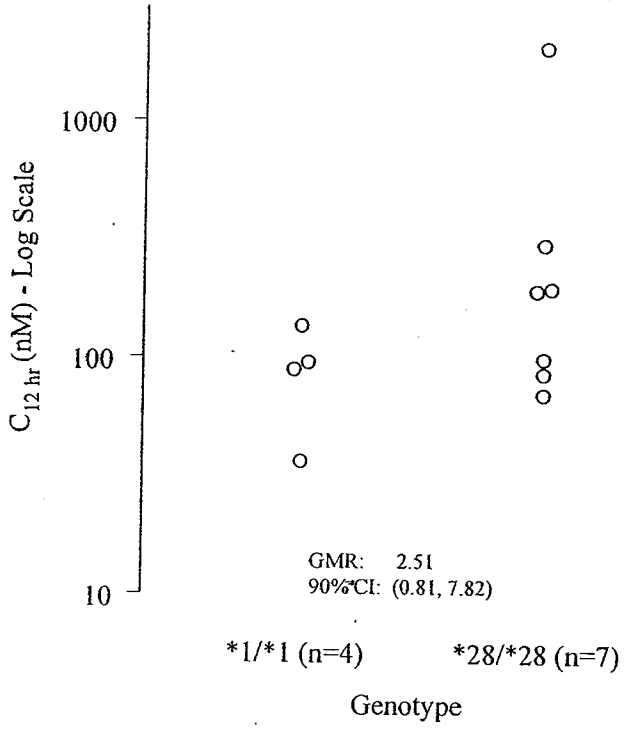


Figure 3

*Individual MK-0518 $C_{12\,hr}$ (nM) Values Following Single Oral Dose of 400-mg MK-0518 in Subjects with UGT1A1*1/*1 or UGT1A1*28/*28, Fasted*



Dec 1: DAVP had no additional comments and stated that MRL's response is acceptable.

4. Please provide an update on the number of females enrolled in your PK studies.

MRL Response to Comment 4 received on Nov 29: A total of 66 females have been enrolled in the Phase I studies.

Dec 1: DAVP had no additional comments.

Clinical

5.MR L believes that the format of the sample Phase I CSR and the prototype Phase II CSR will be acceptable to support the review of the NDA. Does the Agency agree?

FDA Preliminary Response sent on Nov 9: Yes, however, we have the following comments with regard to the ongoing development program of MK-0518:

6. The 24-week data submitted from Protocols 004 and 005 demonstrate a robust virologic response to MK-0518. In addition, the summarized safety data from the Phase II studies presently demonstrate an acceptable safety profile. The 24-week data were not available at the time of the End-of-Phase II meeting, and upon review of the Phase II data, the Division requests reevaluation of your pediatric development program.

MRL Response to Comment 6 received on Nov 29:

7. **Please submit data on both race and gender for all Phase I, II, and III studies including Protocol 023 (Treatment IND ———) and Phase III Protocol 021 (treatment-naïve study).**

MRL Response to Comment 7 received on Nov 29: The table on the next page provides the available data on Gender and Race in the collective Phase I program (PN001, PN002, PN003, PN006, PN008, PN009, PN010, PN011, PN014, PN015, PN016, PN017, PN020, PN024, PN025, PN026, PN028), as of 16-Nov-2006.

	Phase I Program
Gender n(%)	
Male	*236 (78)*
Female	*66 (22)*
Race n(%)	
White	*193 (64)*
Black	*40 (13)*
Asian	*2 (<1)*
Hispanic American	*65 (22)*
Multiracial	*2 (<1)*
Total	*302 (100)*

The table below provides the available data on Gender and Race in Phase II (PN004, PN005) and Phase III studies (PN018, PN019, PN021) as well as the Expanded Access Program (PN023), as of 16-Nov-2006.

	PN004	*PN005*	*PN018*	*PN019*	*PN021*	*PN023*
Gender n(%)						
Male	*157(79)*	*157(88)*	*298(85)*	*315(91)*	*12*	*20*
Female	*41(21)*	*21(12)*	*52(15)*	*32(9)*	*2*	*0*
Race n(%)						

White	*61(31)*	*136(76)*	*271(77)*	*201(58)*	*7*	*8*
Black	*5(3)*	*20(11)*	*23(7)*	*69(20)*	*3*	*6*
Asian	*33(17)*	*3(2)*	*19(5)*	*3(1)*	*0*	*1*
Hispanic American	*58(29)*	*18(10)*	*7(2)*	*65(19)*	*2*	*5*
Others	*41(21)*	*1(1)*	*30(9)*	*9(3)*	*1*	*0*
Total	*198(100)*	*178(100)*	*350(100)*	*347(100)*	*14**	*20*

** There is no race reported for one patient*

Dec 1: There was a general discussion regarding gender and different ethnicities. DAVP requested that MRL confirm if there were plans in place for Protocol 021 (phase 3, treatment-naïve) to enroll a more diverse population representative of the general HIV population, specifically women, Blacks, Asians, and Hispanics. MRL responded that there were plans in place. DAVP questioned what exactly MRL had done to ensure that the study will have adequate representation from those groups that tend to be under represented. MRL replied as follows:

- **Sites were chosen to achieve a diverse enrollment goal**
- **Existence of different locations in the world to ensure enrollment of a diverse population**

DAVP recommended that MRL change its enrollment plans if accrual was not adequate. MRL agreed to monitor accrual to enroll as many women in Protocol 021 and committed to do everything in its power to encourage female enrollment and commented that the current U.S. enrollment of phase 3 treatment-experience patients is reported as 20% as African American and about 20% as Hispanic American.

8. **Please provide an update on the current enrollment in Protocol 023 (Treatment IND ~~~~, and Protocol 021.**

MRL Response to Comment 8 received on Nov 29: As of November 16, 2006 Protocol 023 has enrolled 20 patients and Protocol 021 14 patients.

Dec 1: DAVP has no additional comments.

9. **Please provide an update on Protocol 026 (MK-0518 and TMC-125). The Division requests data from this trial be included in the NDA submission.**

MRL Response to Comment 9 received on Nov 29: Dosing of subjects in Protocol 026 is complete. As discussed with the Division, preliminary results will be shared around year end to support co-dosing of MK-0518 and TMC125 in the expanded access program. We anticipate submitting the Protocol 026 CSR and related data with the last piece of the NDA roll out in April 2007.

Dec 1: DAVP asked MRL if it anticipates submitting Protocol 026 data this month or with the NDA application. MRL responded that preliminary data results would be submitted to DAVP in early January 2007 and the full study report and final results will be provided with the NDA application in April 2007.

10. During the End-of-Phase II meeting, inclusion of information on 'all cause mortality' in the Phase III 48 week CSRs was agreed upon. Please submit this inclusion as a protocol amendment to Protocols 018 and 019.

MRL Response to Comment 10 received on Nov 29: As agreed at the End-of-Phase II meeting, both protocols 018 and 019 have been amended to collect information on "all cause mortality". Specifically, for the patients who discontinue the study prior to Week 48 visit, there is plan for follow-up to assess whether the patient is alive and whether he/she is participating in another clinical study. This amendment is mentioned on page 2 "Summary of Changes" and on page 61 of the amended protocol 019-10 recently submitted to the Agency: "The following information will be collected at Week 48 for patients who discontinue/withdraw prior to that time: 1) mortality; and 2) any participation in another clinical study at Week 48."

Dec 1: DAVP had no additional comments.

FDA clarification for comments 11, 12, and 13 sent to MRL on Nov 21: These comments are in reference to the Case Report Tabulations. Please submit sample derived analysis datasets in addition to the Case Report Tabulations (raw data).

11. Please submit a sample dataset after you submit Module 3 but no later than January 31, 2007.

MRL Response to Comment 11 received on Nov 29: The Case Report tabulations SAS XPT files for MK-0518 Protocol 004 will be provided as a sample dataset within the specified time interval with accompanying documentation.

Dec 1: DAVP asked MRL to comment on the submission of sample derived analysis datasets in addition to the Case Report Tabulations because MRL's previous response was not clear. MRL stated that it prefers to submit complete sample vs. partial sample derived analysis datasets and agreed, per DAVP's request, to submit a complete sample dataset with real data (representative of Protocols 005, 018, and 019) for Protocol 004 by December 2006.

Post-meeting: Dr. Fraser Smith and Monica Zeballos, Pharm. D., of DAVP telephoned Dr. Robert Fromtling of MRL to request if a complete dataset for Protocol 005 could also be provided. MRL agreed to submit complete datasets with real data for Protocols 004 and 005 by December 2006. On December 13, 2006, a teleconference meeting was held between DAVP and MRL representatives seeking agreement on the specifics of the statistical datasets (format & content) for Protocols 004 and 005 to be sent to DAVP by December 2006. The following agreements were reached during this teleconference meeting:

a. **MRL will provide complete submission datasets with statistical review aid (SRA) documentation from Protocols 004 and 005 with a target release date of January 31, 2007 instead of December 2006.**
b. **MRL will provide early results memorandums to allow review of these datasets.**
c. **MRL will provide the CSRs as scheduled in the roll-out on March 15, 2007, and these datasets will not be transmitted again with the CSRs.**
d. **MRL will provide a full listing of the deliverables for the SRA (for each of MK-0518 Protocols 004 and 005 based on the 48-week frozen files) as follows:**

- **Complete sets of Case Report Tabulation (Data as collected) SAS XPT files**
- **Raw HIV RNA and $CD4^+$ cell count SAS XPT datasets as extracted from MRL's official database**
- **Derived HIV RNA and $CD4^+$ cell count analysis datasets to support primary and important secondary efficacy hypotheses**
- **Patient descriptors, patient status and key subgroup identifiers (special populations and prognostic factors)**
- **Analysis programs for derivation from raw data and to produce primary and important secondary efficacy analysis results from analysis datasets for HIV RNA and $CD4^+$ cell count**
- **Documentation/metadata for raw and analysis datasets, variables and programs - DEFINE.PDF**
- **Early Results Memo Weeks 0 to 48**
- **A 'discrepancy report' to address any data changes in Protocols 004 and 005 for Weeks 0 through 24 in HIV RNA and $CD4^+$ cell counts and Patient Status comparing the 24 week frozen files data to the 48 week frozen files data**
- **Annotated CRF mapping data capture on CRF to variables in Case Report Tabulation (CRT Data as collected) SAS XPT files**

Note: On January 31, 2007, MRL submitted the requested efficacy data as agreed upon above.

12. Please ensure that all dates in the datasets are submitted in numeric format, not in character format.

MRL Response to Comment 12 received on Nov 29: All Case Report Tabulations SAS XPT File dates are in the DATE (i.e., numeric) format, with one exception: if a date was captured in a RESPONSE field then it would be in CHAR format.

Dec 1: DAVP had no additional comments.

13. Please ensure that the corresponding study day from randomization is submitted.

MRL Response to Comment 13 received on Nov 29: Study day from randomization, in the NUM format, can be found in the "REL_DY" column on all Case Report Tabulation SAS XPT Files. This is where "study therapy relative start day" is captured. It is calculated using observation date minus trial start date + 1.

Dec 1: DAVP had no additional comments.

Statistics

The Statistical Analysis Plan (SAP) for Phase III Protocols 018 and 019 has been provided to the Agency earlier, but is presented in this BP as well. The SAP conforms to prior agreements reached between MRL and the Agency and established principles of clinical trials analysis.

FDA Preliminary Response sent on Nov 9: At the Type C planning meeting held on August 9, 2006, the Agency agreed that MRL would submit the NDA based on 100% of the Week 16 data from the two Phase III studies (PN018 and 019) and partial (~60%) Week 24 data to support accelerated approval. More specifically, Week 16 will be the primary timepoint. However, the SAP in this package is not updated and is still based on the original protocol in which Week 24 is the primary timepoint, and, therefore, not acceptable. We would like to remind you that the Week 16 data should be analyzed separately for the primary analysis in the two studies. Also, please let us know the Week 36 results when the primary analysis is done.

FDA Clarification sent to MRL on Nov 21: Yes, Week 36 was an error. Please refer to our new statistical comment number 6 below pertaining to the SAP requesting Week 32 results.

MRL Response to Comment sent on Nov 9: The SAP has been updated and was submitted on November 10, 2006 (SN 0283).

We also acknowledge receipt of your October 2, 2006 submission (SN251) in response to our comment 4 for the background package Question 6 provided in our August 7, 2006 facsimile correspondence. However, we have the following comment:

14. Please ensure that the annotated Case Report Forms (CRFs) are submitted and the names of the variables in the annotated CRFs are the same as those in the raw datasets as stripped from your official database.

MRL Response to Comment 14 received on Nov 9: Annotated CRFs will be submitted for all Case Report Tabulation files per FDA Guidance. The Guidance states, "For raw variables, the location of the variable on the annotated CRF should be provided as well as the CRF field name if different from the variable name in the dataset. Providing a hypertext link from each raw data variable in the data definition table to the appropriate location of the blankcrf.pdf also helps the review process."

Dec 1: DAVP had no additional comments.

Additional comments sent to MRL on November 9, 2006

15. Please confirm that you will comply with the implementation of the Physician's Labeling Rule (PLR) [21 CRF 201.56, 201.57] and the Structured Product Labeling (SPL) requirements (http://www.fda.gov/oc/datacouncil/spl.html) when you file the original NDA for MK-0518. For additional information, please refer to the FDA Guidance for Industry on:

- ***Providing Regulatory Submissions in Electronic Format – Content of Labeling*** **(April 2005)**
- ***Draft Labeling for Human Prescription Drug and Biological Products – Implementing the New Content and Format Requirements*** **(January 2006)**

MRL Response to Comment 15 received on Nov 29: We confirm that we will be in compliance with PLR and SPL requirements.

Dec 1: DAVP had no additional comments.

16. We acknowledge receipt of your September 8, 2006 submission (SN239) and September 26, 2006 submission (SN247) in response to our microbiology comment/responses provided to you on August 8, 2006 by facsimile correspondence regarding the background package (SN194). However, we have the following microbiology comments:

a.For the screening genotypic resistance data, please provide the number of resistance-associated substitutions for NNRTIs, NRTIs, and PIs in individual patients in a baseline resistance analysis table, separately from the Monogram electronic data deliveries. We do understand that you may have to use a different list of resistance-associated substitutions from that used by Monogram to establish genotypic resistance.

MRL Response to Comment 16a received on Nov 29: Merck would like to further discuss with the Agency at the pre-NDA meeting the rationale for the request for the number of resistance-associated substitutions for NNRTIs, NRTIs, and PIs from the screening genotypic resistance data for patients enrolled in the treatment-experienced studies; as the HIV isolates from all of the patients enrolled in the Phase II treatment-naïve study were only screened for resistance to efavirenz, tenofovir, and lamivudine, and all patients enrolled into the study had virus susceptible to these isolates, it is our assumption that the Agency's request only relates to the HIV isolates from treatment-experienced study. As we noted in our prior correspondence (SN 239), Merck believes: (1) that the Monogram's combined genotypic and phenotypic assessments of PI, NRTI, and NNRTI resistance is sufficient to establish that patients entering the clinical studies met the enrollment criteria; (2) the number of PI-, NRTI-, and NNRTI-resistance mutations is only relevant to assessing new members of the PI, NRTI, and/or NNRTI classes; and (3) integrase represents a completely novel target and in vitro data do not indicate any cross-resistance with the PI, NRTI, NNRTI, and fusion inhibitor classes, then the number of PI,

NRTI, and NNRTI mutations are not relevant in the assessment of the clinical efficacy of MK-0518. In light of our assessment, Merck would like to better understand the rationale for the Agency's request.

Dec 1: DAVP explained that the number of resistance mutations for NNRTIs, NRTIs, and PIs should be provided for all samples and for all the resistance data (data used to screen for entrance into the study & data generated at the time of virologic failure), per draft guidance document, for the following reasons:

- **To verify genotypic resistance and look at the failure isolates to determine if additional mutations appear for drugs in the OBT regimen**
- **To quantify mutations in the RT and PR genes because the antiviral response may be driven, in part, by other drugs in the OBT regimen**

MRL understood and acknowledged DAVP's explanation but stated that it is not planning to provide the requested data because it contracted with Monogram prior to the release of the draft guidance document and this contract did not include that Monogram provide an electronic transfer of resistance mutations. In addition, MRL made the following points:

- **Integrase inhibitor does not show cross-resistance with the currently available classes and when resistance is generated in cell culture, resistance mutations are in the integrase gene**
- **Monogram resistance information and all of the sequence differences regardless of resistance mutation attribution will be provided to the Division**
- **If critical, MRL can perform an analysis using the — version resistance mutation and apply them to the datasets**

DAVP emphasized the importance of making a final decision based on the totality of the data and tentatively agreed to accept an — /s. Monogram comparison mutation list and a copy of the published paper as a reasonable plan and provide quick feedback. MRL agreed with this request.

b. Please clarify if the — algorithm employed was based upon an all or none scoring system, *i.e.*, 0 or 1, or used a system to indicate some activity, *i.e.*, 0, ½, and 1.

MRL Response to Comment 16b received on Nov 29: We are using a binary PSS algorithm: a drug to which the subject's virus is "sensitive" (Monogram nomenclature) is given a score of 1, and a drug to which the subject's virus shows "reduced susceptibility" (Monogram nomenclature) is given a score of 0.

Dec 1: DAVP had no additional comments.

c. Please include in your NDA submission cellular cytotoxicity study reports of MK-0518.

MRL Response to Comment 16c received on Nov 29: In cell culture experiments showing antiviral activity of MK-0518, cytotoxicity was routinely assessed by visual inspection of cells as opposed to using a quantitative surrogate assay to evaluate cell viability. In these studies there was no evidence of effects on cell growth at concentrations greater than 1000X that required to inhibit HIV-1 replication. In addition, Merck has thoroughly studied the mechanism of action of MK-0518 and has validated the antiviral effect on HIV-1 integrase. The NDA will include data showing that MK-0518 specifically blocks integration in HIV-1-infected cells. Furthermore, in resistance selection experiments performed with HIV-1 in cell culture, MK-0518 selected for specific mutations in the HIV-1 integrase gene, and when these mutations were engineered into new viruses they are shown to confer resistance to MK-0518. Collectively, these studies indicate that MK-0518 exerts a direct and specific effect on HIV-1 integrase and inhibits HIV-1 replication as a consequence thereof. The results of extensive preclinical safety pharmacology and toxicology studies that will be included in the submission provide evidence that MK-0518 is not cytotoxic, and thus it is not planned to include formal cytotoxicity reports for the antiviral experiments in the NDA.

Dec 1: DAVP stated that MRL's response was acceptable but requested the following information:

- **Summary of when the visual inspections were done**
- **Other specifics of the methodology (e.g., host cell types, concentrations routinely evaluated, endpoint of antiviral assay) that will provide confidence that MK-0518 is not cytotoxic**

MRL provided clarification about when the visual inspections were done, concentrations routinely evaluated, and endpoint of antiviral assay. DAVP concluded that based of this information, there were no major issues regarding cytotoxicity.

d. Please provide additional information on 'virologic failure', such as null-response or relapse, in your resistance analysis tables.

MRL Response to Comment 16d received on Nov 29: The resistance analysis tables will contain information on the type of virologic failure (e.g., Non-response, Viral Rebound).

Dec 1: DAVP had no additional comments.

e. Please submit the resistance data in the HIV resistance template format [please refer to the FDA Guidance for Industry on *Guidance on Antiviral Product Development – Conducting and Submitting Virology Studies to the Agency* (June 2006)]. We recommend that you presubmit the 1st dataset when it is available.

MRL Response to Comment 16e received on Nov 29: A preliminary genotypic data set has been submitted (Protocol 005 Screening Genotypic Resistance Data Submission, September 26, 2006 [Serial No. 0247]). Resistance data for Protocols 005, 018, and 019 (treatment-experienced subjects) will be submitted in the suggested format. At the latest,

the first full set of resistance data will accompany submission of the Protocol 005 Clinical Study Reports; submission of the Protocol 005 CSR is currently targeted for March 2007.

For protocol 004, the screening resistance data were used to ensure that all enrolled ART-naïve patients have viruses that are sensitive to EFV, TFV and 3TC. The screening data are therefore less important as prognostic factors in this study than in Protocols 005, 018, and P019. In addition, there is very little resistance data to report for Protocol 004 due to the small number of virologic failures in this study (n = 6), and we would therefore prefer to provide the relevant information within the Clinical Study Report rather than submitting the resistance data separately in the suggested template.

Dec 1: DAVP requested that MRL pool all the resistance data allowing DAVP to look for both frequency and resistance pathways. MRL stated that it will not provide resistance data for Protocol 004 (treatment-naïve) as SAS transport files because there were so few failures but instead this information will be placed in the clinical study report (genotype & phenotype information for all the failure patients) and asked if this approach was acceptable. DAVP make the following points:

- **To include the data, if it was available, because the few failures may make a difference in identifying one or two low frequency pathways**
- **To highlight all the changes and see if similar changes are found in the other datasets and only report those changes, as a first alternative approach**
- **To go through the 6 individuals that failed and identify any changes from baseline noting any mutations vs. other patients in the treatment-experienced population, as a second alternative approach**

MRL agreed to comply with the second approach.

5.MR L will provide a written summary within the Protocol 004 Clinical Study Report highlighting changes or description of all changes from baseline.

f. Please determine for the failure isolates, the average number of amino acid changes in the MK-0518 binding domain of integrase above background.

MRL Response to Comment 16f received on Nov 29: As there is no crystallographic information available for MK-0518 bound to integrase, we do not know the precise boundaries of the MK-0518 binding domain in integrase. We will comply with this request by reporting the total number of amino acid sequence changes observed in the entire integrase protein between baseline and failure isolates.

Dec 1: DAVP stated that it has not had the opportunity to be able to separate resistance data from clinical data and added the following points regarding the existence of rare mutations:

- **Concern that the pathways may be multiple and complex**

- **Whether there are resistance mutations MRL is not identifying in the screens because they occur at low frequency and study sites are not large enough to identify mutations**
- **A comparison between failure isolates and individuals receiving active drug vs. those in the control arm was the key point**

MRL acknowledged DAVP's statements regarding rare mutations and stated that in cases where new resistant mutations are noted, it will subject the virus to additional testing.

New FDA comments sent on Nov 21, for the revised SAP submitted unofficially via email on November 8, 2006 and officially on November 10, 2006 (SN283)

Clinical

1. **The revised SAP states the primary analysis will be performed at Week 16 when "approximately" all subjects have completed Week 16. Please clarify this statement to reflect that 100% of subjects will have completed Week 16 or discontinued at this time of analysis.**

MRL Response to Comment 1 received on Nov 29: Based upon patient tracking, we expect to have all of the enrolled patients to have either completed Week 16 or to have prematurely discontinued the study. We expect to have 100% of subjects accounted for in the analyses.

Dec 1: DAVP had no additional comments.

Statistics

2. **The primary efficacy analysis should use the Non-Completer=Failure (NC=F) approach rather than the more subjective Treatment-Related Discontinuation=Failure (TRD=F) approach. However the TRD=F approach would be useful in sensitivity analyses to assess how robust the primary analysis is to missing data. As you pointed out, in a well conducted trial, where non-treatment related discontinuations including withdrawals, losses to follow-up, missing data and other deviations in the protocol are minimized, non-treatment related discontinuations rates are low and the TRD=F approach should be similar to using NC=F.**

MRL Response to Comment 2 received on Nov 29: As of 23-Nov-06, only 9 (3%) patients in P019 and 8 (2%) patients in P018 discontinued study therapy and majority of them were due to adverse experiences. Therefore, the two approaches are essentially the same since the non-treatment related discontinuation rate is low.

As indicated in the SAP, the TRD=F approach considers a treatment failure endpoint which is directly related to the antiretroviral effect and tolerability of the treatment itself, while the NC=F approach consider a study failure endpoint which also depends on the conduct of the study. The TRD=F approach is to addresses the relevant question of

treatment benefit (safety and efficacy) for the overall patient population who will receive the experimental treatment. For these reasons, we prefer to have the TRD=F approach as primary efficacy analysis

We prefer not to amend the SAP yet again at this late time but point out that results from analyses based upon NC=F will be provided in the submission for all primary and secondary parameters.

Dec 1: DAVP reiterated its position that the primary efficacy analysis should use the NC=F approach rather that the TRD=F approach because the first approach is more subjective that the TRD=F approach. In addition, DAVP stated that during its review, it would treat NC=F as the primary analysis. MRL agreed with these comments.

3.You p ropose to use logistic regression analysis with five covariates in the primary analysis, which may result in small strata. The stratified Cochran-Mantel-Haenszel (CMH) chi-square statistics tends to be more robust to small strata than the logistic regression. Therefore, we recommend use of the stratified CMH test for the primary analysis.

MRL Response to Comment 3 received on Nov 29: We agree with the issue with small numbers of potential patients within strata. This is particularly important for this patient population due to potentially highly heterogeneous background therapy.

However, small numbers of potential patients within strata could be problematic for the stratified CMH tests, as well. For binary covariates (e.g., Yes/No), there will be 2^5=32 stratum. Even patients are equally distributed across strata, each strata would have only ~10 patients. In practice, since there are ~115 patients on placebo, some stratum may have no placebo patients and a post-hoc decision needs to be made to "pool" stratum to allow comparison between MK-0518 and placebo. In the primary logistic regression model, the 5 covariates are main effects. Because of the issue with small strata, there is no plan to consider the "saturated model" which includes all possible interactions between these covariates. In addition, potential heterogeneous treatment effects can be formally assessed in the same model by testing the treatment-by-factor interaction term.

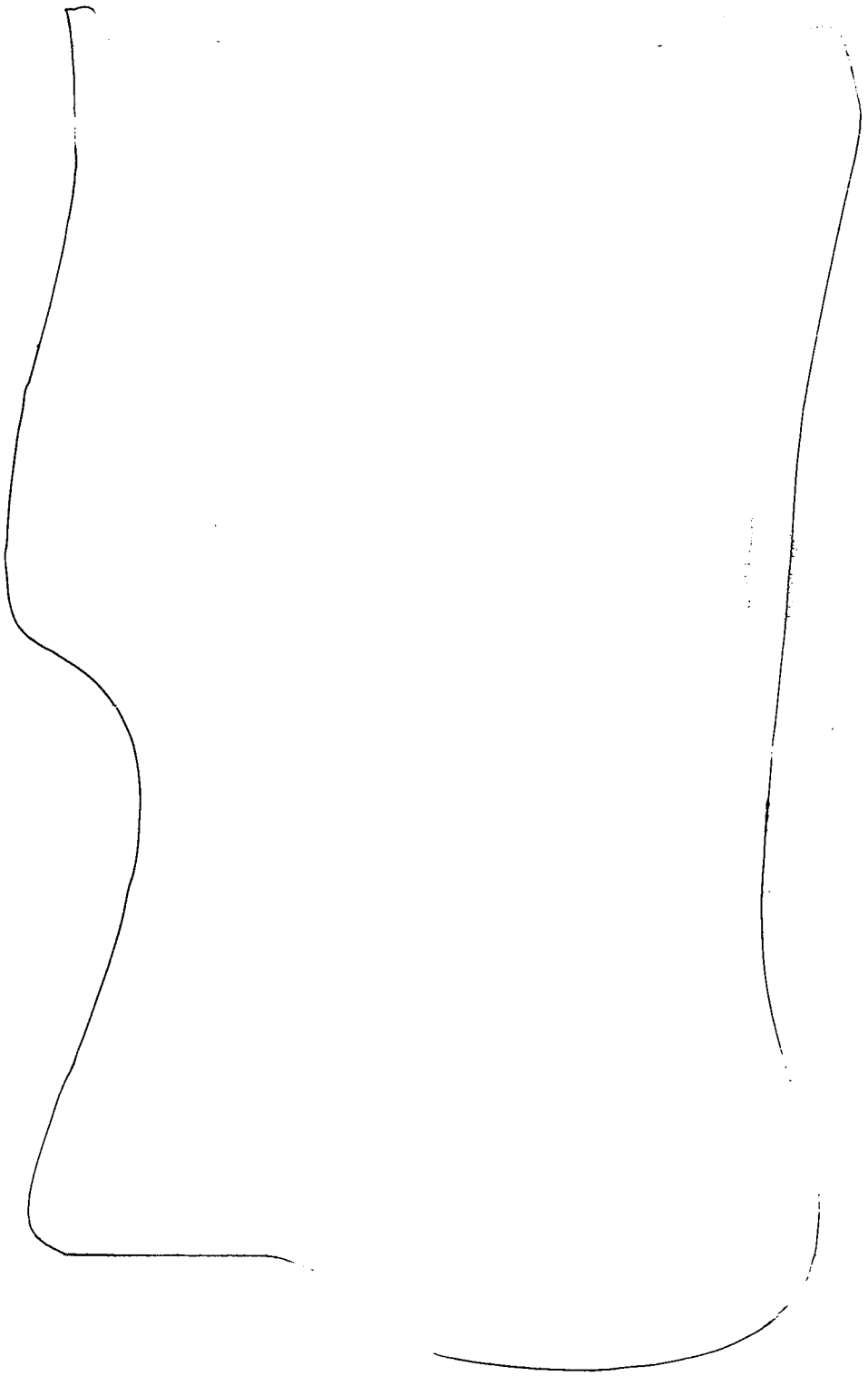
Also, the stratified CMH tests cannot address continuous prognostic factors such as baseline HIV RNA level.

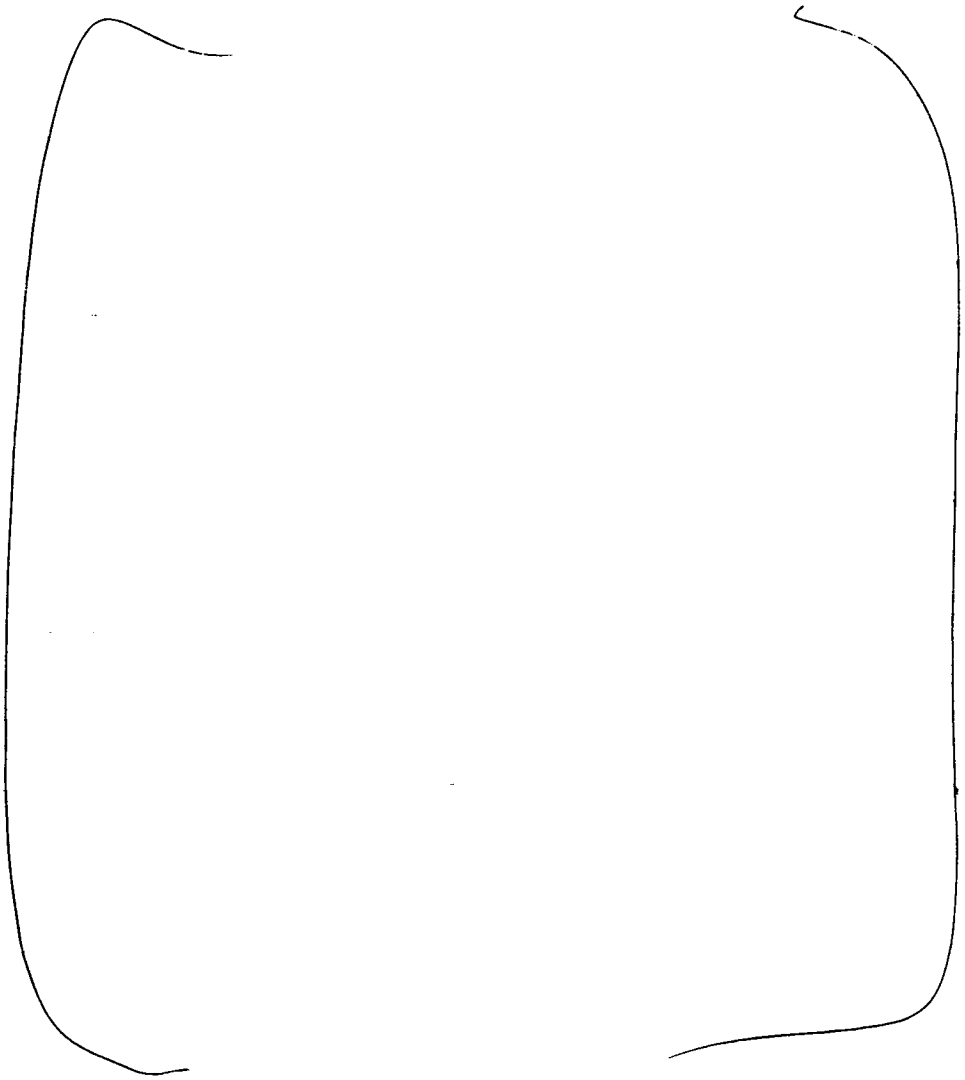
If the distribution of patients across covariate levels is sparse for some covariates, supportive analyses will be performed using the Cochran-Mantel-Haenszel test.

Dec 1: DAVP understood that MRL did not want to use the Cochran-Mantel-Haenszel test because it could adjust for continuous prognostic factors such as baseline HIV RNA levels, without converting them into dichotomous categories, and acknowledged that with very small strata you might not have any patients in one of the treatment arms.

MRL suggested using a logistic regression model as the primary approach and an additional analysis based on the CMH test. DAVP requested that MRL provide both approaches and stated that it prefers the CMH test as the primary approach. MRL agreed with this request.

4.





approval

5. **We prefer that you perform a test for treatment by study interaction at the 0.20 (rather than 0.10) level of significance. A 0.10 significance level for the treatment by study interaction test will not be powerful enough to detect a qualitative interaction and will even have less power to detect a quantitative interaction.**

MRL Response to Comment 5 received on Nov 29: We prefer to test for treatment by study interaction tests at the 0.10 significance level. The plan is to combine the data from both studies after ruling out statistical significance for qualitative interaction (differing directions of treatment effects) but regardless of statistical significance for the quantitative interaction (same direction of treatment effects but treatment effects between studies differ in magnitude). The estimate of treatment benefit from the meta-analysis could be interpreted as the average effect across all patients studied, which may still be relevant in the presence of quantitative interaction. For example, if the treatment

difference in proportion of patients achieving HIV RNA < 400 copies/mL at Week 16 between MK-0518 and placebo is 40% in one study but 35% in the other (quantitative interaction, assumed statistically significant because of large sample), one may also be interested in the average treatment benefit of 37.5% over placebo.

Any potential interactions (whether qualitative or quantitative) will be thoroughly explored and discussed and nominal p-values will be provided.

Dec 1: DAVP reemphasized that MRL perform a test for treatment by study interaction at the 0.20 level of significance. MRL stated the following points:

- **The two identical phase 3 studies were designed to allow meta-analysis thus an interaction test (at 0.10 level) was proposed to see if any differences were seen and to find out why the differences were occurring**
- **Expects consistency of treatment effects across geographic regions**
- **Interactions tests will be performed and the results and the p-value will be provided to the Division for interpretation**
- **Geographical region and size of the study should not impact the quality of the data**
- **Type 1 error may occurred if the 0.20 test was performed**

DAVP mentioned that it was not concern about the type 1 error and stated the following concerns with using the 0.10 level of significance:

- **Sample size is not large enough**
- **Power would be about 60% for detecting the smallest possible qualitative interaction and less than that for a quantitative interaction vs. about 80% if 0.20 was used**

There was no agreement reached for this topic. MRL stated that it will perform a test for treatment by study interaction and thoroughly explore any heterogeneity as to direction, size and to what it is attributed, and will keep the significance level at a 0.10 test understanding that DAVP may apply a different criteria.

6. **In addition to Week 24 analyses, we would also like to see analyses of Week 32 data at the time the primary analysis is performed. For Week 24 analysis, all patients who could have completed the 24-week visit should be included in the denominator. Similarly for Week 32 analysis, all patients who could have completed the 32-week visit should be included in the denominator. For your NDA submission, all data before or at database lock, including the data beyond Week 16, should be submitted.**

MRL Response to Comment 6 received on Nov 29: All data available at the time of the Week 16 analysis will be included in the submission. However, since all patients were enrolled during a relatively short period (~ 5 months), at the time when the last enrolled patient has Week 16 data, only a small number of patients (~10%) will have Week 32 data.

Dec 1: DAVP had no additional comments.

ADDITIONAL TOPICS OF DISCUSSION FROM THE DECEMBER 1, 2006 TELECONFERENCE MEETING:

Advisory Committee Meeting

MRL requested to have the Advisory Committee Meeting for MK-0518 in July 2007, stating that it is ready to meet the April 2007 NDA target submission date, as well as the roll-out of reviewable units prior to April 2007. DAVP responded that it was unable to agree to this timeframe at this time because of the following reasons:

- The Advisory Committee Meeting has to be available and it is usually scheduled between the 4th and 5th month during the review cycle
- DAVP must be able to adequately and thoroughly review all the safety and efficacy data to ensure that MK-0518 is a safe and effective product and that DAVP is confident about its final decision
- DAVP needs to have the opportunity to thoroughly review the data and not feel pressured as the work is performed

MRL understood and agreed with DAVP's reasons.

ACTION ITEMS/SUMMARY:

August 18, 2006.

6.MR L agreed to ensure that patient enrollment in Protocol 021 (phase 3, treatment-naïve) with regard to gender and ethnicity is well represented.

8.MR L will submit a complete sample derived analysis dataset (representative of Protocols 005, 018, and 019) for Protocols 004 and 005 by January 2007 (originally by December 2006).

Post-meeting notes: MRL agreed to submit complete datasets with real data for Protocols 004 and 005 by December 2006. On December 13, 2006, a teleconference meeting was held between DAVP and MRL representatives seeking agreement on the specifics of the statistical datasets (format & content) for Protocols 004 and 005 to be sent to DAVP by January 2007 instead of December 2006. Please see page 15 for the list of agreements reached during the December 13, 2006, teleconference meeting between MRL and DAVP.

9. MRL will provide an ____ vs. Monogram comparison mutation list and a copy of the publication paper for Division's expedited review and comment.

Note: MRL submitted a word document and a copy of the publication by electronic mail correspondence on December 5, 2006, and officially on December 7, 2006 (SN306). On December 20, 2006, DAVP communicated to MRL by electronic mail correspondence that the submitted microbiology information was acceptable.

10. MRL will include cytotoxicity data already submitted to the IND in the NDA application but will not include cytotoxicity study reports of MK-0518.
11. MRL will provide a written summary within the Protocol 004 Clinical Study Report highlighting changes or description of all changes from baseline.
12. MRL will provide the NC=F approach for all key efficacy analyses.
13. MRL will provide the Cochran-Mantel-Haenszel and the logistic regression approaches for the primary analysis and let DAVP decide which one to use in the review process.
14. MRL will submit separate data for Protocols 004, 005, 018, and 019 and a meta-analysis for Protocols 018 and 019 and understands that the drug approval process will be based on the totality body of evidence of the data.

OTHER SUBMISSION:

MRL meeting minutes for this Type B teleconference meeting were officially submitted to the Division on January 5, 2007 (SN337).

7 Page(s) Withheld

X Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 2A

IND 69,928

Merck & Co., Inc.
Attention: Robert A. Fromtling, Ph.D.
Director, Regulatory Affairs
126 E. Lincoln Avenue
P.O. Box 2000, RY33-208
Rahway, NJ 07065-0900

Dear Dr. Fromtling:

Please refer to your Investigational New Drug Application (IND) 69,928 submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MK-0518 (formerly L-000900612).

We also refer to the meeting between representatives of your firm and the FDA on August 9, 2006. The purpose of this Type C meeting was to discuss and gain concurrence on the issues pertaining to the planned filing of the original NDA for MK-0518.

The official minutes of the meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Monica Zeballos, Pharm.D., Regulatory Project Manager, at (301) 796-0840.

Sincerely yours,

{See appended electronic signature page}

Jeff Murray, M.D.
Acting Deputy Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure

RECORD OF FDA/INDUSTRY MEETING

Date of Meeting: **August 9, 2006**

IND: **69,928**

Drug: **MK-0518 (formerly L-000900612) integrase inhibitor**

Sponsor: **Merck & Co., Inc.**

Indication: **Treatment of HIV-1 infection**

Type of Meeting: **Face-to-face Type C (NDA Roll-Out Planning) meeting**

FDA Participants: (Title, Division/Office)

David Roeder, M.S., Associate Director, Regulatory Affairs, Office of Antimicrobial Products (OAP)
Jeff Murray, M.D., M.P.H., Deputy Director, Division of Antiviral Products (DAVP)
Kendall Marcus, M.D., Medical Team Leader, DAVP
Sarah Connelly, M.D. Medical Reviewer, DAVP
Charlene Brown, M.D., M.P.H., Medical Reviewer, DAVP
Kim Struble, Pharm.D., Medical Team Leader, DAVP
Kirk Chan-Tack, M.D., Medical Reviewer, DAVP
Wendy Carter, D.O., Medical Reviewer, DAVP
Stephen Miller, Ph.D., Pharmaceutical Assessment Lead, Division of Pre-Marketing Assessment 2 (DPA2), Office of New Drug Quality Assessment (ONDQA)
Kellie Reynolds, Pharm.D., Clinical Pharmacology Team Leader, Division of Clinical Pharmacology 4 (DCP4), Office of Clinical Pharmacology (OCP), Office of Translational Sciences (OTS)
Ita Yuen, Ph.D., Pharmacology/Toxicology Reviewer, DAVP
Jules O'Rear, Ph.D., Microbiology Team Leader, DAVP
Sung Rhee, Ph.D., Microbiology Reviewer, DAVP
Fraser Smith, Ph.D., Acting Statistical Team Leader, Division of Biometrics 4 (DB4), Office of Biostatistics (OB), Office of Translational Sciences (OTS)
Karen Qi, Ph.D., Statistical Reviewer, DB4, OB, OTS
Anthony DeCicco, R.Ph., Chief, Project Management Staff, DAVP
John O'Malley, Specialist, Information Technology
Monica Zeballos, Pharm.D., Regulatory Project Manager, DAVP

Merck Research Laboratories (MRL) Participants:

Bach-Yen Nguyen, M.D., Senior Director, Clinical Research
Robin Isaacs, M.D., Executive Director, Clinical Research
Robert Frmtling, Ph.D., Director, Regulatory Affairs
Ercem Atillasoy, M.D., Senior Director, Regulatory Affairs
Michael Nessly, M.S., Director, Biostatistics
Marian Iwamoto, M.D., Ph.D., Director, Clinical Pharmacology
Pramod Kotwal, Ph.D., Associate Director, Chemistry Manufacturing and Controls
Daniel Orfe, M.S., Associate Director, Worldwide Regulatory Operations
Keaven Anderson, Ph.D., Executive Director, Late Stage Development, BARDS
Pamela Iori, M.S., Senior Regulatory Coordinator, Regulatory Coordination
Ramon Kemp, D.V.M., Ph.D., Director, Preclinical Safety Assessment

Background:

MRL requested this Type C (NDA Roll-Out Planning) meeting on May 26, 2006 (SN183). The meeting background package (BP) was submitted on June 26, 2006 (SN194) and updated Phase II data (safety and efficacy) were submitted by electronic mail correspondence on July 20, 2006 and officially on July 21, 2006 (SN208). The following communications between MRL and the Division included:

- On July 31, 2006, DAVP sent two questions to MRL by electronic mail correspondence regarding the BP and requested that MRL provide a prompt response to Question 1 (see Attachment A).
- On August 4, 2006, MRL provided DAVP with responses to both Questions sent on July 31, 2006 (see Attachment A and official submission SN219).
- On August 8, 2006, DAVP sent microbiology comments/responses to MRL by facsimile correspondence regarding the BP (Question 5) and previous communications by electronic correspondence on July 28, August 1, and August 4, 2006 (see Attachment B).
- On August 7, 2006, DAVP sent preliminary responses to MRL by telephone facsimile correspondence in reply to the BP questions (see Attachment C).

Objectives:

- To discuss the format and content of three possible filing strategies:

  - Scenario A is a filing based on 100 % of the 24-week data from both ongoing Phase III studies (Protocols 018 and 019) in treatment-experienced patients
  - Scenario B is filing based on an interim analysis of efficacy performed when 50% of patients in both Phase III studies (Protocols 018 and 019) have reached Week 24 and 100% have reached Week 16, including the following:
    a. Safety Update Report (SUR) and Statistical (complete 24-week data) Update Report will be submitted 2 months post filing
    b. Final Clinical St udy Reports (CSRs) with 48-week data for Phase III studies will be available to support traditional approval

- Scenario C (sent to DAVP by electronic correspondence on July 20, 2006 and officially on July 21, 2006 (SN208) is a filing based on 16-week Phase III data, including the following:
  a. SUR will be submitted 2 months after the last filed component
  b. No additional repor ts will be provided during review
  c. Complete Phase III CSRs will be provided post-approval following completion of studies
  d. No Statistical Update Re port

- To discuss the rollout plan for reviewable units, including identification of sections to be rolled out and submission dates and electronic format of such reviewable units

Discussion:

Presentations

Dr. Robert Fromtling from MRL presented an overview highlighting the following topics:

- MK-0518 has a novel mechanism of action (integrase inhibition), will be first in class, and will meet an unmet medical need
- Recent Phase II data out to 24 weeks demonstrate sustained and potent antiretroviral activity in ART-naïve and treatment-experienced patients
- Filing Scenario B is no longer an option
- Favorable safety and tolerability profile
- Review of the proposed filing Scenarios A and C, proposed indication, and dose
- Presentation of the timing and contents of the rolling NDA submission

In response to DAVP's request, Dr. Bach-Yen Nguyen from MRL presented updated clinical data, including:

- Number of patients at Week 24 including the breakout for the Phase II studies (Protocols 005 & 004) and Phase III studies (Protocols 018 & 019) for Scenario C
- All efficacy data (viral load & CD4 count) by baseline Phenotypic Sensitivity Score (PSS) for Protocol 005 by T-20 use in Optimized Background Therapy (OBT) at Week 24 for patients on no T20, naïve T20, and non-naïve T20
- Anticipated cumulative number of patients enrolled (666) in Phase III studies (Protocols 018 and 019)
- Key features of filing Scenarios A and C
- Estimated numbers of patients enrolled in Phase II and Phase III studies at the time of initial NDA submission
- Estimated number of patients receiving MK-0518 in Week 16 (460 patients) and Week 24 (280 patients) for the proposed Scenario C
- Estimated total number of patients from Phase II and III in the safety database

Refer to submission (SN230) dated August 30, 2006 for the complete set of the presentation slides and MRL's meeting minutes.

Questions

On August 7, 2006, DAVP sent preliminary responses to MRL by facsimile telephone correspondence in response to the following questions (see Attachment C). MRL's submission questions are listed first, followed by DAVP's responses in bold. Additional comments, if any, from the August 9, 2006, NDA Roll-Out Planning meeting are located below the initial responses in bold.

Scenario A
Sponsor proposes to submit 100% of the 24-week clinical data (efficacy, safety, PK/PD) from Phase III studies. Safety Update Report (SUR) will be submitted within 2 months following NDA submission.

1. Does the Agency agree that submission of a SUR 2 months post filing, rather than 4 months post filing, will facilitate a more rapid review of the file, e.g., less than 6 months?

   FDA Response: No.

Scenario B
Sponsor proposes to submit interim analysis of efficacy when 50% of patients in the two identical Phase III Protocols combined reach Week 24, provided that the remaining patients have reached Week 16.

2. Does the FDA agree with the proposed plans for submission of interim data to be followed by a SUR, including a statistical update report 2 months post filing as outlined in the meeting background package?

   FDA Response: No. This scenario requires reanalysis of statistical data when the update is provided; therefore, the Division does not agree with submission of interim data followed by a statistical update 2 months post filing.

3. Does the Agency concur that submission of interim data could favorably impact the PDUFA review timelines, i.e., will the original submission of the interim analysis data set the PDUFA date?

   FDA Response: No, please refer to the previous response.

Scenario C (submitted by email on July 27, 2006 and officially on July 21, 2006 SN208)
This scenario is the same as B but with no statistical update report 2 months following submission of the final file pieces.

4. Based on recent Phase 2 data (ART-naïve & experienced-patients), does the Agency concur with MRL's proposal to submit the original NDA based on 16 week Phase 3 data?

   FDA Response: The Phase II data demonstrates a robust response in both ART-naïve and experienced patients who were in the MK-0518 arms. Additional data provided by MRL estimates there will be Week 24 data for 366 patients randomized to MK-0528 400 mg bid in Phase II and III studies. In addition, an estimated 451 patients will have received MK-0518 doses of 400 mg bid or greater by the time of filing in Scenario C. The Division may concur with this proposal pending further internal discussion.

August 9: DAVP stated that the latest Phase II 24-week data are impressive. DAVP proposed that MRL file the NDA with 16-week data (100%) from Phase III studies (Protocols 018 & 019) to support accelerated approval with the following conditions:

- **Simultaneous analysis of all available 24-week data from Phase III**
- **Label will only include 24-week data**
- **A 24-week integrated efficacy analysis of the data**
- **The primary analysis of Week 16 data will be performed separately for the two Phase III studies**
- **Safety database patient requirements will be met**
- **24-week data will be reviewed once**

MRL agreed with DAVP's proposed filing scenario and proposed the following submission approach:

- **To include all available (~61%) 24-week data from Phase III studies**
- **To present tabular and graphical presentation of the Week 24 results**
- **To amend relevant protocols and corresponding Statistical Analysis Plan to state that Week 16 will be the primary endpoint**
- **To likely submit the last roll-out component in April 2007**

MRL stated that if the Week 16 primary analysis is statistically significant it would analyze Week 24 data. DAVP reminded MRL that our previous discussions about statistical significance levels may still be applicable. For example, the 0.001 level of significance may be required for a pooled meta-analysis of Week 24 data if the Phase IIA results from Protocol 005 are negative. DAVP preferred to see separate Week 24 analyses for Studies 018 and 019. MRL agreed to do separate Week 24 analyses as well as a combined meta-analysis.

DAVP agreed with MRL's submission approach and reiterated that MRL submit all available 24-week data. In addition, DAVP stated that both 16-week and 24-week data should be included in Advisory Committee discussions.

DAVP informed MRL that receipt of the last NDA reviewable unit will trigger the PDUFA clock and that the Advisory Committee Meeting could be scheduled 4 months after the PDUFA clock started.

It was agreed that the Phase II study (Protocol 005) could served as a pivotal study.

5. The background package contains a detailed layout (Table) of the rollout plan of the reviewable units. Does the FDA concur with the proposed rollout plan, its reviewable components, and the proposed timeline for the rollout?

FDA Response: The Division concurs with the proposed rollout plan with the following comment:

1. **For the rollout plan of the microbiology reviewable unit please refer to the Division's response sent to you in a separate facsimile correspondence.**

August 9: MRL acknowledged receipt of the August 8, 2006 FDA facsimile correspondence, which included microbiology comments/responses regarding the meeting BP (SN194) and previous electronic communications between Dr. Frontling from MRL and Monica Zeballos from FDA. MRL stated that MRL microbiologists were unable to attend this face-to-face meeting, but agreed to submit responses to the August 8, 2006 correspondence and suggested that MRL/FDA plan a teleconference to discuss and resolve any outstanding microbiology issues. DAVP agreed with this approach.

In addition, DAVP recommended that MRL submit microbiology datasets early and perform an independent analysis of resistance data. MRL acknowledged these recommendations.

6. Does the Agency concur with MRL's approach for electronic submission of the planned NDA?

FDA Response: The Division concurs with the following comments:

2. **Please submit a run or sample eCTD submission prior to the initial submission of the first reviewable NDA component (targeted January 2007).**

August 9: MRL had no objection to providing a sample eCTD, but most likely will send a previously filed eCTD given that it had already submitted over 400 eCTDs, with 6 of them being filings of original applications, both to CDER and CBER. DAVP acknowledged this information and stated that MRL will not need to resubmit a sample eCTD.

3. **Please provide links in the eCTD to patient narratives and a paper copy of the Table of Contents.**

August 9: MRL described the navigation procedures to the patient narratives as follows:

- **Patient narratives will be aggregated into an appendix of the CSRs**
- **Appendix would contain a TOC – List of Patients**
- **Appendix TOC would be hyperlinked and bookmarked to facilitate navigation to the patient narratives**

DAVP acknowledged this information and concurred that MRL will not need to submit a paper copy of the TOC based on the proposed navigation procedures and proposed use of the FDA Electronic Submission Gateway capabilities.

4. **On page 2, section 7 "Summary of Plans for Electronic Submission", please confirm that the Analysis programs (SAS) will include the programs both for deriving the final analysis datasets from the raw datasets and for generating the tables, figures and listings in the CSR, and that the SAS® datasets (XPT) will provide raw and derived data.**

August 9: MRL stated that the requested programs will be incorporated in the appropriate location and will be accessible through the eCTD viewer.

DAVP asked if MRL would be providing appropriate hyperlinks to facilitate the review of submissions. MRL responded that it is its practice to provide eCTDs rich in hypertext links. MRL stated that all citations to references, study reports, sections, tables, and figures will be linked.

5. Please submit virology information in Module 5 Clinical Study Reports **(see *http://www.fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf*) as follows:**

Module 5 Clinical Study Reports

5.3.5.4 Other Study reports and related information

Antiviral information

Biochemical, cell culture, etc. study reports including descriptions of methodolc
Biochemical, cell culture, etc. data
Animal model(s) study reports including descriptions of methodology
Animal model(s) data
In vivo (clinical) study reports including descriptions of methodology
In vivo (clinical) data
Viral load, resistance, other[a]

In vivo (clinical) assays (methodologies and performance characteristics)

Viral load
Genotype
Phenotype
Other

Miscellaneous microbiological information

[a] In *FDA format:* For additional information, please refer to the FDA Guidance for Industry on *Antiviral Product Development--Conducting and Submitting Virology Studies to the Agency* *http://www.fda.gov/cder/guidance/index.htm* (June 2006).

August 9: MRL agreed to adhere to the layout of 5.3.5.4 and comply with the Electronic Common Technical Document guidance.

Additional comments

DAVP concurred with MRL's plan to submit the CMC Module in January 2007 with the understanding that the manufacturing facilities will be ready for inspections at the time of submission of the last reviewable section of the NDA.

Additional topics discussed on August 9

Treatment IND —— (Protocol 023)

DAVP stated that serious adverse events (AEs) cumulative data from the Expanded Access Protocol 023 would not be included in the MK-0518 label, unless unusual or serious safety issues arise. MRL agreed with this approach.

The topic of patients not receiving concomitant use of both MK-0518 and TMC 125 under Treatment IND —— was discussed. DAVP asked MRL to consider performing trough and blood levels. MRL indicated its preference to wait until data are obtained from the drug interaction study (Protocol 026) but stated that it will take this recommendation back for discussion.

Post Meeting Note: On August 9, 2006 Dr. Stephen Miller and Monica Zeballos, Pharm.D., from FDA contacted Dr. Robert Fromtling form MRL by telephone with information that additional review of the Treatment IND within other groups at the FDA still needed to be completed. Therefore, the safe to proceed letter for Treatment IND —— will be sent to MRL by facsimile correspondence no later that August 18, 2006.

Diversity of Study Subjects Enrolled in MK-0518 Development Program

DAVP encouraged MRL to enroll a diverse population (i.e., females and Hispanics) in the MK-0518 Phase III Naïve study. In addition, DAVP requested that MRL provide a summary table of current diversity demographics (gender/ethnicity) for the Phase III studies (Protocol 018 & Protocol 019).

Inclusion of "All Cause Mortality" within MK-0518 Phase III CSRs

DAVP requested that MRL provide "all cause mortality" information within the Phase III CSRs as follows:

- For all patients for 1 yr after enrollment and randomization in MK-0518 studies regardless whether the patient is still continuing on study or have discontinued
- To obtain the cause of death if the patient has died
- To obtain information on patients' enrollment in other clinical trials

MRL expressed its concerns to whether or not patients consented to provide enrollment information in other clinical trials and that it would have to go back and check the informed consent and possibly amend the document to comply with this request.

Action Items/Summary:

1.MR L agreed with DAVP's proposal to filing with 16-week Phase III data (separate primary analyses), a simultaneous 24-week integrated and separate analysis, and inclusion of 24- week data in the label.

2.MR L will amend all relevant protocols and corresponding Statistical Analysis Plan (SAP) to state that Week 16 will be the primary endpoint.

Note: On November 3, 2006 DAVP requested that MRL submit the amended Phase III protocols and the SAP for review. The BP (SN254) for the upcoming Pre-NDA meeting did not satisfy this action item.

3.MR L will submit a request for Type B (Pre-NDA) meeting to be scheduled in early November 2006.

Note: DAVP granted a Pre-NDA meeting on September 12, 2006.

4.MR L will submit responses to FDA August 8, 2006 facsimile correspondence addressing microbiology filing issues.

Note: MRL submitted responses on Sept 8, 2006 (SN239) and Sept 26, 2006 (SN247).

5.DAVP conc urred with MRL's plan to submit the CMC Module in January 2007 with the understanding that the manufacturing facilities will be ready for inspections at the time of submission of the last reviewable section of the NDA.

6.Serious AEs cumul ative data from Treatment IND [redacted] (Protocol 023) will not be included in the MK-0518 label unless safety issues arise.

7.MR L will provide a gender and race demographics table for the Phase III studies in 3-4 weeks.

Note: MRL submitted the table on October 2, 2006 (SN251).

8.MR L will enroll a diverse study population in the Phase III Naïve study.

9.MR L would include information on 'all cause mortality' in the Phase III 48 week CSRs.

Attachment A

FDA questions below were sent to Dr. Fromtling by electronic mail correspondence on July 31, 2006. Dr. Fromtling provided responses (in bold) to the questions on August 4, 2006 by electronic mail correspondence and officially on August 8, 2006 (SN219).

1. Please provide the following information to me (by email) as soon as possible, and be prepared to present this information at the beginning of the upcoming meeting.

   a. For scenario C, the number of patients at Week 24. Please provide the break out for the Phase 2 studies (Protocols 005 & 004) and for the Phase 3 studies (Protocols 018 & 019).

   MRL Response: It is attached as document Type C ESTIMATED #PTS.....

   b. All effica cy data (viral load & CD4 count) for Protocol 005 by T-20 use (patients on no T20, naïve T20, and non-naïve T20).

   MRL Response: Tables with the requested data are attached (Tables Type C Table 9.1....; and Type C Table 9.2...).

2. Regarding the electronic submission of the NDA in eCTD format

   a. Are you registered to comply with the FDA Electronic Submissions Gateway (ESG) capabilities? See the following link for additional information: http://www.fda.gov/esg/

   MRL Response: Merck has just completed a major upgrade regarding our configuration, and is currently conducting internal testing. Once that is complete (within next two weeks) we plan to test our AS2 Gateway connection with FDA and hope to be in production by end of August.

   b. Do you use the "Global Submit Review" software to browse electronic submissions that conform to the eCTD format?

   MRL Response: Merck has chosen an eCTD viewing software package that provides our internal reviewers with the ability to view an eCTD submission with the same views provided by Global Submit Review.

Attachment B

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: August 8, 2006

To: Robert A. Fromtling, Ph.D., Director, Worldwide Regulatory Affairs

Sponsor: Merck & Co., Inc.

Address: P.O. Box 2000 (RY 33-208)
126 East Lincoln Avenue
Rahway, NJ 07065-0900

From: Monica Zeballos, Pharm.D., Regulatory Project Manager

Through: Sung Rhee, Ph.D., Microbiology Reviewer

Concur: Kendall Marcus, M.D., Medical Team Leader
Julian O'Rear, Ph.D., Microbiology Team Leader

IND: 69,928

Drug: MK-0518 (formerly L-000900612)

Subject: Microbiology comments/responses regarding SN194 (BP)

The following comments and responses are being conveyed on behalf of the Microbiology Review Team, and are directed towards your June 26, 2006 submission (SN194, question 5) and the communications by electronic correspondence on July 28, August 1, and August 4, 2006 between Dr. Robert Fromtling of MRL and Monica Zeballos, Pharm.D. of FDA. Please also refer to the Division's preliminary responses dated August 7, 2006 sent to you by telephone facsimile correspondence in reply to the questions posted in submissions dated June 26, 2006 (SN194) and July 21, 2006 (SN208).

FDA comment 1 (sent Dr. Fromtling on July 28, 2006 by electronic correspondence): It's not clear from the background package (SN194) that you are prepared to submit resistance data; therefore, on behalf of Dr. Jules O'Rear, Microbiology Team Leader, I'm conveying the following comment:

We stated at the December 5, 2005 meeting that if the resistance pattern was simple and there were only one or two predominant mutations as is observed for lamivudine and M184V/I, genotyping would be adequate. The guidance on the use of resistance testing in the development of drugs for HIV infection encourages sponsors to begin conducting resistance analyses early in development. We have no record of you providing clinical data on resistance to your integrase inhibitor and cannot comment on the need for phenotypic data. We recommend that you provide the "agreed to" phenotypic data.

We agree that genotypic data for gp160 and protease cleavage sites, coreceptor usage and therapeutic drug monitoring are not needed. With respect to the latter, it is recommended that you carefully evaluate the safety profile of MK-0518 for the potential to increase the dose for improved durability in the deep salvage population.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at (301) 796-0840, if you have any questions regarding the contents of this transmission.

Monica Zeballos, Pharm.D.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products

Attachment C

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: August 7, 2006

To: Robert A. Fromtling, Ph.D., Director, Worldwide Regulatory Affairs

Address: P.O. Box 2000 (RY 33-208)
126 East Lincoln Avenue
Rahway, NJ 07065-0900

From: Monica Zeballos, Pharm.D., Regulatory Project Manager

Through: Sarah Connelly, M.D., Medical Reviewer
Karen Qi, Ph.D., Statistical Reviewer

Concur: Kendall Marcus, M.D., Medical Team Leader
Julian O'Rear, Ph.D., Microbiology Team Leader
Fraser Smith, Ph.D., Acting Statistical Team Leader

IND: 69,928

Drug: MK-0518 (formerly L-000900612)

Subject: Division's preliminary responses regarding BP (SN194) & SN208

Attached are the FDA preliminary responses to the questions that you posed in your submissions dated June 26, 2006 (SN194) and July 21, 2006 (SN208). During our upcoming type C (NDA Roll-Out Planning) meeting with you on August 9, 2006 we will be prepared to clarify any questions you have regarding our responses. However, please note that if there are any major changes to your development plan (based upon our responses herein), we will not be prepared to discuss, nor reach agreement on, such changes at the August 9, 2006 meeting. Any modifications to the development plan that you would like to discuss with the FDA should be submitted as a new meeting request.

Scenario A
Sponsor proposes to submit 100% of the 24-week clinical data (efficacy, safety, PK/PD) from Phase III studies. Safety Update Report (SUR) will be submitted within 2 months following NDA submission.

Question 1: Does the Agency agree that submission of a SUR 2 months post filing, rather that 4 months post filing, will facilitate a more rapid review of the file, e.g., less than 6 months?

FDA Response: No.

Scenario B
Sponsor proposes to submit interim analysis of efficacy when 50% of patients in the two identical Phase III Protocols combined reach Week 24, provided that the remaining patients have reached Week 16.

Question 2: Does the FDA agree with the proposed plans for submission of interim data to be followed by a SUR, including a statistical update report 2 months post filing as outlined in the meeting background package?

FDA Response: No. This scenario requires reanalysis of statistical data when the update is provided; therefore, the Division does not agree with submission of interim data followed by a statistical update 2 months post filing.

Question 3: Does the Agency concur that submission of interim data could favorably impact the PDUFA review timelines, i.e., will the original submission of the interim analysis data set the PDUFA date?

FDA Response: No, please refer to the previous response.

Scenario C (submitted by email on July 27, 2006 and officially on July 21, 2006 SN208)
This scenario is the same as B but with no statistical update report 2 months following submission of the final file pieces. It also includes the following:
- ***SUR to be submitted 2 months after last file component***
- ***No additional reports will be provided during review***
- ***Complete Phase III CSRs will be provided post approval following completion of studies***

Question 4: Based on recent Phase 2 data (ART-naïve & experienced-patients), does the Agency concur with MRL's proposal to submit the original NDA based on 16 week Phase 3 data?

FDA Response: The Phase II data demonstrates a robust response in both ART-naïve and experienced patients who were in the MK-0518 arms. Additional data provided by MRL estimates there will be Week 24 data for 366 patients randomized to MK-0528 400 mg bid in Phase II and III studies. In addition, an estimated 451 patients will have received MK-0518 doses of 400 mg bid or greater by the time of filing in Scenario C. The Division may concur with this proposal pending further internal discussion.

NDA timeline and electronic format (see section 7)

Question 5: The background package contains a detailed layout (Table) of the rollout plan of the reviewable units. Does the FDA concur with the proposed rollout plan, its reviewable components, and the proposed timeline for the rollout?

FDA Response: The Division concurs with the proposed rollout plan with the following comment:

4.For the rollout plan of the microbiology reviewable unit please refer to the Division's response sent to you in a separate facsimile correspondence.

Question 6: Does the Agency concur with MRL's approach for electronic submission of the planned NDA?

FDA Response: The Division concurs with the following comments:

5.Pleas e submit a run or sample eCTD submission prior to the initial submission of the first reviewable NDA component (targeted January 2007).

6.Pleas e provide links in the eCTD to patient narratives and a paper copy of the Table of Contents.

6.On page 2, sec tion 7 "Summary of Plans for Electronic Submission", please confirm that the Analysis programs (SAS) will include the programs both for deriving the final analysis datasets from the raw datasets and for generating the tables, figures and listings in the CSR, and that the SAS® datasets (XPT) will provide raw and derived data.

7.***Please submit viro logy information in Module 5 Clinical Study Reports (see http://www.fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf) as follows:***

Module 5 Clinical Study Reports

5.3.5.4 Other Study reports and related information

Antiviral information

Biochemical, cell culture, etc. study reports including descriptions of methodolc
Biochemical, cell culture, etc. data
Animal model(s) study reports including descriptions of methodology
Animal model(s) data
In vivo (clinical) study reports including descriptions of methodology
In vivo (clinical) data
Viral load, resistance, other[a]

In vivo (clinical) assays (methodologies and performance characteristics)

Viral load
Genotype
Phenotype
Other

Miscellaneous microbiological information

[a] In *FDA format:* For additional information, please refer to the FDA Guidance for Industry on *Antiviral Product Development--Conducting and Submitting Virology Studies to the Agency* http://www.fda.gov/cder/guidance/index.htm (June 2006).

Additional comments

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at (301) 796-0840, if you have any questions regarding the contents of this transmission.

Monica Zeballos, Pharm.D.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products

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

/s/

Jeffrey Murray
11/17/2006 08:24:07 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 69,928

Merck & Co., Inc.
Attention: Philip L. Huang, M.D.
Director, Regulatory Affairs
Sumneytown Pike
P.O. Box 4, BLA-20
West Point, PA 19486

Dear Dr. Huang:

Please refer to your Investigational New Drug Application (IND) 69,928 submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MK-0518 (formerly L-000900612).

We also refer to the meeting between representatives of your firm and the FDA on December 5, 2005. The purpose of this Type B meeting was to gain feedback on issues critical to your program prior to entry into Phase III.

The official minutes of the meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Monica Zeballos, Pharm.D., Regulatory Project Manager, at (301) 796-0840.

Sincerely yours,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Division Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure

RECORD OF FDA/INDUSTRY MEETING

Date of Meeting: December 5, 2005

IND: 69,928

Drug: MK-0518 (formerly L-000900612) integrase inhibitor

Sponsor: Merck & Co., Inc.

Indication: Treatment of HIV-1 infection

Type of Meeting: Face-to-face Type B (End-of-Phase II) meeting

FDA Participants: (Title, Division/Office)

Mark Goldberger, M.D., M.P.H., Office Director, Office of Antimicrobial Products (OAP)
Debra Birnkrant, M.D., Division Director, Division of Antiviral Products (DAVP)
Jeff Murray, M.D., M.P.H., Division Deputy Director, DAVP
Kendall Marcus, M.D., Medical Team Leader, DAVP
Melisse Baylor, M.D. Medical Reviewer, DAVP
Stephen Miller, Ph.D., Pharmaceutical Assessment Lead, Division of Pre-Marketing Assessment 2 (DPA2), Office of New Drug Quality Assessment (ONDQA)
Kellie Reynolds, Pharm.D., Clinical Pharmacology Team Leader, Division of Clinical Pharmacology 4 (DCP4), Office of Clinical Pharmacology (OCP)
Derek Zhang, Ph.D., Clinical Pharmacology Reviewer, DCP4, OCP
Ita Yuen, Ph.D., Pharmacology/Toxicology Reviewer, DAVP
Jules O'Rear, Ph.D., Microbiology Team Leader, DAVP
Sung Rhee, Ph.D., Microbiology Reviewer, DAVP
Greg Soon, Ph.D., Statistical Team Leader, Division of Biometrics 4 (DB4), Office of Biostatistics (OB), Office of Translational Sciences (OTS)
Fraser Smith, Ph.D., Statistical Reviewer, DB4, OB, OTS
Karen Qi, Ph.D., Statistical Reviewer, DB4, OB, OTS
Anthony DeCicco, R.Ph., Chief, Project Management Staff, DAVP
Virginia Behr, B.S., Chief, Project Management Staff, DAVP
Monica Zeballos, Pharm.D., Regulatory Project Manager, DAVP

Merck Research Laboratories (MRL) Participants:

Joshua Chen, Ph.D., Senior Biometrician, Biostatistics
Michael Nessly, M.S., Director, Biostatistics
Marian Iwamoto, M.D., Ph.D., Director, Clinical Pharmacology
John Wagner, M.D., Ph.D., Executive Director, Clinical Research
Philip Huang, M.D., Senior Director, Regulatory Affairs
Tamra Goodrow, Ph.D., Senior Director, Regulatory Affairs
Bach-Yen Nguyen. M.D., Senior Director, Clinical Research
Robin Isaacs, M.D., Executive Director, Clinical Research
Larissa Wenning, Ph.D., Research Fellow, Drug Metabolism
Julie Stone, Ph.D., Senior Research Fellow, Drug Metabolism
Mike Miller, Ph.D., Director, Antiviral Research
Pamela Iori, M.S., Regulatory Coordinator, Regulatory Coordination
Michelle Kloss, Ph.D., Executive Director, Regulatory Affairs
Ramon Kemp, D.V.M., Ph.D., Director, Preclinical Safety Assessment
Hedy Teppler, M.D., Director, Clinical Research

Background:

MRL requested this Type B (End-of-Phase II) meeting on September 27, 2005 (SN103). The meeting background package (BP) was submitted on November 2, 2005 (SN110). On December 1, 2005, DAVP sent two questions to MRL by telephone facsimile correspondence regarding the BP and requested that MRL address them during the face-to-face meeting. On December 2, 2005, MRL provided DAVP with a response to Question 1 (see Attachment A), and indicated that it would be prepared to address Question 2 during the face-to-face meeting. In addition, on December 2, 2005, DAVP sent preliminary responses to MRL by telephone facsimile correspondence in reply to the BP questions (see Attachment B).

Objectives:

- To review:
  - the overall drug development program proposed for MK-0518, including the preliminary Phase III dose selection (to be confirmed in January 2006)
  - plans to establish a Data Safety Monitoring Board (DSMB) for the Phase III studies to address both safety and efficacy considerations
- To gain concurrence that the components of the clinical development program (see below) are adequate to support regulatory approval of MK-0518 for the proposed indication
  - previously outlined Phase I program
  - the Phase III studies described in this submission
  - the dose selected for study in Phase III
  - the proposed extent and duration of clinical exposure in the safety profile
- To understand the feasibility and requirements of an accelerated regulatory submission based on the results of a DSMB review of efficacy performed when 50 % of patients of both Phase III studies combined have efficacy data at Week 24

Discussion:

Introduction

Dr. Debra Birnkrant, Division Director, expressed the Division's feedback and interest with MRL's proposed pivotal clinical development program, including:

- Phase III dose agreement
- Limited proposed safety database (small number of patients will have been exposed at the time of NDA submission)
- Submission timelines

Presentation

In response to DAVP's request and to facilitate discussion of Question 5, Dr. Bach-Yen Nguyen from MRL presented an overview of the following topics (see response to Question 5 for detailed information):

- Highlighting key aspects of the anticipated study timeline and enrollment of key Phase III events
- Safety data available at critical milestones

Refer to submission (SN142) dated February 9, 2006 for the complete set of the presentation slides and MRL's official meeting minutes.

Questions

On December 2, 2005, DAVP sent preliminary responses to MRL by facsimile telephone correspondence in response to the following questions (see Attachment B). MRL's submission questions are listed first, followed by DAVP's responses in bold. Additional comments, if any, from the December 5, 2005, End-of-Phase II meeting are located below the initial responses in bold (Questions 1 and 3 are answered together; DAVP's response can be found following Question 3). Please see Attachment B for the complete version of the submitted questions.

General

1.Does FD A concur that the proposed Phase III studies and program design will be adequate to support the following indication at the time of initial regulatory approval?
Proposed initial indication:

Clinical

3.Does the F DA concur that the design of this protocol is adequate to support initial regulatory approval?

FDA Response: Results of the two proposed Phase III studies should be adequate to support the proposed indication. We agree that the design of these protocols is adequate. Comments regarding these protocols will be communicated to you in the next week.

Dec 5: DAVP agreed with MRL's rationale for choosing the dose of MK-0518 (400 mg p.o. twice a day) and concurred with MRL's preliminary Phase III dose selection based on available safety and efficacy data from the two ongoing Phase II studies (Protocols 004 and 005). MRL agreed to submit more detailed data in support of the selected dose in January, 2006, and requested DAVP's prompt feedback. DAVP agreed to provide feedback within two weeks after receipt of supporting dose data.

MRL asked if the forthcoming comments regarding the Phase III protocols would request changes to the clinical conduct of the studies. DAVP replied with a NO.

General

2.Does FD A concur with plans and timing proposed for pediatric development outlined in Section 7? MRL will be seeking a deferral of pediatric studies at the time of submission of the MK-0518 NDA. Does FDA concur that this program is appropriate for pediatric deferral?

The pediatric program should be ongoing at the time of NDA submission; the submission of pediatric data can be deferred at the time of NDA submission. Please comment on any progress on the development of a pediatric suspension. Please also comment on the type of pediatric studies planned and the timeline for the initiation of such studies.

Clinical

4.Does the FDA concur that the safety database provided by the proposed clinical development program (see Section 7 – Overview of Clinical Development Program) is adequate in terms of total patient numbers and duration of exposure?

The results of these studies would provide a small but acceptable safety database. However, if any safety signal is identified, more data may be needed.

Dec 5: MRL confirmed its understanding of the response.

5.Does the FDA concur with this potentially accelerated regulatory submission? As described (see Section 7 – Overview of Clinical Development Plan), even if a decision to file early were made, the Phase III studies would continue uninterrupted, and outstanding safety data from all patients by Week 24 would be available during review within 3 months from the NDA submission.

We will respond after the face-to-face meeting.

Dec 5: Dr. Bach-Yen Nguyen from MRL, provided the following detailed information:

- **Anticipated program timelines**
- **Plans to submit an interim analysis of efficacy data when 50 % of Phase III patients (Studies 018 and 019 combined) had reached Week 24**
- **The estimated number of patients by length of study drug treatment in Studies 018 and 019 at the time of NDA submission (with submission of data after 50% of patients have reached Week 24 of both Phase III studies combined)**

DAVP acknowledged the information presented and stated that if MRL plan to submit the interim analysis as stated above, it expects that 100 % (all patients) in Studies 018 and 019 will have reached Week 16 on study drug.

The issues of granting priority review with a six month review cycle and the need to go to an Advisory Committee meeting for MK-0518 clinical program were discussed. DAVP stated that it expects the need for an Advisory Committee meeting because MK-0518 is a new molecular entity and it has a new mechanism of action. In addition, DAVP agreed that a priority review with a six month review cycle will be appropriate for MRL's clinical program. As a result, DAVP requested that MRL perform the following:

- **To submit a request for Rolling Review designation under Fast Track designation**
- **To plan to roll-out its clinical data in support of this program**
- **To submit a formal meeting request for a Type C (Planning) meeting to discuss NDA component roll-out plans prior to the Pre-NDA meeting**

MRL agreed with the above requests.

DAVP strongly requested that MRL not disclose the study results publicly until after 100 % of patients have reached Week 16 on study drug to preserve the integrity of the study. MRL indicated that it would take this recommendation back for internal discussion.

There was a general discussion regarding the event that will start the PDUFA review clock for MRL's program. DAVP stated its inability to make commitments at this time.

6.Does FD A concur with MRL's plans to collect genotype data on Phase III clinical samples and include these data in the NDA?

Microbiology Comments:

1.Pleas e perform phenotypic assays on the IN variants that are identified by the genotypic analyses to define the relationship between genotype and phenotype.

Dec 5: MRL agreed with this comment and stated that if the genotypic analyses are robust it will not perform phenotypic assays. DAVP requested that MRL submit phenotypic assay protocols for review. MRL agreed.

2.If the pop ulation sequencing assay does not identify resistant variants in Protocols 018 and 019, please use a more sensitive genotypic assay such as single genome sequencing to detect minor populations of MK-0518 resistance-associated mutants.

Dec 5: MRL agreed with this comment. DAVP requested that MRL test the integrase inhibitor phenotype of some primary isolates in addition to site-directed mutant viruses and submit clinical isolate information.

Clinical Pharmacology

7.Does FD A concur that the Phase I program described at the End of Phase I meeting, as supplemented by the discussions of June 29 and the written response on October 27, will be adequate to support regulatory approval, and that a clinical PK study with a second P-gp inhibitor is not needed?

Based on your data submitted to the FDA, we concur with your drug interaction plan. However, if the human ADME, absolute bioavailability or renal impairment study indicate that renal excretion plays a greater role in the elimination of MK-0518, further defining the role of P-gp in the renal excretion may be warranted.

Dec 5: MRL agreed with the response.

Other Comments:

3.Regar ding the dose-selection for Phase III trials, please submit available exposure-response results in individual patients to confirm your dose selection based on dose-response analysis (e.g., data from Part 2 of Study 004 at Week 8).

Dec 5: MRL stated that due to the high efficacy response in its ongoing Phase II study, the value of exposure-response analysis was limited. In any case, MRL agreed to conduct such analyses in the future.

4.Pleas e explain the rationale for conducting the drug interaction study with midazolam. The in vitro data suggest that MK-0518 is neither an inhibitor nor inducer of CYP3A4.

Dec 5: MRL indicated that the midazolam study was performed to confirm in vitro results.

5.We encourage you to continue to develop population pharmacokinetic model and apply it to Phase III trials. A better sampling scheme covering the dosing interval (12 hours) may be needed instead of only sampling trough concentrations in Phase III trials.

Dec 5: MRL clarified that random sampling was performed in addition to the trough concentrations and that this sampling scheme covered the requested dosing interval in its Phase II studies. DAVP accepted this sampling scheme.

Statistics

8.The followin g antiretroviral efficacy endpoints have been widely used in HIV registration studies: % HIV RNA decrease > 1 log from baseline, % HIV RNA < 400 copies/mL, % HIV RNA < 50 copies/mL, change from baseline in log10 HIV RNA and change from baseline in CD4 cell count. These antiretroviral efficacy endpoints are highly correlated. Based on review of product labels for recently approved antiretroviral agents, it appears that given a statistically significant study result based upon the *a priori* selected primary efficacy endpoint, the other efficacy endpoints may also be presented together with the primary endpoint as part of a table in the labeling/product circular to depict the complete picture of the antiretroviral efficacy. Does the Division concur with this approach to labeling for MK-0518?

Although tables displaying positive secondary endpoint results may be included in the label, negative findings may also be included (e.g., a table showing that the percentage of patients with HIV RNA < 50 copies/mL was the same in both treatment groups).

Dec 5: MRL agreed with the response.

Other Comments:

6.In terim analysis

a) This preliminary response was not discussed during the face-to-face meeting.

8.Pleas e provide subgroup analyses for the following factors: Country, Gender, Age (≤median, >median), Ethnic Origin (Whites, Blacks, Hispanics/Other Races). The primary analysis should be repeated within each subgroup while CMH analyses and Breslow-Day statistics can be used to examine the homogeneity of treatment effects.

Dec 5: MRL agreed to perform subgroup analyses to confirm treatment benefit across predefined patient subgroups. MRL stated that details regarding the type of analyses will be provided in the Statistical Analysis Plan.

Action Items/Summary:

1.MR L will submit a summary of the dose-confirmation interim analysis to support Phase III dose selection in January 2006.
Note: MRL submitted data on January 11, 2006 and received DAVP's concurrence regarding dose selection on January 25, 2006.

2.MR L will submit a request for Rolling Review designation under Fast Track designation.
Note: DAVP granted Rolling Review designation on January 20, 2006.

3.DAVP a greed to provide comments on the Phase III protocols in a timely manner.
Note: DAVP provided comments by facsimile correspondence on December 13, 2005.

4.MR L agreed to the following microbiology requests:
- To submit phenotypic assay protocols for review and clinical isolate information
- To test the integrase inhibitor phenotype of some primary isolates in addition to site-directed mutant viruses

5.MR L agreed to submit a request for a Chemistry End-of-Phase II meeting and to keep DAVP informed on its efforts to develop a pediatric formulation of MK-0518.

6.MR L agreed to submit a formal meeting request for a Type C (Planning) meeting to discuss NDA component roll-out plans prior to the Pre-NDA meeting (meeting target date July/August 2006).

7.MR L agreed to submit complete Week 24 safety and efficacy data at the time of the detailed Safety Update Report (SUR) within two months of initial NDA submission.

8.MR L agreed to submit a copy of the Data Safety Monitoring Board (DSMB) charter as soon as possible.
Note: MRL submitted the DSMB charter on March 10, 2006 (SN155).

9.I f MRL plans to submit the interim analysis of efficacy data when 50 % of patients reached Week 24 in support of a NDA application, MRL agreed that 100 % (all patients) in Studies 018 and 019 will have reached Week 16 on study drug.

10. MRL agreed to discuss internally DAVP's recommendation not to make the study results publicly available until 100 % of all patients have reached Week 16 on study drug.

11. DAVP committed to discuss internally the statistical considerations regarding MRL's proposed Phase III program and provided prompt feedback to MRL.
Note: MRL submitted a summary of statistical plans and issues for analysis of data from Protocols 018 and 019 on December 7, 2005 (by electronic correspondence) and officially on December 13, 2005. On December 13, 2005, DAVP provided concurrence regarding MRL's proposed interim analysis plans.

Attachment A

Below are MRL's responses to FDA's comments sent by electronic mail correspondence on December 1, 2005.

FDA Comment #1a

In the background package, you propose conducting two identical Phase III studies (Studies 018 and 019) with possible submission of efficacy data after 50% of study subjects have reached 24 weeks. If the data were submitted at this time point (when 50% of subjects have reached 24 weeks), please address the following:

- Provide predictions on the length of treatment for other study subjects. At a minimum, please address this question by completing the table below:

Number of Subjects by Length of Study Drug Treatment in Studies 018 and 019 at the Time of NDA submission

	Enrolled	Wk 8	Wk 12	Wk 16	Wk 24	Wk 32	Wk 40
MK-0518/OBT							
OBT							

MRL Response #1a

Table 1 below provides projections of the numbers of subjects by length of study treatment in Studies 018 and 019 at the time of NDA submission, if we proceed with the submission after 50% of study subjects have reached 24 weeks of treatment and demonstrated robust efficacy for MK-0518. Based on Phase II enrollment, the key assumptions are that

1. enrollment in both Protocols 018 and 019 will be completed within 6 months for both studies, and
2. after 50% of patients have enrolled, the remaining patients will enroll within 8 weeks.

It should be noted that, with these assumptions, 100% of patients will have reached 24 weeks of treatment at the time of initial submission.

Table 1- Estimated number of subjects by length of study drug treatment in Protocol 018 and 019 at time of NDA submission

	Enrolled	Wk 8	Wk 12	Wk 16	Wk 24	Wk 32	Wk 40
MK-0518 + OBT	460	460	460	460	**230**	90	10
OBT*	230	230	230	230	**115**	45	5

* If patient randomized to OBT meets the criteria for virologic failure beyond Week 16, and switches to open-label MK-0518, then the number of patients exposed to MK-0518 + OBT will be greater than listed in Table 1 above.

Table 2 below provides an estimate of the safety database from Phase II and III studies available at the time of NDA submission, if we proceed with the submission after 50% of study subjects have reached 24 weeks of treatment and demonstrated robust efficacy for MK-0518.

Table 2- Estimated numbers of patients from Phase II (Protocols 004 and 005) and Phase III (Protocols 018 and 019) exposed to MK-0518 at doses of ≥ 400 mg b.i.d at key milestones (Wk 16 and Wk 24) at time of NDA submission

	Estimated numbers of patients (by study and overall)
Phase II - PN 004 - PN 005	 80 pts with ≥ 24 wks 180 pts with ≥ 24 wks
Phase III - PN 018 - PN 019	 ≥ 115 pts with ≥ 24 wks + ~ 115 with 16 wks* ≥ 115 pts with ≥ 24 wks + ~ 115 with 16 wks*
Total # of patients From Phase II & III[§]	490 pts with ≥ 24 wks + ~ 230 with 16 wks*

*Based on Phase II enrollment, after 50% of patients have enrolled, it is anticipated that the remaining patients will enroll within 8 weeks.
[§]Additional safety data will be available from Phase I studies, Compassionate Use Program, and the pediatric program.

FDA Comment #1b

- Describe the type of safety data that will be submitted to the Division within three months of the original NDA submission

MRL Response #1b

Within three months of the original NDA submission, updated safety data will be provided as a Safety Update Report (SUR). Table 3 below provides an estimate of the safety database from Phase II and III studies available at the time of the SUR. Again, the key assumptions are that

1. enrollment in both Protocols 018 and 019 will be completed within 6 months for both studies.
2. after 50% of patients have enrolled, the remaining patients will enroll within 8 weeks.

Table 3- Estimated numbers of patients from Phase II (Protocol 004 and 005) and Phase III (Protocol 018 and 019) exposed to MK-0518 at doses of ≥ 400 mg b.i.d at key milestone (Wk 24) at the time of the SUR

	Estimated numbers of patients (by study and overall)
Phase II - PN 004 - PN 005	 80 pts with ≥ 24 wks 180 pts with ≥ 24 wks
Phase III - PN 018 - PN 019	 230 pts with ≥ 24 wks 230 pts with ≥ 24 wks
Total # of patients From Phase II & III[§]	720 pts with ≥ 24 wks

FDA Comment #1c

- Clarify whether efficacy data will be updated following the original NDA submission

MRL Response #1c

Efficacy data will be updated in the form of a statistical report, in the similar time frame as the SUR. Below, Table 4 provides a summary of Phase III data that will be submitted to the Agency in the event of an NDA submission triggered by the interim analysis; as noted above, the key underlying assumptions are that enrollment in both Protocols 018 and 019 will be completed within 6 months for both studies, and that after 50% of patients have enrolled, the remaining patients enroll within 8 weeks.

Table 4 – Proposed Phase III Data Rollout with Positive Interim Analysis

	Initial submission	~3 Month Update
Primary Endpoint Efficacy Data Provided	50% pts at Wk 24 All available data (Wks 0-40) will be summarized (see Table 1)	~100% pts at Wk 24 All available data (Wks 0-40) will be summarized

FDA Comment #2

If these data are submitted after 50 % of subjects have reached 24 weeks, please explain how you plan to maintain the study integrity, particularly if the results are favorable and are publicly available.

- Specifically, how will blinding be handled and how will you encourage continued compliance?

- When and how do you plan to make the study results publicly available?

MRL Response #2

See Dr. Bach-Yen Nguyen's response to BP Question 5 (slide presentation SN142).

Attachment B

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: December 2, 2005

To: Philip L. Huang, M.D.

From: Monica Zeballos, Pharm.D., Regulatory Project Manager

Through: Melisse Baylor, M.D., Medical Reviewer
Derek Zhang, Ph.D., Clinical Pharmacology Reviewer
Sung Rhee, Ph.D., Microbiology Team Leader
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Julian O'Rear, Ph.D., Microbiology Team Leader
Greg Soon, Ph.D., Statistical Team Leader

IND: 69,928: SN110

Drug: MK-0518 (also known as L-000900612)

Subject: Division responses for IND 69,928: SN110

Attached are the FDA preliminary answers to the questions that you posed in your submission dated November 1, 2005 (SN110). During our upcoming End-of-Phase II meeting with you on December 5, 2005 we will be prepared to clarify any questions you have regarding our responses. However, please note that if there are any major changes to your development plan (based upon our responses herein), we will not be prepared to discuss, nor reach agreement on, such changes at the December 5, 2005 meeting. Any modifications to the development plan that you would like to discuss with the FDA should be submitted as a new meeting request.

General

Question 1: The background package describes the overall clinical development plan for MK-0518 (see Section 7 – Overview of Clinical Development Plan), and provides a Phase III protocol based on the Division's comments on MRL's concept sheets (see Section 8 – Attachments; Attachment 3 Protocol 019). Based on the available data (see Section 4 – Updated Phase I Data, Section 5 – Updated Phase II Data, and Section 6 – Rationale for Phase III Dose Selection), does FDA concur that the proposed Phase III studies and program design will be adequate to support the following indication at the time of initial regulatory approval?
Proposed initial indication: *MK-0518 is indicated in combination with other anti-retroviral agents for the treatment of HIV–1 infection in treatment-experienced patients with evidence of HIV–1 replication despite ongoing antiretroviral therapy.*

Clinical

Question 3: The background package provides the Phase III protocol (see Section 8 – Attachments; Attachment 3 – Protocol 019) developed based on Division feedback to MRL's Phase III concept sheets. MRL proposes to conduct two identical Phase III studies with 345 patients each, consistent with the protocol provided, to establish the safety and efficacy of MK-0518 as described in the initial indication above (see Section 7 – Overview of Clinical Development Program). Does the FDA concur that the design of this protocol is adequate to support initial regulatory approval?

FDA Response: Results of the two proposed Phase III studies should be adequate to support the proposed indication. We agree that the design of these protocols is adequate. Comments regarding these protocols will be communicated to you in the next week.

General

Question 2: As described in this background package (see Section 7 – Overview of Clinical Development Program), pediatric studies are anticipated to be ongoing at the time of initial marketing application. Based on the draft Guidance entitled "How to Comply with the Pediatric Research Equity Act," MRL believes the MK-0518 program would qualify for pediatric deferral. Does FDA concur with plans and timing proposed for pediatric development outlined in Section 7? MRL will be seeking a deferral of pediatric studies at the time of submission of the MK-0518 NDA. Does FDA concur that this program is appropriate for pediatric deferral?

FDA Response: The pediatric program should be ongoing at the time of NDA submission; the submission of pediatric data can be deferred at the time of NDA submission. Please comment on any progress on the development of a pediatric suspension. Please also comment on the type of pediatric studies planned and the timeline for the initiation of such studies.

Clinical

Question 4: It is anticipated that at the time of the release of the marketing application, the safety database will include approximately 900 to 1000 subjects who have received any dose of MK-0518 [from the Phase I, II, and III salvage studies], approximately 700 subjects receiving at least the marketed dose for at least 24 weeks, and approximately 160 subjects receiving at least the marketed dose for at least 48-weeks. In addition, limited safety data from the Compassionate

Use Program is expected to be available at the time of NDA filing. Does the FDA concur that the safety database provided by the proposed clinical development program (see Section 7 – Overview of Clinical Development Program) is adequate in terms of total patient numbers and duration of exposure?

FDA Response: The results of these studies would provide a small but acceptable safety database. However, if any safety signal is identified, more data may be needed.

Question 5: MRL plans to establish a DSMB to review safety and efficacy data from the Phase III studies. The primary responsibility of the DSMB is to ensure the safety of the subjects participating in both Phase III studies. Given the uncertainty in estimating the effectiveness of OBT in Phase III, and in the interest of addressing the unmet medical need in a timely manner, MRL proposes that the DSMB review an interim analysis of efficacy performed when 50% of patients of both Phase III studies combined have efficacy data at Week 24. If superiority of MK-0518 (+ OBT) over placebo (+ OBT) is demonstrated, MRL is interested in filing the initial NDA with this interim efficacy data rather than waiting for all 690 patients to have Week 24 data. Does the FDA concur with this potentially accelerated regulatory submission? As described (see Section 7 – Overview of Clinical Development Plan), even if a decision to file early were made, the Phase III studies would continue uninterrupted, and outstanding safety data from all patients by Week 24 would be available during review within 3 months from the NDA submission.

FDA Response: We will respond after the face-to-face meeting.

Question 6: Preliminary genotypic analysis of a small number of Phase II clinical samples has been done in-house using a population sequencing assay. This assay is currently research-use-only but is being validated for use in the remainder of the Phase II studies. Does FDA concur with MRL's plans to collect genotype data on Phase III clinical samples and include these data in the NDA?

Microbiology Comments:

2.Pleas e perform phenotypic assays on the IN variants that are identified by the genotypic analyses to define the relationship between genotype and phenotype.

3.If the pop ulation sequencing assay does not identify resistant variants in Protocols 018 and 019, please use a more sensitive genotypic assay such as single genome sequencing to detect minor populations of MK-0518 resistance-associated mutants.

Clinical Pharmacology

Question 7: MRL previously submitted, as part of the End-of-Phase I background package, a summary of Phase I studies (completed, ongoing, or planned). During the meeting on June 29, the Division requested MRL address the role of P-gp on both absorption and elimination of MK-0518. This request was discussed internally and MRL provided a written response on October 27. In brief, we believe that our stated drug interaction plan (proposed in the End-of-Phase I background package) is sufficient to define the effect of potent inhibitors of enzymes and/or transporters on the pharmacokinetics of MK-0518, and a clinical PK study with a second

inhibitor of P-gp is not warranted. Also as requested, an *in vitro* study has been conducted to examine the potential of MK-0518 to inhibit P-gp. The results (communicated in the submission of October 27) indicate that, at concentrations up to 100 μM, MK-0518 does not inhibit P-gp. The current background package provides updated Phase I data from studies with MK-0518 (see Section 4 – Updated Phase I data). Does FDA concur that the Phase I program described at the End of Phase I meeting, as supplemented by the discussions of June 29 and the written response on October 27, will be adequate to support regulatory approval, and that a clinical PK study with a second P-gp inhibitor is not needed?

FDA Response: Based on your data submitted to the FDA, we concur with your drug interaction plan. However, if the human ADME, absolute bioavailability or renal impairment study indicates that renal excretion plays a greater role in the elimination of MK-0518, further defining the role of P-gp in the renal excretion may be warranted.

Other Comments:

6.Regar ding the dose-selection for Phase III trials, please submit available exposure-response results in individual patients to confirm your dose selection based on dose-response analysis (e.g., data from Part 2 of Study 004 at Week 8).

7.Pleas e explain the rationale for conducting the drug interaction study with midazolam. The in vitro data suggest that MK-0518 is neither an inhibitor nor inducer of CYP3A4.

8.We encourage you to continue to develop population pharmacokinetic model and apply it to Phase III trials. A better sampling scheme covering the dosing interval (12 hours) may be needed instead of only sampling trough concentrations in Phase III trials.

Statistics

Question 8: The following antiretroviral efficacy endpoints have been widely used in HIV registration studies: % HIV RNA decrease > 1 log from baseline, % HIV RNA < 400 copies/mL, % HIV RNA < 50 copies/mL, change from baseline in log10 HIV RNA and change from baseline in CD4 cell count. These antiretroviral efficacy endpoints are highly correlated. Based on review of product labels for recently approved antiretroviral agents, it appears that given a statistically significant study result based upon the *a priori* selected primary efficacy endpoint, the other efficacy endpoints may also be presented together with the primary endpoint as part of a table in the labeling/product circular to depict the complete picture of the antiretroviral efficacy. Does the Division concur with this approach to labeling for MK-0518?

FDA Response: Although tables displaying positive secondary endpoint results may be included in the label, negative findings may also be included (e.g., a table showing that the percentage of patients with HIV RNA <50 copies/mL was the same in both treatment groups).

9. **It is crucial to collect drug-adherence information and confirm reasons for discontinuation by investigators (e.g., death or events leading to death, disease progression, immunologic failure, adverse events, loss to follow-up, withdrawal of consent, non-compliance, pregnancy, protocol violations, not discontinued or not known to be discontinued but data were missing at the final visit). The underlying reasons for discontinuation should be interpreted. For example, how many of the patients who withdrew consent or were lost to follow-up had adverse events that could have been related to the treatment they were taking (like nausea and diarrhea)?**

10. **Please provide subgroup analyses for the following factors: Country, Gender, Age (≤median, >median), Ethnic Origin (Whites, Blacks, Hispanics/Other Races). The primary analysis should be repeated within each subgroup while CMH analyses and Breslow-Day statistics can be used to examine the homogeneity of treatment effects.**

We are providing the above information via telephone facsimile for your convenience.
THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.
Please feel free to contact me at (301) 796-0840 if you have any questions regarding the contents of this transmission.

_____

David Araojo, Pharm.D., for Monica Zeballos, Pharm.D.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products

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
4/21/2006 03:53:21 PM

RECORD OF FDA/INDUSTRY MEETING

Date of Meeting: **June 29, 2005**

IND: **69,928**

Drug: **L-000900612 (Integrase Inhibitor)**

Sponsor: **Merck & Co., Inc.**

Indication: **Treatment of HIV-1 infection**

Type of Meeting: **Face-to-face Type B (End-of-Phase I) meeting**

Center for Drug Evaluation and Research (CDER) Participants:

Mark Goldberger, M.D., Director, Office of Drug Evaluation IV
Arzu Selen, Ph.D., Deputy Director, Division of Pharmaceutical Evaluation III

Division of Antiviral Drug Products (DAVDP) Participants:

Debra Birnkrant, M.D., Division Director
Jeffrey Murray, M.D., M.P.H., Deputy Division Director
Rosemary Johann-Liang, M.D., Medical Team Leader
Melisse Baylor, M.D., Medical Reviewer
Ita Yuen, Ph.D., Pharmacology/Toxicology Reviewer
Derek Zhang, Ph.D., Clinical Pharmacology Reviewer
Jules O'Rear, Ph.D., Microbiology Team Leader
Sung Rhee, Ph.D., Microbiology Reviewer
Lisa Naeger, Ph.D., Microbiology Reviewer
Rafia Bhore, Ph.D., Acting Statistics Team Leader
Susan Zhou, Ph.D., Statistics Reviewer
Kim Struble, Pharm.D., Senior Clinical Analyst
Virginia Behr, Chief, Project Management Staff
Monica Zeballos, Pharm.D., Regulatory Project Manager

Merck Research Laboratories (MRL) Participants:

Joshua Chen, Ph.D., Sr. Biometrician, CBARDS
Mike Nessly, Master Statistician, Director, CBARDS
Marian Iwamoto, Ph.D., M.D., Director, Clinical Pharmacology

John Wagner, Ph.D., M.D., Sr. Director, Clinical Pharmacology
Philip Huang, M.D., Director, Regulatory Affairs-Domestic
Tamra Goodrow, Ph.D., Sr. Director, Regulatory Affairs-Domestic
Bach-Yen Nguyen. M.D., Sr. Director, Clinical Research
Robin Isaacs, M.D., Exec. Director, Clinical Research
Larissa Wenning, Ph.D., Director, Clinical Drug Metabolism
Lamon Alani, Ph.D., Exec. Director, PR & D
A. Christine Huber, Ph.D., Director, Preclinical Strategy & Safety
Ed Hill, B.S., Sr. Regulatory Coordinatior
Julie Stone, Sr. Research Fellow, Drug Metabolism

BACKGROUND:

MRL requested this End-of-Phase I meeting on April 8, 2005. The meeting was rescheduled from May 27, 2005 to June 29, 2005 due to late submission of the background package (BP). The meeting BP was submitted on May 25, 2005 (SN065). On June 24, 2005, DAVDP draft comments were sent by telephone facsimile correspondence to MRL in reply to the BP questions (see attachment A).

OBJECTIVES:

To discuss:

- the overall drug development program proposed for L-000900612
- the potential for Fast Track designation
- the proposed scope and specifics of the Phase I program

DISCUSSION:

MRL opens the meeting by presenting updated summary data of its two ongoing Phase II dose-ranging studies (Protocol 004 (treatment-naïve patients) and Protocol 005 (heavily pre-treated patients)) including:

- Preliminary blinded safety data summarizing all clinical adverse experiences (AEs) and specific clinical AEs from Protocol 004 (35 patients enrolled) and Protocol 005 (31 patients enrolled)
- Preliminary blinded efficacy data from Protocol 005 (52 patients enrolled)
- Preliminary safety data summarizing serious AEs and laboratory AEs from Protocol 005

Refer to submission dated July 27, 2005 (SN080).

Comments to the following questions were provided by facsimile telephone correspondence to MRL on June 24, 2005 (see attachment A). MRL submission questions are listed first, followed by DAVDP responses in bold. Additional comments, if any, from the June 29, 2005, End-of-Phase I meeting are located below the initial responses. Please see attachment A for the complete version of the submitted questions.

General

1. Does the FDA concur that L-000900612 is appropriate for submission under Fast Track designation? Does the FDA concur that L-000900612 can be submitted, reviewed, and approved under the accelerated approval mechanism, with priority review?

   DAVDP agrees that it is appropriate to submit L-000900612 under Fast Track designation. For additional information, please refer to the FDA Guidance for Industry on *Fast Track Drug Development Programs-Designation, Development, and Application Review* http://www.fda.gov/cder/guidance/5645fnl.htm (July 2004).

   DAVDP agrees that an accelerated approval based on Subpart H regulations for the use of L-000900612 in highly treatment-experienced patients with limited options may be warranted. Although a priority review is likely, the decision about a priority review will be made at the time of the NDA filing meeting.

   June 29: MRL plans to submit a request for Fast Track designation.

Note: Questions No. 2 and 6 are grouped together because they shared the same answer.

2. Does the FDA concur that the proposed clinical development program will support the following broad indication: "... is

6. Does the FDA concur with this approach?
   Does the FDA agree that efficacy and safety data from these two Phase III studies through 16 weeks of therapy (rather than 24 weeks of therapy) accompanied by Phase II data demonstrating longer term safety and durability of response are sufficient to support registration of an agent for treatment of HIV infection in heavily treatment experienced patients (i.e., salvage indication)?

   At this time, there are too little data to provide more than general comments on a proposed indication or on the Phase III program for L-000900612. It is too early in the development of L-000900612 to specifically comment on efficacy endpoints and analysis of Phase III trials. We will be happy to discuss these issues at an End-of-Phase II meeting.

   In your description of the drug development program, you have proposed:
   - **one Phase II trial in treatment-naïve subjects,**
   - **one Phase II trial in highly treatment-experienced subjects with limited treatment options, and**
   - **two Phase III trials in highly treatment-experienced subjects with limited treatment options.**

   We agree that two adequate and well-controlled trials are needed for approval of an antiretroviral. If both Phase III studies are conducted in highly treatment-experienced

subjects with limited options, adequate 24 week data would be acceptable for an indication limited to the population studied in these trials (i.e., highly treatment-experienced with limited options). Furthermore, depending on the timing of the application, an indication for this population may warrant a review for accelerated approval based on Subpart H regulations.

Furthermore, please provide your development plans for subjects who are treatment-experienced but have treatment options.

Because early Phase II antiviral activity data in Protocol 004 are promising, we are willing to be flexible with your development program. However, there are no long-term safety data as of yet for L-000900612, a new class of antiretroviral, and Phase III drug development will be strongly influenced by long-term safety data from Phase II.

The study protocol does not include criteria for determination of dose of L-000900612 to be used at dose optimization in Protocol 004. Please propose specific criteria for determination of the dose to be used in Phase III trials.

June 29: MRL understands DAVDP's position and the answers to the above questions; however, the sponsor expresses the desire to use Phase II data for dose selection for Phase III trials as a possible way forward without waiting until an End-of-Phase II meeting is scheduled. DAVDP states that MRL's clinical development program has no formal algorithm for dose selection and that early dose selection cannot take durability of response into account. MRL explains that the clinical development program and dose selection is based on the following assumptions:

- **All the doses used in Protocols 004 and 005 show efficacy**
- **Dose selection is based on week 8 data of Protocol 004, but week 16 data will be available prior to initiation of Phase III trials**
- **Doses used in Protocols 004 and 005 are all feasible provided there are no safety issues**

DAVDP states its willingness to work with MRL and suggests the following:

- **MRL can submit the protocol or concept sheets for Phase III trials and change the dose as long as DAVDP is informed of such change and the justification for the change.**
- **MRL can submit Phase III draft protocols prior to dose selection for Division's review and comment.**

Clinical Pharmacology

3. Does the FDA concur that the Phase I program adequately addresses potential drug-drug interactions to permit Phase III studies of L-000900612 for the treatment of HIV infection in combination with other anti-retroviral agents?

In general, DAVDP concurs with your drug interaction program with the following comments:

a) In vitro data demonstrated that L-000900612 is a P-gp substrate. We encourage you to further assess the role of P-gp in L-000900612's absorption and elimination. A drug interaction study with a known potent P-gp inhibitor (but not a UGT1A1 inhibitor) is recommended. This recommendation is based on the drug interaction results that ritonavir, a known UGT1A1 inducer, had less effect on L-000900612's pharmacokinetics than other UGT1A1 inducers (rifampin and efavirenz). Because ritonavir is also a P-gp inhibitor, the lack of significant effect of ritonavir on L-000900612 could be due to the counteracting effects of inducing UGT1A1 and inhibiting P-gp by ritonavir.

June 29: MRL presents a brief overview of L-000900612 as a P-gp substrate. There is a general discussion regarding P-gp and its role in absorption and the renal elimination of L- 000900612.

Refer to submission dated July 27, 2005 (SN080), for sponsor's presentation regarding items a) to e).

MRL believes that P-gp-mediated efflux in the gut is unlikely to play a large role in absorption of L-000900612 based on the assumption that intestinal P-gp could be saturated and there are no data suggesting saturated absorption of L-000900612. During the discussion, MRL also refers to the results of a dose-proportionality study that included doses up to 1600 mg as a confirmation of lack of P-gp mediated effects on absorption of L-000900612.

MRL thinks that P-gp may play some role in renal elimination of L-000900612; however, MRL does not believe that the renal elimination pathway is important based on a mean value of 9 % to 14 % of dose being excreted unchanged in urine. During the discussion, MRL states that while it cannot comment on the individual values at this meeting, it is possible that individual values may be up to 20 % (dose excreted as unchanged drug in urine). DAVDP states that given the size of these types of studies, and the anticipated variability, an individual value of approximately 20 % cannot be considered as negligible or an unimportant pathway. MRL agrees to provide individual renal excretion data.

To further address the point raised by MRL about the lack of role of intestinal P-gp based on lack of a saturation phenomena, DAVDP refers to the L-000900612 and ritonavir interaction study and repeats the concern that counteracting effects of inducing UGT1A1 and inhibiting P-gp by ritonavir in the L-000900612-ritonavir interaction study may still explain the outcome in this study. To clarify these observations, DAVDP suggests a drug interaction study with a known potent P-gp inhibitor (but not a UGT1A1 inhibitor) to assess the role of intestinal P-gp in absorption of L-000900612.

Given the need for additional information and discussion on the role of P-gp on both absorption and elimination of L-000900612, DAVDP suggests a separate meeting to discuss this topic.

MRL expresses the difficulty of finding a good P-gp inhibitor to conduct such a study. DAVDP suggests ketoconazole as a suitable candidate because it inhibits P-gp but not UGT1A1, and in addition, CYP3A does not play a role in metabolism of L-000900612. MRL acknowledges that it will consider this suggestion and further discussion around the P-gp effects will continue in future interactions.

b) Please evaluate the inhibitory potency of L-000900612 on P-gp, e.g., in vitro transporter study using P-gp-expressing cell systems and digoxin as a marker in comparison with other known P-gp inhibitors.

June 29: MRL agrees to evaluate the inhibitory potency of L-000900612 on P-gp in an in vitro system.

c) Please provide information about the solubility-pH profile of L-000900612.

June 29: MRL presents solubility-pH profile information of L-000900612 at room temperature ranging from pH = 2.3 to pH = 9.8. DAVDP acknowledges the solubility-pH profile data.

d) The poloxamer formulation seems to have a different PK profile compared to other formulations, e.g., profile described in Figure E-7 (P.E-15) and the limited absorption of 600 mg b.i.d in HIV patients (600 mg b.i.d. had similar plasma exposure to 400 mg b.i.d. in HIV patients). Please explain. Please also compare PK of this formulation in HIV patients vs. in healthy subjects, if data are available.

June 29: MRL presents the following information regarding the poloxamer formulation vs. the lactose formulation:

- **Poloxamer has similar or higher C_{12hr}, with lower C_{max}, and AUC (lower peak-to-trough ratio is desirable) compared to lactose**
- **Poloxamer is chosen for further development based on favorable PK profile**
- **Dose proportionality of either formulation is difficult to assess with small numbers of subjects and closely spaced doses**
- **PK of poloxamer is similar in HIV positive patients vs. healthy subjects**

DAVDP acknowledges the PK data.

e) Please explain the inconsistency in L-000900612 400 mg steady-state PK data (Table 12 on P.28 and Table 15 on P.30) in control cohorts (Protocol 008 vs. Protocol 010).

June 29: In response to the above request, MRL presents the intersubject variability in L-000900612 PK parameters for the 400mg dose of polaxamer formulation concluding:

- **Individual PK data from Protocols 008 and 010 cover generally the same range as observed in other studies with the same dose and formulation**

DAVDP acknowledges that the PK data illustrate a high degree of intersubject variability.

Lastly, DADVP encourages MRL to consider obtaining exposure-response information from its population PK study such that in addition to obtaining covariate information, as planned, it can be designed to explore exposure-response relationships. This may assist in design of the Phase III trials and in dose selection. MRL agrees to consider these recommendations.

Safety Assessment

4. Does the FDA concur that the proposed preclinical safety assessment program, including ongoing carcinogenicity studies at the time of NDA submission, will meet registration requirements for L-000900612, under accelerated approval conditions?

   The proposed preclinical safety assessment program will meet the registration requirements for NDA filing provided there are no safety issues that may require additional preclinical studies.

5. Does the Agency concur with this general study design and agree that, in the absence of any unique untoward toxicity, the study endpoints outlined above will be sufficient to support the planned clinical pediatric study?

   DAVDP concurs with this general study design.

Clinical Program

6. Please see answer to question 2.

7. Does the FDA agree with the proposed size of the safety database for L-0009006l2?

   A safety database of 700 subjects is consistent with what is described in the Guidance. [For additional information, please refer to the FDA Guidance for Industry on *Antiretroviral Drugs Using Plasma HIV RNA Measurements — Clinical Considerations for Accelerated and Traditional Approval* http://www.fda.gov/cder/guidance/3647fnl.pdf (October 2002)]. However, at this time, there is no long-term information on the safety of L-000900612 in HIV-infected subjects, and it is impossible to determine what type of safety database is needed without more information.

   June 29: DAVDP states that a safety database should contain adequate clinical control data in order to provide an accurate determination of the safety of L-000900612. DAVDP acknowledges the use of a control arm for 24 weeks in Protocol 004. However, this protocol will likely not support safety in treatment-naïve

patients because of two reasons: 1) small study population, and 2) different L-000900612 doses used. Therefore, it is necessary to have a control arm and it is important to consider the adequacy of control data when designing Phase III trials. MRL acknowledges this information.

8. Does the FDA agree that the proposed Phase II/III program with Phase III studies out to 48 weeks in heavily pretreated HIV-infected patients, together with the preclinical toxicology and pediatric plans outlined in this background package (see Section 7 – Overall Clinical Development Program) will fulfill traditional approval requirements?

Again, it is too early to address issues around traditional approval. However, in general we expect safety and efficacy results from two 48 weeks, Phase III trials in support of traditional approval.

9. Does the FDA agree that the proposed Phase II/III program, together with the pediatric plans outlined in this background package (see Section 7 – Overall Clinical Development Program) will fulfill the requirement to study a diverse patient population (i.e., therapy-experienced and therapy-naïve) and

The pediatric development plan for L-000900612 should include HIV-infected children of age and older. It should also include the development of an age-appropriate formulation for children younger than 6 years of age.

In Part I of Protocol 04, 33 of the 35 subjects were male. Please consider innovative ways of increasing the enrollment of females in your trials, particularly in Phase III trials.

In addition, please attempt to enroll patients whose race and ethnicity reflect the HIV-infected population in the United States.

As your development program progresses, please develop trials that adequately address hepatotoxicity of your drug, particularly in patients with underlying liver disease.

June 29: MRL states the following information regarding its dosing plans:

DAVDP states that these plans are reasonable and coincide with the President's Emergency Plan for AIDS Relief (PEPFAR) initiatives. DAVDP agrees with MRL's approach in conducting dosing as discussed above since there are so little data in the pediatric population.

There is a general discussion regarding the inclusion of other special populations in Phase III trials. DAVDP strongly recommends including women and HBV and HCV co-infected patients in Phase III trials.

10. Recently available data from the tipranavir studies, RESIST 1 and RESIST 2, and for TMC114 (Abstract 164LB presented at the 12th Conference on Retrovirus and Opportunistic Infections) suggest that it may become increasingly difficult to demonstrate superiority of a new investigational antiretroviral agent in combination with optimized background therapy (OBT) if a substantive number of subjects receive OBT that includes potent antiretroviral regimens such as TMC 114 or tipranavir+enfurvitide. In this changing environment, we are interested in the Agency's current thoughts on the design of Phase III studies to evaluate novel antiretroviral agents in HIV-infected patients failing current therapy and with limited treatment options (this topic was emailed to DAVDP on June 17, 2005).

It is too early to discuss the specific design of Phase III trials in highly treatment-experienced subjects with limited options. The design will be influenced by what other antiretrovirals drugs are commercially available at the time of the initiation of these trials. We strongly recommend blinding of all Phase III clinical trials.

June 29: MRL raises the general concern about the need for a large sample size and the inability to demonstrate efficacy depending on Phase III trials design and the control data used. DAVDP states the following recommendations and concerns for Phase III trials:

- **Goal is to have an adequate and well-controlled clinical control data**
- **The concern that the proposed two Phase III trials (highly treatment-experienced patients) have limited safety data**
- **Double blinding of studies at least until 16 weeks**
- **DSMB review of number of AIDS defining events (captured as clinical endpoints separate from safety measures), and AEs**

OTHER DISCUSSION POINTS ON JUNE 29:

Accelerated approval

The issue of 16 week data vs. 24 week data to seek accelerated approval base on Subpart H regulations is discussed. DAVDP states that FDA's policy for an accelerated approval, in heavily pre-treated HIV infected patients, is to have 24 week data.

In addition, DAVDP recommends the consideration of the following general study design issues for Phase III trials:

- **Use of active control**
- **Active control that would allow blinding**
- **OBT with L-000900612 demonstrating superiority**
- **Use of L-000900612 plus another drug in development**
- **Cooperation with other sponsors**

Other Development Plans

The topic of a "two investigational" drug model is discussed further. There are three issues that need to be addressed:

- **Need to show the contribution of L-000900612**
- **Drug availability**
- **Determination of a clinical endpoint for the control trials**

Both participants conclude that the "two investigational" drug model is complex and the concept needs further exploration.

Lastly, there is a discussion regarding the use of virologic endpoints and clinical endpoints. DAVDP notes that proportion of subjects with 1 $\log_{10}$ or greater decrease in HIV RNA at week 24 was used in the most recent approval of an antiretroviral drug in the heavily pre-treated population. DAVDP requests that MRL submits proposals for clinical trial designs and use of specific endpoints.

ACTION ITEMS:

- MRL plans to submit a request for Fast Track designation.
- MRL plans to provide the 2 week blinded virologic data from 40 patients in the treatment-experienced patient study from Protocol 005.
- MRL confirms the submission of the safety data reports from 53 week toxicity study in dogs (expect submission in August 2005).
- MRL agrees to evaluate the inhibitory potency of L-000900612 on P-gp in an in vitro system.
- MRL agrees to submit individual renal clearance data for Division's review and comment (expect submission in August, 2005).
  Post-meeting Note: Not stated as a summary item; however, it was earlier agreed that discussion on potential P-gp interaction studies will continue.
- MRL agrees to submit concept papers for its clinical drug development program for Division's review and comment.
- MRL can submit the protocol or concept sheets for Phase III trials and change the dose as long as DAVDP is informed of such change and the justification for the change.
- MRL agrees to submit available efficacy data unblinded by treatment group once preliminary dose selection is made.
- DAVDP agrees to review and provide feedback for Phase 3 draft protocols prior to dose selection.

Attachment A

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: June 24, 2005

To: Philip L. Huang, M.D.

From: Monica Zeballos, Pharm.D., Regulatory Project Manager, HFD-530

Through: Melisse Baylor, M.D., Medical Reviewer, HFD-530

Ita Yuen, Ph.D., Pharmacology/Toxicology Reviewer, HFD-530
Derek Zhang, Ph.D., Clinical Pharmacology Reviewer, HFD-530
Sung Rhee, Ph.D., Microbiology Team Leader, HFD-530
Susan Zhou, Ph.D., Statistical Reviewer, HFD-530

Concur: Rosemary Johann-Liang, M.D., Medical Team Leader, HFD-530
James Farrelly, Ph.D., Pharmacology/Toxicology Team Leader, HFD-530
Kellie Reynolds, Pharm.D., Clinical Pharmacology Team Leader, HFD-530
Julian O'Rear, Ph.D., Microbiology Team Leader, HFD-530
Stephen Miller, Ph.D., Chemistry Team Leader, HFD-530
Guoxing Soon, Ph.D., Statistical Team Leader, HFD-530

IND: 69,928, SN 065

Drug: L-000900612

Subject: Review Team responses for IND 69,928 SN 065

Attached are the FDA draft answers to the questions that you posed in your submission dated May 25, 2005 (SN065). During our upcoming End-of-Phase I meeting with you on June 29, 2005 we will be prepared to clarify any questions you have regarding our responses. However, please note that if there are any major changes to your development plan (based upon our responses herein), we will not be prepared to discuss, nor reach agreement on, such changes at

the June 29, 2005 meeting. Any modifications to the development plan that you would like to discuss with the FDA should be submitted as a new meeting request.

General

MRL Question #1: L-000900612 is a novel pharmaceutical product for the treatment of a life-threatening condition: the drug is intended to address an urgent and unmet medical need in heavily pre-treated HIV-infected patients. Furthermore, as described in Section 6 – Phase II Clinical Experience in HIV-infected Patients to Date, preliminary clinical data from PN004 demonstrated that L-000900612 significantly reduced HIV viral load after 10 days of monotherapy, suggesting a potential to meet the unmet medical need for new HIV agents. As such, L-000900612 fulfills the two criteria outlined in the Guidance entitled "Fast Track Drug Development Programs – designation, Development, and Application Review":

1. **that the drug is intended to treat a serious or life-threatening condition (see Section 2 – Introduction), and**
2. **that the drug has the potential to address unmet medical needs and this potential is being evaluated in the planned drug development program – the Phase III program is designed to study efficacy of L-000900612 in heavily pre-treated HIV infected patients failing current therapy, and having documented resistance to at least one drug in each of the 3 classes of licensed oral ARTs (NRTI, NNRTI, and PI).**

Does the FDA concur that L-000900612 is appropriate for submission under Fast Track designation? Does the FDA concur that L-000900612 can be submitted, reviewed, and approved under the accelerated approval mechanism, with priority review?

FDA Response:

DAVDP agrees that it is appropriate to submit L-000900612 under Fast Track designation. Please submit to the Division your request for Fast Track designation. For additional information, please refer to the FDA Guidance for Industry on *Fast Track Drug Development Programs-Designation, Development, and Application Review* http://www.fda.gov/cder/guidance/5645fnl.htm (July 2004).

DAVDP agrees that an accelerated approval based on Subpart H regulations for the use of L-000900612 in highly treatment experienced patients with limited options may be warranted. Although a priority review is likely, the decision about a priority review will be made at the time of the NDA filing meeting.

MRL Question #2: The background package describes the completed, ongoing, and/or planned studies with L-000900612. Does the FDA concur that the studies outlined in this background package (see See Section 5 – Human Pharmacokinetics, Drug Metabolism, and Clinical Pharmacology, Section 6 – Phase II Clinical Experience in HIV-infected Patients to Date and Section 7 – Overall Clinical Development Program) are adequate overall to support approval of L-000900612 for other anti-retroviral agents? Does the FDA concur that the proposed clinical development program will support the following broad indication: "..

MRL Question #6: In addition to the two ongoing phase II dose-ranging studies in treatment naïve (Protocol 004) and heavily pre-treated patients failing current therapies and with documented resistance to 3 classes of oral ARTs (Protocol 005), MRL proposes to conduct two similarly designed phase III confirmatory studies in heavily pre-treated HIV infected patients failing current therapy, and having documented resistance to at least one drug in each of the 3 classes of licensed oral ARTs (NRTI, NNRTI, and PI). This includes patients who have some remaining therapeutic options as well as patients with no remaining therapeutic options.

- **The primary efficacy objective for each Phase III study is to demonstrate superiority of >0 log10 copies/mL advantage of L-000900612 plus OBT over OBT alone, and the primary efficacy objective for the Phase III program is to demonstrate superiority of >0.5 log10 copies/mL advantage of L-000900612 plus OBT over OBT alone using pre-specified meta-analysis of data from both Phase III studies. Does the FDA concur with this approach?**
- **Does the FDA agree that efficacy and safety data from these two Phase III studies through 16 weeks of therapy (rather than 24 weeks of therapy) accompanied by Phase II data demonstrating longer term safety and durability of response are sufficient to support registration of an agent for treatment of HIV infection in heavily treatment experienced patients (i.e., salvage indication)?**

FDA Response:

At this time, there are too little data to provide more than general comments on a proposed indication or on the Phase III program for L-000900612. It is too early in the development of L-000900612 to specifically comment on efficacy endpoints and analysis of Phase III trials. We will be happy to discuss these issues at an End-of-Phase II meeting.

In your description of the drug development program, you have proposed:

- one Phase II trial in treatment-naïve subjects,
- one Phase II trial in highly treatment-experienced subjects with limited treatment options, and
- two Phase III trials in highly treatment-experienced subjects with limited treatment options.

We agree that two adequate and well-controlled trials are needed for approval of an antiretroviral. If both Phase III studies are conducted in highly treatment-experienced subjects with limited options, adequate 24 weeks data would be acceptable for an indication limited to the population studied in these trials (i.e., highly treatment-experienced with limited options). Furthermore, depending on the timing of the application, an indication for this population may warrant a review for accelerated approval based on Subpart H regulations.

Furthermore, please provide your development plans for subjects who are treatment-experienced but have treatment options.

Because early Phase II antiviral activity data in Protocol 004 are promising, we are willing to be flexible with your development program. However, there are no long-term safety data as of yet

for L-000900612, a new class of antiretroviral, and Phase III drug development will be strongly influenced by long-term safety data from Phase II.

The study protocol does not include criteria for determination of dose of L-000900612 to be used at dose optimization in Protocol 004. Please propose specific criteria for determination of the dose to be used in Phase III trials.

Clinical Pharmacology

MRL Question #3: The background package describes the completed, ongoing, and/or planned Phase I studies with L-000900612 (See Section 5 – Human Pharmacokinetics, Drug Metabolism, and Clinical Pharmacology). This Phase I program has been designed to support the development of L-000900612 as an effective compound in combination therapy for the treatment of HIV infection. A key issue in the program has been to adequately address potential drug-drug interactions. Does the FDA concur that the Phase I program adequately addresses potential drug-drug interactions to permit Phase III studies of L-000900612 for the treatment of HIV infection in combination with other anti-retroviral agents?

FDA response:

In general, DAVDP concurs with your drug interaction program with the following comments:

a) In vitro data demonstrated that L-000900612 is a P-gp substrate. We encourage you to further assess the role of P-gp in L-000900612's absorption and elimination. A drug interaction study with a known potent P-gp inhibitor (but not a UGT1A1 inhibitor) is recommended. This recommendation is based on the drug interaction results that ritonavir, a known UGT1A1 inducer, had less effect on L-000900612's pharmacokinetics than other UGT1A1 inducers (rifampin and efavirenz). Because ritonavir is also a P-gp inhibitor, the lack of significant effect of ritonavir on
L-000900612 could be due to the counteracting effects of inducing UGT1A1 and inhibiting P-gp by ritonavir.

b) Please evaluate the inhibitory potency of L-000009612 on P-gp, e.g., in vitro transporter study using P-gp-expressing cell systems and digoxin as a marker in comparison with other known P-gp inhibitors.

c) Please provide information about the solubility-pH profile of L-0009612.

d) The poloxamer formulation seems to have a different PK profile compared to other formulations, e.g., profile described in Figure E-7 (P.E-15) and the limited absorption of 600 mg b.i.d in HIV patients (600 mg b.i.d. had similar plasma exposure to 400 mg b.i.d. in HIV patients). Please explain. Please also compare PK of this formulation in HIV patients vs. in healthy subjects, if data are available.

e) Please explain the inconsistency in L-000900612 400 mg steady-state PK data (Table 12 on P.28 and Table 15 on P.30) in control cohorts (Protocol 008 vs. Protocol 010).

Safety Assessment

MRL Question #4: The preclinical toxicology studies summarized in the attached table (see Table 1, Section 5d – Safety Assessment) have been conducted and reports submitted for the Agency's review. In addition, the 12 month segment of a toxicity study in dogs, a fertility study in male rats, a toxicokinetic study in rat pups, and carcinogenicity range finding studies in mice are ongoing and will be completed shortly for the Agencies review. The two year carcinogenicity studies in rats and mice are scheduled to be initiated in 4Q2005. The in-life phase of the two year carcinogenicity studies will be completed in 4Q2007, and final reports available in 3Q2008. Assuming that no unacceptable toxicity is seen in the ongoing and/or planned studies, MRL considers the studies outlined above and the plans for completion of the two year carcinogenicity study to be adequate to support registration of L-000900612 under accelerated approval guidance. Does the FDA concur that the proposed preclinical safety assessment program, including ongoing carcinogenicity studies at the time of NDA submission, will meet registration requirements for L-000900612, under accelerated approval conditions?

FDA Response:

The proposed preclinical safety assessment program will meet the registration requirements for NDA filing provided there are no safety issues that may require additional preclinical studies.

MRL Question #5: A pediatric study with L-000900612 is planned with the objective to

ts. The typical age range will vary from 2 to 16 years old and the study duration is expected to be greater than 1 year to provide long-term safety and efficacy data. In support of this pediatric study, a range-finding and an 8-week definitive study with daily gavage dosing in 5 day old rats is planned. Key endpoints planned for evaluation on the definitive study include: physical signs, body weights, female- and male-specific developmental landmarks, ophthalmic examinations, hematology and serum biochemistry, assessment of learning and memory, motor activity, sensorimotor function, and reproductive performance. Necropsy with assessment of selected organ weights and selected histomorphological examinations will be conducted. In addition, general reproductive and developmental toxicology studies in rats and rabbits and chronic toxicology studies in rats and dogs as well as long term human exposure will have been completed and results submitted for the Agencies review prior to initiation of the clinical Pediatric study. Does the Agency concur with this general study design and agree that, in the absence of any unique untoward toxicity, the study endpoints outlined above will be sufficient to support the planned clinical pediatric study?

FDA Response:

DAVDP concurs with this general study design.

Clinical Program

MRL Question #6: Please see answer to question 2.

MRL Question #7: It is anticipated that at the time of submission of the L-000900612 NDA, the safety database will include approximately 1000 subjects or patients who have received any dose of L-000900612 (from the Phase I, II, and III studies), approximately 700 subjects or patients receiving at least the marketed dose for at least 24-weeks, and approximately 80 subjects or patients receiving at least the marketed dose for at least 48-weeks. In addition, it is anticipated that some safety data from a compassionate use/expanded access study would be available at the time of filing. Does the FDA agree with the proposed size of the safety database for L-000900612?

FDA Response:

A safety database of 700 subjects is consistent with what is described in the Guidance. However, at this time, there is no long-term information on the safety of L-000900612 in HIV-infected subjects, and it is impossible to determine what type of safety database is needed without more information.

MRL Question #8: Does the FDA agree that the proposed Phase II/III program with Phase III studies out to 48 weeks in heavily pretreated HIV-infected patients, together with the preclinical toxicology and pediatric plans outlined in this background package (see Section 7 – Overall Clinical Development Program) will fulfill traditional approval requirements?

FDA Response:

Again, it is too early to address issues around traditional approval. However, in general we expect safety and efficacy results from two 48 weeks, Phase III trials in support of traditional approval. Perhaps in order

MRL Question #9: Does the FDA agree that the proposed Phase II/III program, together with the pediatric plans outlined in this background package (see Section 7 – Overall Clinical Development Program) will fulfill the requirement to study a diverse patient population (i.e., therapy-experienced and therapy-naïve) and

FDA Response:

The pediatric development plan for L-000900612 should include HIV-infected children of age and older. It should also include the development of an age-appropriate formulation for children younger than 6 years of age.

In Part I of Protocol 04, 33 of the 35 subjects were male. Please consider innovative ways of increasing the enrollment of females in your trials, particularly in Phase III trials.

In addition, please attempt to enroll patients whose race and ethnicity reflect the HIV-infected population in the United States.

As your development program progresses, please develop trials that adequately address hepatotoxicity of your drug, particularly in patients with underlying liver disease.

MRL Question #10 (emailed on June 17, 2005): Recently available data from the tipranavir studies, RESIST 1 and RESIST 2, and for TMC114 (Abstract 164LB presented at the 12th Conference on Retrovirus and Opportunistic Infections) suggest that it may become increasingly difficult to demonstrate superiority of a new investigational antiretroviral agent in combination with optimized background therapy (OBT) if a substantive number of subjects receive OBT that includes potent antiretroviral regimens such as TMC 114 or tipranavir+enfurvitide. In this changing environment, we are interested in the Agency's current thoughts on the design of Phase III studies to evaluate novel antiretroviral agents in HIV-infected patients failing current therapy and with limited treatment options.

FDA Response:

It is too early to discuss the specific design of Phase III trials in highly treatment-experienced subjects with limited options. The design will be influenced by what other antiretrovirals are commercially available at the time of the initiation of these trials. We **strongly** recommend blinding of all Phase III clinical trials.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at (301) 827-2481 if you have any questions regarding the contents of this transmission.

Monica Zeballos, Pharm.D.
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/s/

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