

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204790Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 204790

SUPPL # 0

HFD # 530

Trade Name Tivicay

Generic Name dolutegravir

Applicant Name Viiv Healthcare

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

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

YES NO

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

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

d) Did the applicant request exclusivity?

YES NO

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

5

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

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

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

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES NO

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

NDA#

NDA#

NDA#

2. Combination product.

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

YES NO

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

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a)

is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

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

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

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

YES NO

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

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

YES NO

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

YES NO

If yes, explain:

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

YES NO

If yes, explain:

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

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

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

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

Investigation #1 YES NO

Investigation #2 YES NO

Investigation #1
!
!
YES ! NO
Explain: ! Explain:

Investigation #2
!
!
YES ! NO
Explain: ! Explain:

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

YES NO

If yes, explain:

=====

Name of person completing form: Sohail Mosaddegh
Title: Regulatory Project Manager
Date: 07/10/2013

Name of Office/Division Director signing form: Debra Birnkrant
Title: Director, Division of Antiviral Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

SOHAIL MOSADDEGH
08/07/2013

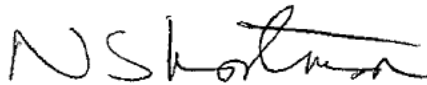
DEBRA B BIRNKRANT
08/07/2013

CONFIDENTIAL

m1.3.3 Debarment Certification

DEBARMENT CERTIFICATION

ViiV Healthcare Company certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application [NDA 204790:Original NDA for Tivicay (dolutegravir) Tablets (50 mg)].



Neil Shortman
Head of Regulatory
ViiV Healthcare

17th October 2012

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 204790 BLA #	NDA Supplement # 0 BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Dolutegravir Established/Proper Name: TIVICAY Dosage Form: tablet		Applicant: ViiV Healthcare Company Agent for Applicant (if applicable):
RPM: Sohail Mosaddegh		Division: Antiviral Products
<u>NDA and NDA Efficacy Supplements:</u> NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)	<u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u> Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)): Provide a brief explanation of how this product is different from the listed drug. ☐ This application does not rely upon a listed drug. ☐ This application relies on literature. ☐ This application relies on a final OTC monograph. ☐ This application relies on (explain) <u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u> <u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u> ☐ No changes ☐ Updated Date of check: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.	
❖ Actions		
• Proposed action • User Fee Goal Date is <u>08/17/2013</u>	☒ AP ☐ TA ☐ CR	
• Previous actions (<i>specify type and date for each action taken</i>)	☒ None	

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

² For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics ³	
Review priority: ☐ Standard ☒ Priority Chemical classification (new NDAs only): Type 1 ☒ Fast Track ☐ Rx-to-OTC full switch ☐ Rolling Review ☐ Rx-to-OTC partial switch ☐ Orphan drug designation ☐ Direct-to-OTC NDAs: Subpart H ☐ Accelerated approval (21 CFR 314.510) ☐ Restricted distribution (21 CFR 314.520) Subpart I ☐ Approval based on animal studies ☐ Submitted in response to a PMR ☐ Submitted in response to a PMC ☐ Submitted in response to a Pediatric Written Request BLAs: Subpart E ☐ Accelerated approval (21 CFR 601.41) ☐ Restricted distribution (21 CFR 601.42) Subpart H ☐ Approval based on animal studies REMS: ☐ MedGuide ☐ Communication Plan ☐ ETASU ☐ MedGuide w/o REMS ☒ REMS not required Comments:	
❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	☐ Yes ☐ No
❖ Public communications (<i>approvals only</i>)	
Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
Press Office notified of action (by OEP)	☒ Yes ☐ No
Indicate what types (if any) of information dissemination are anticipated	☐ None ☒ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other Information Alert

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i>	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i>	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(i)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
[505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
[505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i>	☐ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "**No**," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "**No**," continue with question (5).

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). <i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i> <i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i>	☐ Yes ☐ No

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ⁴	Included
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Approval 08/12/2013
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	08/12/2013
• Original applicant-proposed labeling	12/16/2012
• Example of class labeling, if applicable	NA

⁴ Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	☐ Medication Guide ☒ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	08/12/2013
• Original applicant-proposed labeling	12/16/2012
• Example of class labeling, if applicable	NA
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
• Most-recent draft labeling	06/12/2013
❖ Proprietary Name • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.	Acceptable: 03/14/2013 06/03/2013 & 03/14/2013 Verified
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	☒ RPM 02/28/2013 (PLR format) ☒ DMEPA 05/22/2013 ☒ DMPP/PLT (DRISK) 06/07/2013 ☒ ODPD (DDMAC) 06/10/2013 & 06/06/2103 ☐ SEALD ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	RPM filing review 02/13/2013, memo 02/13/2013
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)	☒ Not a (b)(2) ☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics (<i>approvals only</i>) • Date reviewed by PeRC <u>06/12/2013</u> If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)	☒ Included

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	☒ Verified, statement is acceptable
❖ Outgoing communications (<i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i>)	5/29/2013, 5/23/2013, 5/9/2013, 4/29/2013, 4/26/2013, 4/24/2013, 4/23/2013, 4/19/2013, 4/19/2013, 4/15/2013, 4/11/2013, 4/9/2013, 4/1/2013, 3/19/2013, 3/18/2013, 3/15/2013, 3/15/2013, 3/15/2013, 3/14/2013, 3/14/2013, 2/15/2013, 2/14/2013, 2/7/2013, 1/29/2013, 1/4/2013
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	☒ No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	☒ N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	☐ No mtg 09/20/2012 & 07/10/2012
• EOP2 meeting (<i>indicate date of mtg</i>)	☐ No mtg 02/11/2011, 09/08/2010, 07/26/2010, 07/13/2010
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	Late cycle meeting with applicant- 06/12/2013 Mid-cycle meeting with applicant 03/27/2013
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	☐ None 08/12/2013
Division Director Summary Review (<i>indicate date for each review</i>)	☐ None 08/06/2013
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	☐ None 06/21/2013
PMR/PMC Development Templates (<i>indicate total number</i>)	☐ None 6
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	NA
• Clinical review(s) (<i>indicate date for each review</i>)	05/17/2013 Filing review 02/07/2013
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	☒ None

⁶ Filing reviews should be filed with the discipline reviews.

❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	05/17/2013 (see clinical review)
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	☒ Not applicable
❖ Risk Management - REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) - REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) - Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	☐ None Review 07/15/2013, no REMS recommended
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	☐ None requested 05/14/2013
Clinical Microbiology ☐ None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	☒ None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	☐ None 07/11/2013 & 05/17/2013 Filing review: 01/23/2013
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	☒ None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	☒ None
Statistical Review(s) (<i>indicate date for each review</i>)	☐ None 05/14/2013 Filing review: 01/31/2013
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	☒ None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	☒ None
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	☐ None 05/17/2013 Filing review: 01/31/2013
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	☐ None 05/30/2013
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	☒ None
• Supervisory Review(s) (<i>indicate date for each review</i>)	☐ None 05/09/2013 & 05/08/2013
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	☐ None 05/08/2013 Filing review: 01/28/2013
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	☒ None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	☐ None 03/18/2013
❖ ECAC/CAC report/memo of meeting	☐ None 02/28/2013 Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	☒ None requested

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	☐ None 07/25/2013
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	☒ None
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	☐ None 07/24/2013, 05/17/2013 Filing review: 02/21/2013 Biopharmaceutics review: 05/16/2013 Filing review 02/13/2013
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	☒ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	See CMC 05/17/2013 review
☐ Review & FONSI <i>(indicate date of review)</i>	
☐ Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷)</i>	Date completed: see CMC 07/24/2013 review ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	☒ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

⁷ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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/s/

SOHAIL MOSADDEGH
08/12/2013



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: June 12, 2013, 12:00 PM to 1:30 PM
Meeting Location: Teleconference

Application Number: NDA 204790
Product Name: dolutegravir (GSK1349572) tablets, 50mg
Indication: Treatment of HIV infection
Sponsor/Applicant Name: ViiV Healthcare Company

Meeting Chair: Kim Struble
Meeting Recorder: Sohail Mosaddegh

FDA ATTENDEES

1. Carolyn L. Yancey, D, Senior Medical Officer, Risk Management Analyst
2. Charu Mullick, MD, Medical Officer
3. Dave Roeder, ADRA OAP
4. Debra Birnkrant, MD, Director
5. Edward M Cox, MD, MPH, Director, Office of Antimicrobial Products
6. Elizabeth Thompson, MS, Regulatory Project Manager
7. Jeffrey Murray, MD, MPH, Deputy Director
8. Jeffrey Florian, PhD, Pharmacometrics Reviewer
9. Julian O'Rear, PhD, Virology Team Lead
10. Kendall Marcus, MD, Associate Director of Safety
11. Kim Struble, PharmD, Medical Team Lead
12. Kim Taylor, Operations Research Analyst, Office of Planning and Informatics
13. Kyong Hyon, Safety Regulatory Project Manager
14. Mark Seaton, PhD, Pharmacology/Toxicology Reviewer, DAVP
15. Morgan Walker, PharmD, MBA, Division of Medication Error Prevention and Analysis
16. Nathan Caulk, MS, BSN, RN, Patient Labeling Reviewer
17. Shirley K Seo, PhD, Clinical Pharmacology Team Lead
18. Sohail Mosaddegh, PharmD, Regulatory Project Manager
19. Stanley Au, PharmD, Clinical Pharmacology Reviewer
20. Stephen Miller, PhD, CMC-Lead, ONDQA
21. Su-Young Choi, PharmD, PhD, Clinical Pharmacology Reviewer

(b) (4)

SPONSOR ATTENDEES

1. Garrett Nichols, MD, Project Team Leader, GSK

2. Sherene Min, MD, MPH, Physician Lead, GSK
3. Steve Piscitelli, PharmD, Clinical Pharmacology Lead, GSK
4. Mark Underwood, PhD, Virology Lead, GSK
5. Lloyd Curtis, MD, Safety Lead, GSK
6. Jessica Lim, MS, Stats Lead, GSK
7. Sherry Watson, BS, CMC Regulatory, GSK
8. Christine Caivano, PharmD, Labeling, Regulatory, GSK
9. Betty Nies, MS, Regulatory Advertising & Promotion, GSK
10. Martha Anne Auld, RPh, Regulatory Lead, GSK
11. John Pottage, M.D., CMSO, ViiV
12. Neil Shortman, BS, Head, Regulatory Affairs, ViiV
13. Jim Demarest, PhD, Head, Virology, ViiV
14. Mark Shaefer PharmD, Head NA Medical Affairs, ViiV

BACKGROUND

- The purpose of a Late-Cycle meeting (LCM) is to share information and to discuss any substantive review issues, Advisory Committee (AC) meeting plans (if scheduled), and the objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application.
- NDA 204790 (dolutegravir, GSK1349572, tablets, 50mg) was submitted on December 17, 2012 for review with a proposed indication of treatment for HIV-1 in adults and adolescents. It is being reviewed a priority review under the PDUFA V “The Program: with an action date of August 17, 2013.
- No previous action has been taken on this NDA.

LCM Agenda

1. Introductory Comments
 - Welcome, Introductions, Ground rules, Objectives of the meeting
2. Discussion of Substantive Review Issues
 - No substantial review issues were identified or discussed
3. Discussion of Upcoming Advisory Committee Meeting
 - No AC meeting is scheduled
4. Current Assessment of the need for REMS or other risk management actions
 - At this time a REMS is not indicated
5. Major labeling issues

- No major labeling issues were identified. Minor labeling issues were discussed, excluding the virology section of the PI. GSK/ViiV will resubmit labeling based on the LCM labeling discussions.

6. Postmarketing Requirements/Postmarketing Commitments

- FDA will send GSK/ViiV language for the PREA PMRs and PMCs to reach agreement on the timelines for PMR/C Milestones.

7. Wrap up and Action Items

- FDA will send virology labeling comments
- FDA will send Patient Packaging labeling comments
- GSK/ViiV will submit revised labeling
- FDA will send PMC(s) and PMR(s) language

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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/s/

KIMBERLY A STRUBLE
06/25/2013

From: [Thompson, Elizabeth](mailto:Thompson.Elizabeth)
To: marthaanne.a.auld@gsk.com
Cc: [Mosaddegh, Sohail](mailto:Mosaddegh.Sohail); [Thompson, Elizabeth](mailto:Thompson.Elizabeth)
Subject: Dolutegravir information request NDA204790
Date: Wednesday, May 29, 2013 2:48:06 PM
Importance: High

Martha Anne-

As mentioned during today's call, the dolutegravir NME will trigger PREA postmarketing requirements for both, the INI-naïve and the INI-experienced populations. Below is the draft language the Agency is considering for the PREA requirement, and information necessary for the Pediatric Review Committee.

- 1) Please submit a request for deferral of pediatric studies in the INI-experienced population ages 4 weeks to less than 18 years.
- 2) Please fill out estimated dates for the following milestones: protocol submission date, study completion date, final report submission date.

Conduct a trial to evaluate pediatric pharmacokinetics, safety and antiviral activity study of twice daily dolutegravir in HIV-1 infected integrase inhibitor-experienced pediatric subjects 4 weeks to less than 18 years of age. Initial evaluation of dolutegravir exposure must be performed in an initial pharmacokinetic study or substudy to allow dose selection. Using doses selected based on the PK study/substudy, and agreed upon with the FDA, conduct a longer-term pediatric safety and antiviral activity assessment of dolutegravir plus background regimen assessing activity on the basis of continued HIV-1 RNA virology response and safety monitoring over at least 24 weeks of dosing.

Protocol Submission date:
Study Completion date:
Final Report Submission date:

We need this information by COB Friday, May 31, 2013.

Regards,

Beth

Elizabeth Thompson, M.S.
LCDR, U.S. Public Health Service
Senior Regulatory Project Manager
FDA/CDER/OND/DAVP
10903 New Hampshire Avenue
Bldg #22, Rm 6334 (new Rm# effective 4-4-13)
Silver Spring, MD 20993
301-796-0824 (office); 301-796-9883 (fax)
elizabeth.thompson@fda.hhs.gov

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/s/

ELIZABETH G THOMPSON
05/29/2013



NDA 204790

LATE CYCLE MEETING BRIEFING PACKAGE

ViiV Healthcare Company
c/o GlaxoSmithKline
Attention: Martha Anne Auld, RPh
Senior Director, Infectious Diseases, Regulatory Affairs
P.O. Box 13398, Bldg 5.5218, Five Moore Drive
Research Triangle Park, NC 27709

Dear Ms. Auld:

Please refer to your New Drug Application (NDA) dated December 16, 2012, received December 17, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for dolutegravir (GSK1349572) tablets, 50mg.

We also refer to the Late-Cycle meeting (LCM) meeting scheduled for June 12, 2013. Attached is our briefing package, including our agenda for this meeting.

If you have any questions, call Sohail Mosaddegh, PharmD, Regulatory Project Manager, at (301) 796-4876 or (301) 796-1500.

Sincerely yours,

{See appended electronic signature page}

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

ENCLOSURE:
Late-Cycle Meeting Briefing Package

LATE-CYCLE MEETING BRIEFING PACKAGE

Meeting Date and Time: June 12, 2013, 12:00 PM to 1:30 PM
Meeting Location: Teleconference

Application Number: NDA 204790
Product Name: dolutegravir (GSK1349572) tablets, 50mg
Indication: Treatment of HIV infection
Sponsor/Applicant Name: ViiV Healthcare Company

INTRODUCTION

The purpose of a Late-Cycle meeting (LCM) is to share information and to discuss any substantive review issues, Advisory Committee (AC) meeting plans (if scheduled), and the objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues, whether it will be reviewed by the Agency in the current review cycle, and, if so, whether the submission would constitute a major amendment and trigger an extension of the PDUFA goal date. If you submit any new information in response to the issues identified in this briefing package prior to this LCM or the Advisory Committee meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

CURRENT SUBSTANTIVE REVIEW ISSUES

At this time we do not have any substantive review issues. However, if we learn of any issues from the outstanding CMC and bioanalytical inspections, then the agenda will be modified accordingly.

ADVISORY COMMITTEE MEETING

An Advisory Committee meeting is not planned.

REMS OR OTHER RISK MANAGEMENT ACTIONS

We have not identified any issues related to risk management.

LCM AGENDA

1. Introductory Comments – 5 minutes (Sohail Mosaddegh/Kimberly Struble)

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Major labeling issues –80 minutes (all review disciplines)

Please note the labeling discussion may be modified depending on subsequent revisions to the labeling. We will discuss with you any revisions to the agenda prior to June 12, 2013.

- Indications and Usage
 - Points to be considered when initiating therapy
- Dosage and Administration, Drug Interactions, Use in Special Populations, Clinical Pharmacology
 - Recommendations for treatment-experienced, INSTI-experienced subjects
 - Use in subjects with severe renal impairment
 - Use with potent inducers
 - Use in subjects with severe renal impairment and receiving potent inducers
 - Dosing recommendations for coadministration with fosamprenavir/ritonavir
- Warnings and Precautions
 - Effects on serum liver biochemistries in HBV/HCV co-infected subjects
- Adverse Reactions
 - Display of Adverse Drug Reactions (all grades and drug related), selected laboratory abnormalities, and Less common ADR (myositis (b)(4))
- Pregnancy: Animal Data and Nonclinical Toxicology
 - Sections updated with twice daily exposure information
- Microbiology
 - Display of resistance and cross-resistance data
- Description of Clinical Studies
 - Display of virologic response rates by baseline demographics/characteristics
 - Display of Spring-1 and Viking data

3. Wrap up and Action Items –5 minutes (Sohail Mosaddegh/Kimberly Struble)

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/s/

JEFFREY S MURRAY
05/23/2013



NDA 204790

INFORMATION REQUEST

ViiV Healthcare
c/o GlaxoSmithKline
Attention: Martha Anne Auld, RPh
Senior Director, Infectious Diseases, Regulatory Affairs
Five Moore Drive, P.O. Box 13398, Bldg 5.5218
Research Triangle Park, NC 27709

Dear Ms. Auld:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dolutegravir (GSK1349572) tablets, 50mg.

We are reviewing the Chemistry, Manufacturing and Control section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

A: Please respond to the following CMC information requests by May 12, 2013.

1. We acknowledge the response to IR #15 and 16 in your March 29, 2013 amendment to the Agency letter dated March 15, 2013. We recommend that the dissolution acceptance criterion be tightened to Q ^{(b) (4)} at 20 minutes based on the following information:
 - a) Data for all Phase 3 clinical batches shows dissolution ^{(b) (4)} at 20 minutes.

(b) (4)

2. Reference is made to IR #7 in the Agency letter dated March 15th. The response to IR #7 in the amendment dated March 29th is not acceptable. (b) (4)

[Redacted]

3. Insufficient information has been provided in the NDA (b) (4)

[Redacted]

If you have additional data to support the specificity/accuracy of the drug substance and drug product impurity method please submit this information. If such data are not available at this time, we may consider a Post-Marketing Commitment regarding method validation.

4. Reference is made to IR #10 in the Agency letter dated March 15, 2013. We acknowledge the response to IR #10 in your March 29, 2013 amendment confirming that all changes beyond the ranges/variations provided for in section 3.2.P.3.3 would be provided in accordance with 21 CFR 314.70. We note that 3.2.P.3.3 includes the statements (b) (4)

[Redacted]

The Agency's expectation is that the potential impact of changes to process parameters, including those designated as non critical process parameters as well as the parameters in Master Batch Record, be assessed under the firm's quality system at the time of the change. As appropriate, changes with a potential to adversely affect product quality should be notified to the Agency in accordance with 21 CFR 314.70. Please revise the 3.2.P.3.3 statement referenced above accordingly.

B: Follow up Comment from Ware facility inspection

1. You propos

(b) (4)

Hold periods managed under your quality system should be supported by adequate data for relevant quality attributes (e.g., blend uniformity, impurities, (b) (4) microbiological tests, etc) to demonstrate the proposed hold time does not adversely impact drug product quality. Confirm that your proposed hold time would be supported by adequate data that would be available for evaluation during future inspections.

If you have any questions, call Althea Cuff, Regulatory Health Project Manager, at (301) 796-4061.

Sincerely,

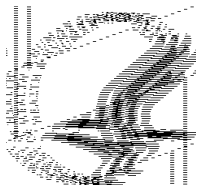
{See appended electronic signature page}

Rapti D. Madurawe, Ph.D.
Branch Chief, Branch V
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

RAPTI D MADURawe
05/09/2013



MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

Date: April 29, 2013

NDA: 204,790

Drug: GSK1349572 (Dolutegravir, DTG)

To: Martha Anne A. Auld, RPh
Senior Director, Infectious Diseases, Global Regulatory Affairs
(919) 483-9347
marthaanne.a.auld@gsk.com

Sponsor: ViiV Healthcare Company

Subject: Virology comments

Please describe in more detail how the OSS scores for VIKING-3 were determined and calculated, (i.e., cutoffs for ARVs, what algorithm was used and was partial scoring used (e.g., NRTIs).

Please respond by May 06, 2013 and feel free to contact me at 301-796-4876 or 301-796-1500 if you have any questions regarding the contents of this transmission.

Sohail Mosaddegh, PharmD
Regulatory Project Manager
Division of Antiviral Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

SOHAIL MOSADDEGH
04/29/2013

Cuff, Althea

From: Martha Anne Auld [marthaanne.a.auld@gsk.com]
Sent: Friday, April 26, 2013 11:21 AM
To: Cuff, Althea
Cc: Sherry Watson; Heather Peterson
Subject: RE: NDA 204790 - Information Request

Hi Althea,
Thank you for your email; please consider this email as confirmation of its receipt.
We will work with the team to address your question/comment and will be in touch if there are any questions.
Thank you.

Kind regards,

Martha Anne

~~~~~  
Martha Anne Auld, R.Ph.  
Global Regulatory Affairs - Infectious Diseases  
marthaanne.a.auld@gsk.com  
telephone: internal: 7/8 703-9347 external: (919) 483-9347  
cell phone: (b) (6)  
facsimile: (919) 315-8319

---

**From:** Cuff, Althea [mailto:Althea.Cuff@fda.hhs.gov]  
**Sent:** Friday, April 26, 2013 11:08 AM  
**To:** Martha Anne Auld  
**Subject:** FW: NDA 204790 - Information Request

Martha,

The 8 April 2013 response to our 01 April 2013, Information Request, to question 3c states that the drug product specification will be updated to include a microbial limits test specification. Batches of drug product will not be routinely tested but will comply with the microbial limits specifications provided in section 3.2.P.5 of the application when tested.

Provide the microbial limits test method and a summary of the method suitability studies

(b) (4) 21  
CFR 211.165 (a) and (b) require appropriate laboratory determination of conformance to release specifications. Please provide a commitment to conduct microbial limits testing on each batch of drug product or provide a summary of the in-process controls and tests that will be used to demonstrate microbiological control of the manufacturing process (see question #3 of the 1 April 2013 document).

use confirm receipt of this e-mail.

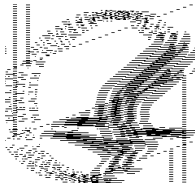
nks,

***Althea Cuff, MS***  
***Regulatory Health Project Manager***  
***Food & Drug Administration, CDER***  
***Office of New Drugs Quality Assessment II***  
***301-796-4061***

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/s/  
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ALTHEA CUFF  
04/26/2013



MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

---

**Date:** April 24, 2013

**NDA:** 204,790

**Drug:** GSK1349572 (Dolutegravir, DTG)

**To:** Martha Anne A. Auld, RPh  
Senior Director, Infectious Diseases, Global Regulatory Affairs  
(919) 483-9347  
marthaanne.a.auld@gsk.com

**Sponsor:** ViiV Healthcare Company

**Subject:** Clinical site closure comments submitted 04/19/13 (SDN 019)

---

Please refer to the submission dated April 19, 2013 and the April 23, 2013 teleconference, regarding summary of reasons for closure of Dr. Joseph Gathe's site for ING113086, ING111762 and ING112574. Please submit to your NDA:

- whether or not the clinical efficacy and safety data from these sites are reliable
- and a statement stating you have no pending/ongoing issues with remaining sites from the trials submitted in the NDA.

Please respond by May 03, 2013 and feel free to contact me at 301-796-4876 or 301-796-1500 if you have any questions regarding the contents of this transmission.

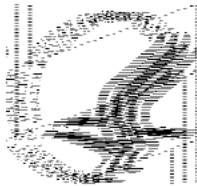
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Sohail Mosaddegh, PharmD  
Regulatory Project Manager  
Division of Antiviral Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

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/s/  
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SOHAIL MOSADDEGH  
04/24/2013



MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

**Date:** April 23, 2013

**NDA:** 204,790

**Drug:** GSK1349572 (Dolutegravir, DTG)

**To:** Martha Anne A. Auld, RPh  
Senior Director, Infectious Diseases, Global Regulatory Affairs  
(919) 483-9347  
marthaanne.a.auld@gsk.com

**Sponsor:** ViiV Healthcare Company

**Subject:** Bioanalysis Comments

**Dolutegravir bioanalysis**

1. For the bioanalysis reports supported by the validation report RD2007/01425 (bioanalysis for studies ING111207, ING111322, ING111405, ING111521, ING111602, ING111603, ING111604, ING111853, ING111854, ING111856, ING112276, ING112934, ING112941, and ING111961), the method was validated and performed with a linear range of 5-5000 ng/mL in plasma. Some subjects in these studies had  $C_{max}$  values higher than 5000 ng/mL. However, in the bioanalysis report of each study, no information is available regarding repeated analysis due to concentrations above the upper quantitation limit. Please provide more detailed information including, a list of samples above the quantitation limit in each study, the dilution factor(s) applied, the dilution QC data with the dilution factor specified, and the concentration obtained for each sample after re-analysis. Please provide the information summarized in a table.
2. According to your dolutegravir method validations (RD2007-01425, RD2010/00175, 2011N112453, 2011N112679, 2012N149534) (b) (4) Please clarify what measures were taken (b) (4) during the method validation experiments. In particular, please specify (b) (4) Please also indicate whether the bioanalysis for individual trials were performed under conditions (b) (4)

### **Rilpivirine bioanalysis (LAI116181)**

3. Please submit the rilpivirine method validation report number (SH08-J01-TR288/BA1099) that was generated (b) (4). The rilpivirine method validation report that was submitted was generated (b) (4). Also, please indicate if rilpivirine was protected from light for all method validation experiments conducted (b) (4) (SH08-J01-TR288/BA1099) and during the bioanalysis of rilpivirine samples from the LAI116181 trial.
4. Please also submit the BA28 rilpivirine method validation report and all the related amendments that contain the long term rilpivirine stability data up to 1528 days at -18°C that (b) (4) is referencing and indicate whether this is the same method used (b) (4) in their partial validation.
5. For the rilpivirine method validation conducted (b) (4) (b) (4) please provide further information (b) (4)
6. For rilpivirine, according to the information provided, the samples were stored at -20°C or lower at the clinical site. Please provide information on whether there is available long term rilpivirine stability data to cover both the duration and the specific storage temperature for the rilpivirine subject samples at the clinical site.

### **Tenofovir Bioanalysis (ING111604)**

7. Currently, only 38 days of long term tenofovir stability at -30°C. was submitted. According to the information provided, the samples were stored at -30°C or lower for less than one month at the clinical site and at the bioanalytical laboratory, samples were stored at -30°C and analyzed within one month of receipt. Please provide further information on there is sufficient long term tenofovir stability data that covers both the duration and the specific storage temperature for the tenofovir subject samples from the day samples were first drawn until the day the last sample was analyzed, including any reanalysis.

### **Boceprevir Bioanalysis (ING115697)**

8. Please provide an update on the status of the boceprevir bioanalysis.

Please respond by May 07, 2013 and feel free to contact me at 301-796-4876 or 301-796-1500 if you have any questions regarding the contents of this transmission.

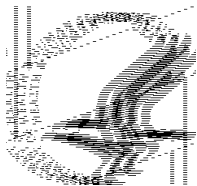
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Sohail Mosaddegh, PharmD  
Regulatory Project Manager  
Division of Antiviral Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

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/s/  
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SOHAIL MOSADDEGH  
04/23/2013



**MEMORANDUM OF FACSIMILE:**

**Date:** April 19, 2013  
**NDA:** 204790  
**Drug:** TIVICAY (dolutegravir) 50 mg Tablet  
**To:** Martha Anne Auld, R.Ph. Senior Director, Global Regulatory Affairs  
**Sponsor:** ViiV Healthcare Company c/o GSK  
**From:** Stacey Min, Pharm.D., Regulatory Project Manager  
**Subject:** NDA 204790 Information Request

---

Please refer to your NDA 204790, Tivicay for the treatment of HIV-1 infection in adults. We also refer to your December 16, 2012, original NDA submission and the February 13, 2013 Safety Update submission. We are reviewing your submission and have the following comment and request for additional information. Please provide a response by close of business Tuesday, April 23, 2013.

**Clinical Comment:**

Please provide a full narrative for Subject 487202 from ING114915 who withdrew due to meeting predefined liver stopping criteria as discussed in the 60-day Safety Update Report. In particular, provide history surrounding barbiturate use and/or abuse and whether this subject had previous or subsequent liver-related abnormalities. Additionally, please provide all available and pertinent laboratory data or abdominal studies (ultrasounds, CT etc).

If you have any questions regarding this correspondence, please contact me at (301) 796-4253.

---

Stacey Min, Pharm.D.  
Regulatory Project Manager  
Division of Antiviral Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

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/s/  
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STACEY MIN  
04/19/2013



NDA 204790

**METHODS VALIDATION  
MATERIALS RECEIVED**

ViiV Healthcare Company  
Attention: Martha Anne Auld, R.Ph.  
GlaxoSmithKline LLC  
PO Box 11398  
5 Moore Drive  
Bldg 5.5218  
Research Triangle Park, NC 27709  
FAX: (919) 315-8319

Dear Martha Anne Auld:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for TIVICAY® (dolutegravir) Tablets, 50 mg and to our April 11, 2013, letter requesting sample materials for methods validation testing.

We acknowledge receipt on April 19, 2013, of the additional sample material that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Michael L. Trehy  
MVP Coordinator  
Division of Pharmaceutical Analysis  
Office of Testing and Research  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research

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/s/  
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MICHAEL L TREHY  
04/19/2013

**From:** Schumann, Katherine  
**To:** ["marthaanne.a.auld@gsk.com"](mailto:marthaanne.a.auld@gsk.com)  
**Subject:** NDA 204790 dolutegravir - clinical information request  
**Date:** Monday, April 15, 2013 10:23:00 AM

---

Dear Martha Anne,

Thank you for taking my call a few minutes ago. Please find below an additional, unrelated request for clinical information under NDA 204790 (dolutegravir):

Please provide information for the following cases in the phase 3 trials.

1. Provide a narrative for the subject in the Sailing trial with absolute QTcF exceeding 500 msec.
2. Subject 2467 in Sailing: provide HCV viral load values after liver chemistry elevations returned to baseline.

Let me know if you have any questions. As I mentioned earlier, my phone number below (301-796-1182) is out of service for the moment. For urgent matters, you can reach me via email or the Division's main number: 301-796-1500. When my phone is fixed, I'll send you a quick note.

Warm Regards,

Katie

Katherine Schumann, M.S.  
Regulatory Project Manager  
FDA/CDER/OND/OAP  
Division of Antiviral Products  
10903 New Hampshire Ave., Bldg. 22, Room 6237  
Silver Spring, MD 20993-0002  
Phone: (301) 796-1182  
Fax: (301) 796-9883  
Email: [Katherine.Schumann@fda.hhs.gov](mailto:Katherine.Schumann@fda.hhs.gov)

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/s/  
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KATHERINE SCHUMANN  
04/15/2013



NDA 204790

**REQUEST FOR METHODS  
VALIDATION MATERIALS**

ViiV Healthcare Company  
Attention: Martha Anne Auld, R.Ph.  
GlaxoSmithKline LLC  
PO Box 11398  
5 Moore Drive  
Building 5.5218  
Research Triangle Park, NC 27709  
FAX: (919) 315-8319

Dear Martha Anne Auld:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for TIVICAY® (dolutegravir) tablets.

We will be performing methods validation studies on for TIVICAY® (dolutegravir) tablets, 50 mg, as described in NDA 204790.

In order to perform the necessary testing, we request the following additional sample material:

**Sample**

2 g dolutegravir sodium drug substance

Please include the MSDSs and the Certificates of Analysis for the sample material.

Forward these materials via express or overnight mail to:

Food and Drug Administration  
Division of Pharmaceutical Analysis  
Attn: MVP Sample Custodian  
1114 Market Street, Room 1002  
St. Louis, MO 63101

Please notify me upon receipt of this FAX. You may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (michael.trehy@fda.hhs.gov).

Sincerely,

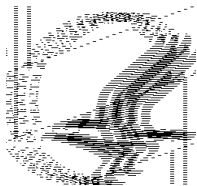
*{See appended electronic signature page}*

Michael L. Trehy, Ph.D.  
MVP coordinator  
Division of Pharmaceutical Analysis  
Office of Testing and Research  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research

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/s/  
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MICHAEL L TREHY  
04/11/2013



MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

---

**Date:** April 09, 2013

**NDA:** 204,790

**Drug:** GSK1349572 (Dolutegravir, DTG)

**To:** Martha Anne A. Auld, RPh  
Senior Director, Infectious Diseases, Global Regulatory Affairs  
(919) 483-9347  
marthaanne.a.auld@gsk.com

**Sponsor:** ViiV Healthcare Company

**Subject:** Clinical Comments

---

Provide the information requested for the following cases in the Sailing and Viking-3 trials. If this information is not available, then please indicate in your response.

1. Melena AE, subject 658 Sailing: was an upper GI endoscopy or other investigations performed? Was the event considered to be secondary to upper GI bleeding? Is the AE resolved or ongoing?
2. Gastric mucosal lesion, subject 1977 Sailing: provide follow-up regarding outcome (resolved or not). Was the subject on aspirin or another medication with the potential for gastric mucosal damage? State whether this gastric abnormality was pre-existing or new onset.
3. Erosive gastritis AE, subject 1022 Viking-3: provide follow-up regarding outcome (resolved or not).
4. Rhabdomyolysis AE, subject 627 Sailing: provide (if available) CK values during the episode of rhabdomyolysis.
5. Subject 0942 in Sailing: provide HBV viral load values when peak liver chemistry elevations were observed.
6. For the following subjects, confirm dolutegravir rechallenge was not performed after improvement in liver chemistries: 1201, 2467, and 0942.
7. Provide a narrative explaining finding of new-onset deafness in subject 2274 in Sailing. Is this AE resolved?

Please respond by April 12, 2013 and feel free to contact me at 301-796-4876 or 301-796-1500 if you have any questions regarding the contents of this transmission.

---

Sohail Mosaddegh, PharmD  
Regulatory Project Manager  
Division of Antiviral Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

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/s/  
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SOHAIL MOSADDEGH  
04/09/2013



NDA 204790

**INFORMATION REQUEST**

ViiV Healthcare  
c/o GlaxoSmithKline  
Attention: Martha Anne Auld, RPh  
Senior Director, Infectious Diseases, Regulatory Affairs  
Five Moore Drive, P.O. Box 13398, Bldg 5.5218  
Research Triangle Park, NC 27709

Dear Ms. Auld:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for dolutegravir (GSK1349572) tablets, 50mg.

We are reviewing the Chemistry, Manufacturing and Control section of your submission and have the following comments and information requests. We request a prompt written response by April 8, 2013, in order to continue our evaluation of your NDA.

Drug Substance:

1. We agree with the current (b) (4) acceptance criteria proposed for the potential genotoxic impurities (b) (4) in the specification (b) (4). As changes are likely over product lifecycle, in order to ensure detectability and continued minimization of the risk of genotoxic impurities above acceptable levels in the drug substance, we recommend that,
  - a) (b) (4) be listed as specified impurities in the specification (b) (4)
  - b) (b) (4) be listed as specified impurities in the specification (b) (4)

Drug Product:

2. In the Pharmaceutical Development Section P.2.4, it is stated that (b) (4). However, the bulk container closure system was not described in P.7. Please clarify if the bulk container closure system is to be used for the commercial drug products and has sufficient supporting stability data.

Microbiology:

3. Microbial limits testing of the finished drug product may be waived if adequate manufacturing process control is demonstrated. Provide the following information to ensure that microbiologically adulterated materials do not enter the manufacturing process:
- a. The maximum holding/processing times [REDACTED] (b) (4)
  - b. The results of microbial limits testing and specified organism testing conducted on the primary stability batches of drug product.
  - c. One or more of the following control strategies may be employed to ensure that adequate microbiological quality of the finished drug product is achieved. Alternate control strategies may be employed if adequate justification is provided.
    - i. In-process microbial limits testing [REDACTED] (b) (4)
    - ii. Microbial limits testing of the drug substance and all excipients entering the manufacturing process.
    - iii. Microbial limits testing on each batch of drug product until a satisfactory product history demonstrating compliance with microbial limits specifications is established.
  - d. A commitment to conduct microbial limits testing as part of the stability protocol.

If you have any questions, call Althea Cuff, Regulatory Health Project Manager, at (301) 796-4061.

Sincerely,

*{See appended electronic signature page}*

Rapti D. Madurawe, Ph.D.  
Branch Chief, Branch V  
Division of New Drug Quality Assessment II  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/  
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RAPTI D MADURAWA  
04/01/2013



NDA 204790

**MID-CYCLE COMMUNICATION**

ViiV Healthcare Company  
c/o GlaxoSmithKline  
Attention: Martha Anne Auld, RPh  
Senior Director, Infectious Diseases, Regulatory Affairs  
Five Moore Drive, P.O. Box 13398, Bldg 5.5218  
Research Triangle Park, NC 27709

Dear Ms. Auld:

Please refer to your New Drug Application (NDA) dated December 16, 2012, received December 17, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for dolutegravir (GSK1349572) tablets, 50mg.

We also refer to the teleconference between representatives of your firm and the FDA on March 27, 2013. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call Sohail Mosaddegh, PharmD, Regulatory Project Manager, at (301) 796-4876 or (301) 796-1500.

Sincerely yours,

*{See appended electronic signature page}*

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

Enclosure:  
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MID-CYCLE COMMUNICATION**

**Meeting Date and Time:** March 27, 2013 9:30 AM to 11:00 AM

**Application Number:** NDA 204790  
**Product Name:** dolutegravir (GSK1349572) tablets, 50mg  
**Indication:** Treatment of HIV infection  
**Applicant Name:** ViiV Healthcare Company

**Meeting Chair:** Debra Birnkrant, MD  
**Meeting Recorder:** Sohail Mosaddegh, PharmD

**FDA ATTENDEES**

1. Charu Mullick, MD, Medical Officer
2. Debra Birnkrant, MD, Director
3. Elizabeth Thompson, MS, Regulatory Project Manager
4. Greg Soon, PhD, Statistical Team Lead
5. Jeffrey Murray, MD, MPH, Deputy Director
6. Jeffry Florian, PhD, Pharmacometrics Reviewer
7. Karen Winestock, Chief, Project Management Staff, DAVP
8. Kim Struble, PharmD, Medical Team Lead
9. Lin Qi, PhD, Chemist
10. Lisa Naeger, PhD, Virology Reviewer
11. Maotang Zhou, PhD, Chemist
12. Mark Seaton, PhD, Pharmacology/Toxicology Reviewer, DAVP
13. Shirley K Seo, PhD, Clinical Pharmacology Team Lead
14. Sohail Mosaddegh, PharmD, Regulatory Project Manager
15. Stanley Au, PharmD, Clinical Pharmacology Reviewer
16. Su-Young Choi, PharmD, PhD, Clinical Pharmacology Reviewer
17. Thomas Hammerstrom, PhD, Biometric Reviewer
18. Wendy Carter, DO, Medical Officer
19. Kim Taylor, Operations Research Analyst, Office of Planning and Informatics

(b) (4)

**APPLICANT ATTENDEES**

1. Martha Anne Auld, RPh, Senior Director, Infectious Diseases, Global Regulatory Affairs
2. Lloyd D. Curtis, MA MRCP, Medical Director, Signal Evaluation & Risk Management, Global Clinical Safety and Pharmacovigilance
3. Jessica Lim, MA, Manager, Clinical Statistics

4. Sherene Min, MD, MPH, Physician Integrase Project Leader, ID MDC
5. W. Garrett Nichols, MD, M.S., Project Leader, ID MDC
6. Stephen Piscitelli, PharmD, Director, Clinical Pharmacology, ID MDC
7. Mark Underwood, PhD, Lead Integrase Virologist, ID MDC
8. Sherry, Watson, Director, CMC Pre-Approval, GRA
9. James M. Goodrich, PhD, MD, Vice President Global Medical Strategy
10. Neil Shortman, Vice President, Head of Regulatory

## INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

## SIGNIFICANT ISSUES

None

## INFORMATION REQUESTS/ADVICE/DISCUSSION

The following topics were discussed and Information Requests (IR) will be sent to the applicant in the future or have already been sent.

Chemistry, Manufacturing, and Controls: (IR sent 04/01/213)

We agree with the current (b) (4) acceptance criteria proposed for the potential genotoxic impurities (b) (4)

(b) (4) in the specification (b) (4) As changes are likely over product lifecycle, in order to ensure detectability and continued minimization of the risk of genotoxic impurities above acceptable levels in the drug substance, we recommend that,

- (b) (4) be listed as specified impurities in the specification (b) (4)
- (b) (4) be listed as specified impurities in the specification (b) (4)

Clinical Pharmacology:

- The clinical significance of decreased dolutegravir exposures in subjects with severe renal impairment is being evaluated. (IR pending)
- The significance of decreased dolutegravir exposures in the presence of fosamprenavir needs further evaluation. The subgroup analysis in the SAILING trial suggests that

subjects taking fosamprenavir had significantly lower exposures of dolutegravir. The clinical pharmacology review team is evaluating the necessity of dose adjustment of dolutegravir to 50 mg twice daily when used with fosamprenavir. (IR sent 03/19/2013)

Clinical: (IR pending)

Hepatotoxicity: Our safety review of hepatobiliary disorders and concerning hepatic cases is currently ongoing. At this point of review, concerning cases appear to be categorized as follows-

- Hepatitis B and C flare or reactivation following discontinuation of HBV treatment agent/s
- Liver involvement as a component of severe hypersensitivity reactions
- Hepatitis C IRIS; in some cases DTG related liver injury could not be ruled out.

We are reviewing hepatobiliary adverse events and hepatic laboratory analysis from phase 3 trials and other available data to form an overall assessment. We will be reviewing the proposed labeling e.g., the labeling you have proposed for Immune Reconstitution syndrome under section 5 and other liver-related labeling in Section 6. As the hepatic safety review is not complete, a final decision regarding proposed labeling has not been made.

Pediatric indication:

Discussions are ongoing within the Division and planned with the Pediatric Review Committee regarding granting an indication for adolescents and including information in sections 2, 6 and 14 versus no formal indication and including safety and activity data in section 8 only. Issue for granting indication or not relates to only 10 subjects with complete data (i.e. datasets) through Week 24, specifically safety. We have reviewed the remaining 14 subjects with the safety update that included line listings for AEs, SAEs, etc; however, complete data/datasets were not available and this may be considered “interim data”. To date we have not granted a pediatric indication based on interim data and have typically reviewed complete datasets prior to granting a pediatric indication.

#### **MAJOR SAFETY CONCERNS/RISK MANAGEMENT**

None

#### **ADVISORY COMMITTEE MEETING**

Advisory Committee meeting is not expected.

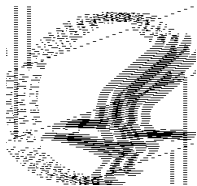
#### **LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES**

|                                                              |          |
|--------------------------------------------------------------|----------|
| Send Labeling/PMR/PMC to Applicant                           | 05/17/13 |
| Send Agency Late-Cycle Meeting Briefing Package to Applicant | 05/30/13 |
| Hold Late-Cycle Meeting with Applicant                       | 06/11/13 |
| Action Date                                                  | 08/16/13 |

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/s/  
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DEBRA B BIRNKRANT  
04/08/2013



MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

---

**Date:** March 19, 2013

**NDA:** 204,790

**Drug:** GSK1349572 (Dolutegravir, DTG)

**To:** Martha Anne A. Auld, RPh  
Senior Director, Infectious Diseases, Global Regulatory Affairs  
(919) 483-9347  
marthaanne.a.auld@gsk.com

**Sponsor:** ViiV Healthcare Company

**Subject:** IR/Comments

---

Please provide rationale for your proposed dolutegravir dosing recommendation (50mg BID) when it is used with nevirapine.

Please respond by April 02, 2013 and feel free to contact me at 301-796-4876 or 301-796-1500 if you have any questions regarding the contents of this transmission.

---

Sohail Mosaddegh, PharmD  
Regulatory Project Manager  
Division of Antiviral Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

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/s/  
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SOHAIL MOSADDEGH  
03/19/2013



NDA 204790

**METHODS VALIDATION  
MATERIALS RECEIVED**

ViiV Healthcare Company  
Attention: Martha Anne Auld, R.Ph.  
GlaxoSmithKline LLC  
PO Box 11398  
5 Moore Drive  
Bldg 5.5218  
Research Triangle Park, NC 27709  
FAX: (919) 315-8319

Dear Martha Anne Auld:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for TIVICAY® (dolutegravir) Tablets, 50 mg and to our February 7, 2013, letter requesting sample materials for methods validation testing.

We acknowledge receipt on March 15, 2013, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email ([Michael.Trehy@fda.hhs.gov](mailto:Michael.Trehy@fda.hhs.gov)).

Sincerely,

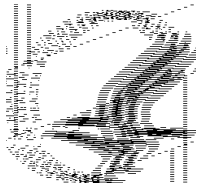
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Michael L. Trehy  
MVP Coordinator  
Division of Pharmaceutical Analysis  
Office of Testing and Research  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research

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/s/  
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MICHAEL L TREHY  
03/18/2013



MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

---

**Date:** March 15, 2013

**NDA:** 204,790

**Drug:** GSK1349572 (Dolutegravir, DTG)

**To:** Martha Anne A. Auld, RPh  
Senior Director, Infectious Diseases, Global Regulatory Affairs  
(919) 483-9347  
marthaanne.a.auld@gsk.com

**Sponsor:** ViiV Healthcare Company

**Subject:** Comments regarding datasets

---

Please refer to your proposed labeling submitted December 17, 2012 for NDA 204790. Please provide the following information for raw datasets (not derived datasets) used in snapshot analysis for phase 3 trials:

1. Name of the raw datasets used for analysis, and
2. Specific variables in these raw datasets that were used for snapshot analysis.

Please respond by March 18, 2013 and feel free to contact me at 301-796-4876 or 301-796-1500 if you have any questions regarding the contents of this transmission.

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Sohail Mosaddegh, PharmD  
Regulatory Project Manager  
Division of Antiviral Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

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/s/  
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SOHAIL MOSADDEGH  
03/15/2013



NDA 204790

**INFORMATION REQUEST**

ViiV Healthcare  
c/o GlaxoSmithKline  
Attention: Martha Anne Auld, RPh  
Senior Director, Infectious Diseases, Regulatory Affairs  
Five Moore Drive, P.O. Box 13398, Bldg 5.5218  
Research Triangle Park, NC 27709

Dear Ms. Auld:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for dolutegravir (GSK1349572) tablets, 50mg.

We are reviewing the Chemistry, Manufacturing and Control section of your submission and have the following comments and information requests. We request a prompt written response by March 29, 2013, in order to continue our evaluation of your NDA.

**Drug Substance:**

1. We find the manufacturing process description for the drug substance provided in Section S.2.2 has insufficient detail to allow the agency to make a knowledgeable assessment of the application. In order to evaluate the adequacy of your control strategy to consistently manufacture quality drug substance at commercial scale, provide a complete description of your drug substance manufacturing process that includes ranges or set points for parameters with supporting justification. You can either revise the manufacturing process description in section S.2.2 or include a master batch record. The Agency's expectation is that the potential impact of changes to process parameters, including those with low criticality, be assessed under the firm's quality system at the time of the change. As appropriate, changes with a potential to adversely affect product quality should be notified to the Agency in accordance with 21 CFR 314.70.
2. We note that you have indicated in section S.2.2 that regulatory action for post approval changes to non-critical process parameters (NCPP) would be taken in conformance with regulations and guidance for minor changes. Please confirm, if a change to an NCPP has a substantial or moderate potential impact to product quality (e.g. as might occur in the case of changes beyond ranges previously studied), you would conform to the requirements for regulatory notification as described in 21 CFR §314.70 (b) or (c).

3. You have indicated in section S.4.1 that the release tests for dolutegravir sodium (assay) content by HPLC, related substances by HPLC, and solid state form (b) (4) may be performed (b) (4). Please indicate the criteria for determining when these tests would be performed (b) (4).
- (b) (4) We recommend that the solid state form (b) (4) test be performed (b) (4).
4. (b) (4) Please propose a control strategy for (b) (4) impurities based on appropriate risk assessment to ensure that the drug substance over its lifecycle will not be inadvertently contaminated by any (b) (4) impurities.
5. In Table 12 of Section S.2.6, you state in footnote 4: “The criterion of the amount (b) (4) (b) (4) is (b) (4) based on the limit for unspecified impurities.” (b) (4) Please clarify how the amount (b) (4) (b) (4) was determined (b) (4) (b) (4).

### Drug Product

6. The following comments pertain to the determination of degradation products in the drug product:
- Please explain (b) (4) HPLC analysis for dolutegravir tablets, 50 mg.
  - Method validation should include samples stored under relevant stress conditions: light, heat, humidity, acid/base hydrolysis, and oxidation (ICH Q3B (R2)). Please provide representative chromatograms of the stressed samples using the analytical procedure for drug-related impurities in Dolutegravir Tablets, 50 mg (3.2.P.5.2 & 5.3).
  - It is stated (b) (4) Please provide data to demonstrate the capability of your HPLC method (b) (4).
7. (b) (4) We recommend inclusion of a test (b) (4) in the drug product specification.
8. Microbial test
9. Please provide the following to confirm appropriate drug product control:

- a) An assessment [redacted] (b) (4) in the drug product [redacted] (b) (4)
- b) Representative drug product release and stability data to confirm that dolutegravir sodium [redacted] (b) (4) remain unchanged over drug product manufacturing and stability.

10. The manufacturing process and process control descriptions provided in Section P.3.3 has insufficient detail to allow the agency to make a knowledgeable assessment of the application. For example no information is provided about the following:

- a) Equipment type and size for each unit operation
- b) [redacted] (b) (4) process parameters [redacted] (b) (4)
- c) [redacted] (b) (4)
- d) [redacted] (b) (4)
- e) [redacted] (b) (4)
- f) Process parameters [redacted] (b) (4)

Confirm that the process parameter ranges as provided in the MBR (Master Batch Record) in section 3.2.R supplements the drug product manufacturing process description provided in section 3.2.P.3.3, and that the MBR provides operating ranges/set points for the process parameters not included in section 3.2.P.3.3. Additionally, confirm that notification of all changes beyond the ranges/variations provided for in the application, including those of process parameters as described in the MBR, would be provided in accordance with 21 CFR 314.70.

11. We note that the manufacturing process currently does not include [redacted] (b) (4)

[redacted]

12. Table 12 of P.2.3 indicates [redacted] (b) (4)

[redacted]

## Biopharmaceutics

13. There are insufficient data (e.g. dissolution profiles comparison with f2 statistical testing, in-vitro in-vivo correlation (IVIVC models) or in-vivo bioequivalence studies) to determine whether batches manufactured throughout the proposed manufacturing ranges would result in products that are bioequivalent. Submit adequate justification, including (but not limited to) the following information:
- a) f2 statistical testing and dissolution profile comparisons of DTG tablets manufactured across the proposed (b)(4) ranges (b)(4)
  - b) f2 statistical testing and dissolution profile comparisons of DTG tablets manufactured across the proposed mixing ranges (b)(4)
  - c) f2 statistical testing and dissolution profile comparisons of DTG tablets manufactured across the proposed tablet hardness (b)(4)
14. Provide manufacturing ranges ((b)(4) mixing times, tablet hardness etc.) for the pivotal Phase 3 batches.
15. Provide the mean ( $\pm$ SD) dissolution data in a tabulated and graphical form for the pivotal Phase 3 batches.
16. The proposed acceptance criterion of  $Q = (b)(4)$  at (b)(4) will not be able to reject batches that are outside the proposed tablet hardness range (b)(4). Update the acceptance criterion to enable rejection of batches outside the acceptable hardness range and other CQA's.
17. Provide dissolution data for batches used in the relative bioavailability study ING113674 (Relative bioavailability study of three different tablet formulations of GSK1349572 50 mg and the Dose Proportionality of and Effect of Food on the Selected Formulation in healthy male and female volunteers), if available.

If you have any questions, call Althea Cuff, Regulatory Health Project Manager, at (301) 796-4061.

Sincerely,

*{See appended electronic signature page}*

Rapti D. Madurawe, Ph.D.  
Branch Chief, Branch V  
Division of New Drug Quality Assessment II  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/  
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RAPTI D MADURawe  
03/15/2013

**To:** Martha Anne Auld (marthaanne.a.auld@gsk.com)  
**Subject:** NDA-204790 Labeling comments clarification needed

Hello:  
Please see responses below.  
Take care

Sohail Mosaddegh, Pharm.D.  
Lieutenant Commander, USPHS  
Regulatory Health Project Manager  
FDA/CDER/OND/OAP/Division of Antiviral Products  
10903 New Hampshire Ave., Bldg. 22, Room 6377  
Silver Spring, MD 20993-0002  
Phone: (301) 796-4876  
Fax: (301) 796-9883  
Email: [Sohail.Mosaddegh@FDA.HHS.GOV](mailto:Sohail.Mosaddegh@FDA.HHS.GOV)

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**From:** Martha Anne Auld [<mailto:marthaanne.a.auld@gsk.com>]  
**Sent:** Friday, March 15, 2013 11:44 AM  
**To:** Mosaddegh, Sohail  
**Subject:** RE: NDA-204790 Labeling PMR/PMC Discussion Comments (COR-NDAIR-23)

Hi Sohail,  
Thank you again for your note and for alerting me to it via voicemail.  
We have a few questions/clarifications for you and the team, please. The following questions have come from our stats team (green font text).

There are two aspects of your proposed approach for which we would like to check our understanding:

- 1) Does the Division plan to re-derive the MAXON variable after subsetting the data based on AVISNUM? As shown in the following example, MAXON is based on all available visits.

Example: maximum toxicity is on-treatment and after Week 48 (e.g., for a subject with Week 60 data at time of database cut)

| <i>Visit (AVISIT)</i> | <i>DAIDS Toxicity Grade (LBTOX)</i> | <i>Toxicity Emergent Flag (LBTRTEM)</i> | <i>Randomized phase Maximum On-treatment Grade flag (MAXON)</i> |
|-----------------------|-------------------------------------|-----------------------------------------|-----------------------------------------------------------------|
| <i>Day 1</i>          | <i>Grade 1</i>                      | <i>0</i>                                | <i>0</i>                                                        |
| <i>Week 24</i>        | <i>Grade 1</i>                      | <i>0</i>                                | <i>0</i>                                                        |
| <i>Week 48</i>        | <i>Grade 2</i>                      | <i>1</i>                                | <i>0</i>                                                        |
| <i>Week 60</i>        | <i>Grade 3</i>                      | <i>1</i>                                | <i>1</i>                                                        |

By excluding Week 60 (AVISNUM=140), there is no longer an observation with MAXON=1. The correct maximum emergent toxicity to use is now Grade 2.

This interpretation is correct. The Week 60 data would no longer be included in the Week 48 analysis for the product label and therefore, the maximum toxicity for the above example is Grade 2 at Week 48.

- 2) Please note that not all Withdrawal (AVISNUM=510) records are appropriate to use. As shown in the following example, the Withdrawal record would not be applicable to the proposed analysis for a subject who withdraws after the Week 60 visit.

**A post-treatment worsening occurs within 30 days of discontinuation during the Week 60 window**

| <i>Visit (AVISIT)</i> | <i>DAIDS Toxicity Grade (LBTOX)</i> | <i>Toxicity Emergent Flag (LBTRTEM)</i> | <i>Randomized phase Maximum On-treatment Grade flag (MAXON)</i> | <i>Worsening Emergent Toxicity within 30 days of IP discontinuation (MAXEMFU)</i> |
|-----------------------|-------------------------------------|-----------------------------------------|-----------------------------------------------------------------|-----------------------------------------------------------------------------------|
| <i>Day 1</i>          | <i>Grade 1</i>                      | <i>0</i>                                | <i>0</i>                                                        | <i>0</i>                                                                          |
| <i>Week 24</i>        | <i>Grade 1</i>                      | <i>0</i>                                | <i>0</i>                                                        | <i>0</i>                                                                          |
| <i>Week 48</i>        | <i>Grade 2</i>                      | <i>1</i>                                | <i>1</i>                                                        | <i>0</i>                                                                          |
| <i>Week 60</i>        | <i>Grade 1</i>                      | <i>0</i>                                | <i>0</i>                                                        | <i>0</i>                                                                          |
| <i>Follow-Up</i>      | <i>Grade 3</i>                      | <i>1</i>                                | <i>0</i>                                                        | <i>1</i>                                                                          |

Since this post-treatment worsening occurred beyond the Week 48 window, it would not be applicable to the proposed analysis used in the label. i.e., not all AVISNUM=510 should be used; only those within 30 days of a Week 48 or earlier discontinuation.

Correct, unfortunately our pre-NDA communications did not clearly communicate our standard definition for the Week 48 analysis for product labeling for your team. Our expectation for the MAXEMFU was for this to flag only through the Week 48 analysis visit window and not for subjects' values beyond this time point. However, at this time we accept your analysis as above that for a few subjects, the AVISNUM=510 will not be appropriate. Please provide us a list of all the subject ID numbers from each Phase 3 trial that fit the criteria of having their MAXEMFU beyond the Week 48 (or Week 24 for treatment-experienced phase 3 trials) analysis window and are therefore inappropriately included in using the AVISNUM=510 variable.

When we are ready to submit the updated, additional information, I'll need your thoughts on where to place it on the backbone. My first impression is that it would be in the same module with the ISS (m5), maybe a subfolder of some type. We will put the revised labeling in the appropriate folder in m1.

Thanks for your help with this Sohail. Please let me know if there are any questions. I hope that you have a good weekend.

kind regards,

*Martha Anne*

---

**From:** Mosaddegh, Sohail [<mailto:Sohail.Mosaddegh@fda.hhs.gov>]  
**Sent:** Thursday, March 14, 2013 1:19 PM  
**To:** Martha Anne Auld  
**Subject:** NDA-204790 Labeling PMR/PMC Discussion Comments (COR-NDAIR-23)

Hello:  
Please see attached.  
Thanks

*Sohail Mosaddegh, Pharm.D.  
Lieutenant Commander, USPHS  
Regulatory Health Project Manager  
FDA/CDER/OND/OAP/Division of Antiviral Products  
10903 New Hampshire Ave., Bldg. 22, Room 6377*

Silver Spring, MD 20993-0002  
Phone: (301) 796-4876  
Fax: (301) 796-9883  
Email: [Sohail.Mosaddegh@FDA.HHS.GOV](mailto:Sohail.Mosaddegh@FDA.HHS.GOV)

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/s/  
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SOHAIL MOSADDEGH  
03/15/2013



NDA 204790

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

ViiV Healthcare  
c/o GlaxoSmithKline, LLC  
Five Moore Drive, P.O. Box 13398, Bldg 5.5218  
Research Triangle Park, NC 27709

ATTENTION: Martha Anne Auld, R.Ph.  
Senior Director, Global Regulatory Affairs

Dear Ms. Auld:

Please refer to your New Drug Application (NDA) dated December 16, 2012, and received December 17, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Dolutegravir Tablets, 50 mg.

We also refer to your correspondence dated December 16, 2012, received December 17, 2012, requesting review of your proposed proprietary name, Tivicay. We have completed our review of the proposed proprietary name and have concluded that it is acceptable.

The proposed proprietary name, Tivicay, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your December 16, 2012 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Danyal Chaudhry, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3813. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Sohail Mosaddegh at (301) 796-4876.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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FRANKLIN T STEPHENSON  
03/12/2013

CAROL A HOLQUIST  
03/14/2013

Executive CAC

Date of Meeting: February 26, 2013

Committee: David Jacobson-Kram, Ph.D., DABT, OND IO, Chair  
Abby Jacobs, Ph.D., OND IO, Member  
Paul Brown, Ph.D., OND IO, Member  
Whitney Helms, Ph.D., DHOT, Alternate Member  
Hanan Ghantous, Ph.D., DABT, DAVP Team Leader  
Mark Seaton, Ph.D., DABT, DAVP Presenting Reviewer

Author of Draft: Seaton

**The following information reflects a brief summary of the Committee discussion and its recommendations.**

NDA #204-790

Drug Name: Dolutegravir

Sponsor: ViiV Pharmaceuticals

Background:

The new drug application (NDA) package for dolutegravir (DTG) has been submitted to the Agency. The applicant is seeking marketing approval for the drug as a treatment for HIV infection in combination with other antiretroviral agents in adults and children). The proposed dosage for DTG is 50 mg once daily in treatment naïve and treatment experienced INI- naïve, HIV-infected adults and INI- naïve children 12 to 18 years old, weighing  $\leq 40$  kg. The DTG dose is 50 mg twice daily in INI-resistant subjects. The applicant has conducted two-year carcinogenicity studies in mice and rats. The two studies are presented below.

Mouse Carcinogenicity Study

Dolutegravir carcinogenicity in CD-1 mice was assessed at doses of 0 (water), 0 (0.5% HPMC/0.1% Tween 80 in water), 7.5, 25 and 500 mg/kg/day by oral gavage. Dose selection was based on saturation of absorption and concern over GI effects over the long term. Dose spacing was based on AUC. In female mice, the difference in survival between the high dose group animals and the vehicle control animals was statistically significant ( $p = 0.0321$ ). No drug-related tumors were observed in mice. Systemic exposures at the 7.5, 25 and 500 mg/kg/day doses were 3x, 6x, and 18x in males, and 3x, 9x, and 22x in females than in humans at the recommended clinical dose of 50 mg QD, based on AUC.

## Rat Carcinogenicity Study

Dolutegravir carcinogenicity in Sprague Dawley rats was assessed at doses of 0 (water), 0 (0.5% HPMC/0.1% Tween 80 in water), 2, 10, and 50 mg/kg/day by oral gavage. Dose selection was based on MTD (GI irritation and hemorrhage of the glandular stomach mucosa in males at 500 mg/kg/day) and saturation of absorption. The survival rate across the dose groups was similar to control. No drug-related tumors were observed in rats. Systemic exposures at the 2, 10, and 50 mg/kg/day doses were 2x, 6x, and 13x in males, and 5x, 14x, and 21x in females than in humans at the recommended clinical dose of 50 mg QD, based on AUC.

## Executive CAC Recommendations and Conclusions:

### Mouse:

- The Committee agreed that the study was adequate, noting prior Exec CAC concurrence with the protocol.
- The Committee concurred that there were no drug-related neoplasms.

### Rat:

- The Committee agreed that the study was adequate, noting prior Exec CAC concurrence with the protocol.
- The Committee concurred that there were no drug-related neoplasms.

David Jacobson-Kram, Ph.D.  
Chair, Executive CAC

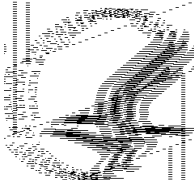
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/Division File, DAVP  
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/Seaton, DAVP  
/Mosaddegh, DAVP  
/ASeifried, OND IO

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/s/  
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ADELE S SEIFRIED  
02/27/2013

DAVID JACOBSON KRAM  
02/28/2013



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**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Division of Antiviral Products  
Food and Drug Administration  
Silver Spring, MD 20993

MEMORANDUM OF ELECTRONIC MAIL CORRESPONDENCE

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**Date:** February 15, 2013

**NDA:** 204,790

**Drug:** GSK1349572 (Dolutegravir, DTG)

**To:** Martha Anne A. Auld, RPh  
Senior Director, Infectious Diseases, Global Regulatory Affairs  
(919) 483-9347  
marthanne.a.auld@gsk.com

**Sponsor:** ViiV Healthcare Company

**Subject:** Comments regarding your Pediatric Safety Update

---

Please refer to your NDA 204790 submitted 12/17/2012.

In addition to the planned safety update submission, please provide details for the events summarized in the submission. Please include all subjects enrolled in the study (i.e. the safety information should not be limited to the 10 subjects who are included in the Legacy Report).

Adverse events:

| SID | Study drug start date | AE Preferred term | Medra HLT | SOC | AE serious | Hospitalization | death | AE Grade | AE start date | AE end date | AE outcome            | AE related to study drug (DTG) | AE related to background ART |
|-----|-----------------------|-------------------|-----------|-----|------------|-----------------|-------|----------|---------------|-------------|-----------------------|--------------------------------|------------------------------|
|     |                       |                   |           |     | Y/N        | Y/N             | Y/N   | 0-4      |               |             | e.g. ongoing/resolved | Y/N                            | Y/N                          |

Laboratory toxicity:

| SID | Study drug start date | Lab e.g. ALT | Baseline value | ULN   | LLN   | Lab tox | Worse grade tox | event serious | event start date | event end date | event out-come        | event related to study drug (DTG) | event related to background ART |
|-----|-----------------------|--------------|----------------|-------|-------|---------|-----------------|---------------|------------------|----------------|-----------------------|-----------------------------------|---------------------------------|
|     |                       |              |                | value | value | G1-4    | Y/N             | Y/N           |                  |                | e.g. ongoing/resolved | Y/N                               | Y/N                             |

---

Please feel free to contact me at 301-796-4876 or 301-796-1500 if you have any questions regarding the contents of this transmission.

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Sohail Mosaddegh, PharmD  
 Regulatory Project Manager  
 Division of Antiviral Products  
 Center for Drug Evaluation and Research  
 Food and Drug Administration

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/s/  
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SOHAIL MOSADDEGH  
02/15/2013



NDA 204790

**FILING COMMUNICATION**

ViiV Healthcare  
c/o GlaxoSmithKline  
Attention: Martha Anne Auld, RPh  
Senior Director, Infectious Diseases, Regulatory Affairs  
Five Moore Drive, P.O. Box 13398, Bldg 5.5218  
Research Triangle Park, NC 27709

Dear Ms. Auld:

Please refer to your New Drug Application (NDA) dated December 16, 2012, received December 17, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for dolutegravir (GSK1349572) tablets, 50mg.

We also refer to your amendments dated December 17, 2012, January 16, 2013, January 29, 2013, January 31, 2013 and February 13, 2013.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to: <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>). Therefore, the user fee goal date is August 17, 2013.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by May 24, 2013. In addition, the planned date for our internal mid-cycle review meeting is March 13, 2013. We are not currently planning to hold an advisory committee meeting to discuss this application.

At this time, we are notifying you that we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

### **PROMOTIONAL MATERIAL**

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), and patient PI. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and patient PI, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We acknowledge receipt of your request for a partial deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

We note that you have submitted pediatric studies with this application for pediatric patients 12 years to less than 18 years. Once the review of this application is complete we will notify you whether you have fulfilled the pediatric study requirement for this age group.

If you have any questions, call Sohail Mosaddegh, PharmD, Regulatory Project Manager, at (301) 796-4876 or (301) 796-1500.

Sincerely yours,

*{See appended electronic signature page}*

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

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/s/  
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DEBRA B BIRNKRANT  
02/14/2013



NDA 204790

**REQUEST FOR METHODS  
VALIDATION MATERIALS**

ViiV Healthcare Company  
Attention: Martha Anne Auld, R.Ph.  
GlaxoSmithKline LLC  
PO Box 11398  
5 Moore Drive  
Building 5.5218  
Research Triangle Park, NC 27709

Dear Martha Anne Auld:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for TIVICAY® (dolutegravir) tablets.

We will be performing methods validation studies on for TIVICAY® (dolutegravir) tablets, 50 mg, as described in NDA 204790.

In order to perform the necessary testing, we request the following sample materials and equipments:

**Method, current version**

- Determination of content, identification and uniformity of content in dolutegravir tablets, 50 mg by HPLC
- Determination of drug-related impurities in dolutegravir tablets, 50 mg by HPLC  
[redacted] (b) (4)
- Determination of related substances by HPLC
- Alternate method for determination of related substance [redacted] (b) (4)
- [redacted] by HPLC
- Determination of [redacted] (b) (4) content by HPLC
- Determination of [redacted] (b) (4) content by HPLC

**Samples and Reference Standards**

- 500 mg dolutegravir sodium reference standard
- 50 TIVICAY® (dolutegravir) tablets, 50 mg
- 20 mg [redacted] (b) (4)
- 100 mg of dolutegravir sodium containing approximately [redacted] (b) (4)
- 20 mg of [redacted] (b) (4) reference standard
- 20 mg of [redacted] (b) (4) reference standard
- 20 mg of [redacted] (b) (4) reference standard
- 20 mg of [redacted] (u) (4) reference standard

|          |         |                                 |
|----------|---------|---------------------------------|
| 20 mg of | (b) (4) | reference standard if available |
| 20 mg of | (b) (4) | reference standard              |
| 20 mg of | (b) (4) | reference standard              |
| 20 mg of | (b) (4) | reference standard              |
| 20 mg of | (b) (4) | reference standard              |

**Equipment**

(b) (4)

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration  
Division of Pharmaceutical Analysis  
Attn: Sample Custodian  
1114 Market Street, Room 1002  
St. Louis, MO 63101

Please notify me upon receipt of this FAX. You may contact me by telephone (314-539-3815), FAX (314-539-2113), or email ([michael.trehy@fda.hhs.gov](mailto:michael.trehy@fda.hhs.gov)).

Sincerely,

*{See appended electronic signature page}*

Michael L. Trehy, Ph.D.  
MVP coordinator  
Division of Pharmaceutical Analysis  
Office of Testing and Research  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research

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/s/  
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MICHAEL L TREHY  
02/07/2013

**Subject: FW: DTG comment for site information**

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**From:** Mosaddegh, Sohail  
**Sent:** Tuesday, January 29, 2013 11:10 AM  
**To:** Martha Anne Auld (marthaanne.a.auld@gsk.com)  
**Subject:** DTG comment for site information

Hello:

The clinical study report for study ING111762 states subjects enrolled at a Russian Federation site (083523) were excluded from efficacy analysis as a result of data integrity issues. The same investigator/site also enrolled subjects in study ING113086. We are requesting the following related information:

- 1) Submit details about the nature of non-compliance identified at site 083523.
- 2) Please confirm whether this site enrolled subjects in the remaining two adult phase 3 trials.
- 3) Additionally, we are requesting assurance that the remaining Russian Federation sites in phase 3 trials are acceptable with respect to data integrity issues.

Please submit the above information to your NDA by 01/31/13.

Thanks

*Sohail Mosaddegh, Pharm.D.  
Lieutenant Commander, USPHS  
Regulatory Health Project Manager  
FDA/CDER/OND/OAP/Division of Antiviral Products  
10903 New Hampshire Ave., Bldg. 22, Room 6377  
Silver Spring, MD 20993-0002  
Phone: (301) 796-4876  
Fax: (301) 796-9883  
Email: [Sohail.Mosaddegh@FDA.HHS.GOV](mailto:Sohail.Mosaddegh@FDA.HHS.GOV)*

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/s/  
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SOHAIL MOSADDEGH  
01/29/2013



NDA 204790

**NDA ACKNOWLEDGMENT**

ViiV Healthcare  
c/o GlaxoSmithKline  
Attention: Martha Anne Auld, RPh  
Senior Director, Infectious Diseases, Regulatory Affairs  
Five Moore Drive, P.O. Box 13398, Bldg 5.5218  
Research Triangle Park, NC 27709

Dear Ms. Auld:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: (dolutegravir, GSK1349572) tablet, 50mg

Date of Application: December 16, 2012

Date of Receipt: December 17, 2012

Our Reference Number: NDA 204790

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 February 15, 2013, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited 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

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If you have any questions, call me at 301-796-4876 or 301-796-1500.

Sincerely,

{ See appended electronic signature page }

Sohail Mosaddegh, PharmD  
Regulatory Project Manager  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SOHAIL MOSADDEGH  
01/04/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

IND 75382

MEETING MINUTES

ViiV Healthcare  
c/o GlaxoSmithKline  
Attention: Martha Anne Auld, RPh  
Senior Director, Infectious Diseases, Regulatory Affairs  
Five Moore Drive, P.O. Box 13398, Bldg 5.5218  
Research Triangle Park, NC 27709

Dear Ms. Auld:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for GSK1349572 (dolutegravir, DTG).

We also refer to the meeting between representatives of your firm and the FDA on September 20, 2012. The purpose of the meeting was to discuss proposals for the content and format of your New Drug Application (NDA) for DTG, present the results of the three Phase 3 studies [ING113086 (SPRING-2), ING114467 (SINGLE) and ING112574 (VIKING-3)], and provide update on Phase 3 ING111762 (SAILING).

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Sohail Mosaddegh, PharmD, Regulatory Project Manager, at (301) 796-4876 or (301) 796-1500.

Sincerely yours,

*{See appended electronic signature page}*

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

Enclosure:  
Meeting Minutes



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** B  
**Meeting Category:** Pre-NDA

**Meeting Date and Time:** September 20, 2012 9:00 AM to 10:30 AM  
**Meeting Location:** 10903 New Hampshire Avenue  
White Oak Building 22, Conference Room: 1417  
Silver Spring, Maryland 20903

**Application Number:** IND 75382  
**Product Name:** GSK1349572 (dolutegravir, DTG)  
**Indication:** Treatment of HIV-1 infection  
**Sponsor/Applicant Name:** ViiV Healthcare

**Meeting Chair:** Debra Birnkrant, MD, Director  
**Meeting Recorder:** Sohail Mosaddegh, PharmD, Regulatory Project Manager

**FDA ATTENDEES**

1. Debra Birnkrant, MD, Director
2. Jeffrey Murray, MD, MPH, Deputy Director
3. Amalia Himaya, Acting Chief, Project Management Staff
4. Antoine El Hage, PhD, Office of Scientific Investigations
5. Charu Mullick, MD, Medical Officer
6. Greg Soon, PhD, Statistical Team Lead
7. Jeffrey Florian, PhD, Pharmacometrics Reviewer
8. Karen Winestock, Chief, Project Management Staff
9. Kim Struble, PharmD, Medical Team Lead
10. Lisa Naeger, PhD, Virology Reviewer
11. Morgan Walker Pharm.D, MBA, safety Evaluator
12. Shirley K Seo, PhD, Acting Clinical Pharmacology Team Lead
13. Sohail Mosaddegh, PharmD, Regulatory Project Manager
14. Stanley Au, PharmD, Clinical Pharmacology Reviewer
15. Yi Zhang, PhD, Pharmacometrics fellow
16. Yodit Belew, MD, Clinical Reviewer

**SPONSOR ATTENDEES**

GlaxoSmithKline LLC:

1. Martha Anne Auld, RPh, Senior Director, Regulatory Affairs (RA)

2. Lloyd D. Curtis, MA MRCP, Medical Director, Signal Evaluation & Risk Management
3. Ella Jaczynska, Vice President, RA
4. Jessica Lim, MA, Manager, Clinical Statistics
5. Sherene Min, MD, Physician Integrase Project Leader
6. W. Garrett Nichols, MD, MS, Project Leader, Vice President
7. Steve Piscitelli, PharmD, Director, Clinical Pharmacology
8. Mark Underwood, PhD, Lead Integrase Virologist

Shionogi & Co., Ltd:

9. Roger M. Echols, MD, Global Medical Lead
10. Kazunori Ohno, MPH, RPh, Global Project Manager

ViiV Healthcare:

11. Neil Shortman - Vice President, Head of Regulatory
12. James Goodrich, PhD, MD, Vice President, Global Medical Strategy

## BACKGROUND

Dolutegravir (DTG, GSK1349572) is an integrase strand transfer inhibitor (INSTI) being developed for the treatment of human immunodeficiency virus (HIV)-1 infection in adult and adolescent patients 12 years ( $\geq 40$ kg) of age and older. Dolutegravir is jointly owned by Shionogi & Co., Ltd and ViiV Healthcare, who are working with GlaxoSmithKline LLC (GSK) to develop the product.

IND 75382 was submitted to DAVP in October 2007, with several additional meetings since then with FDA to discuss the development plans for DTG. This pre-NDA meeting was requested by ViiV to discuss proposals for the content and format of the New Drug Application (NDA) for DTG and the results of the four Phase 3 studies:

1. ING113086 (SPRING-2), a Phase 3, randomized, double blind study of the safety and efficacy of GSK1349572 50 mg once daily to raltegravir 400 mg twice daily both administered with fixed-dose dual nucleoside reverse transcriptase inhibitor therapy over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects
2. ING114467 (SINGLE), a Phase 3, randomized, double-blind study of the safety and efficacy of GSK1349572 plus abacavir-lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1
3. ING111762 (SAILING), a Phase 3, randomized study of the safety and efficacy of GSK1349572 50 mg plus optimized background therapy (OBT) administered once daily compared to raltegravir plus OBT over 48 weeks in treatment experienced, INI-naïve adult subjects
4. ING112574 (VIKING-3), A Phase 3 study to demonstrate the antiviral activity and safety of dolutegravir in HIV-1- infected adult subjects with history of treatment failure on an integrase inhibitor

ViiV predicts to submit the initial NDA in December 2012, to include:

- A clinical Pharmacology package describing the pharmacokinetics and the pharmacokinetic/pharmacodynamic relationship of DTG across a broad range of studies in both healthy and HIV-infected subjects
- A Phase 2 package, which will include efficacy data as well as enabling dose-ranging data and longer-term efficacy and safety data in antiretroviral therapy-naïve and integrase inhibitor-resistant subjects
- A Phase 3 package designed to assess DTG across a broad range of treatment experience in HIV-infected patients and to support an unrestricted indication for the treatment of HIV-infected patients. The initial application for the term clinical safety data for approximately 1400 subjects receiving DTG at the recommended dose or higher for 24 weeks or longer

## DISCUSSION

ViiV's questions were submitted in a meeting briefing package on August 20, 2012 and DAVP sent to ViiV preliminary meeting comments (attached) on September 14, 2012. Only certain questions were discussed in the meeting and they are listed in **bold** and organized by discipline,

followed by DAVP's preliminary response, as conveyed in the September 14 letter, in *italics*. Meeting discussion immediately follows each question and response in regular font.

ViiV started the discussion with a presentation (attached) summarizing the efficacy and safety findings of DTG to date from the Phase 3 trials. ViiV's slide presentations are attached at the end of this document.

## CLINICAL

**20. For ViiV Healthcare (ViiV) sponsored studies, we propose to provide case report forms (CRFs) for patient deaths (& case narratives) and adverse events (AEs) leading to withdrawal (& case narratives for withdrawals for adverse events of special interest) in module 5 with the applicable clinical study reports. We would not provide case report forms for ongoing studies for which there are no available study reports. Exceptions are noted below:**

- **Phase 1 of the Expanded Access Program - ING115502 (investigator INDs, named patient programs outside the US), no case report forms are available [only serious adverse event (SAE) forms are available]**
- **Phase 2 of the Expanded Access Program - ING114916 (Expanded Access/Treatment Protocol) – CRF information is available for SAEs and discontinuations due to dolutegravir related AEs.**

**Does the Agency agree with this approach?**

*FDA response: Please clarify what you mean by “ongoing studies for which there are no available study reports”. We expect at least an interim study report for all the Phase 3 pivotal trials that will be submitted with the NDA. Thus for these studies, there should be CRFs and case narratives available.*

Discussion: ViiV clarified that a study report will be included for all the pivotal Phase 3 trials and the Phase 2 trials. DAVP agreed the proposed submission plan is acceptable.

**6. Two cases of hepatic enzyme elevation from ING113086 (SPRING-2) were reported as IND Safety Reports (INDSRs). However, the overall rates of liver enzyme elevations were comparable for DTG and RAL in ING113086, and were lower for DTG+ABC/3TC versus TDF/FTC/EFV in ING114467 (SINGLE). No additional cases of ALT elevations with concomitant bilirubin elevations, without an alternative explanation or cause (e.g., hepatitis B or C, concomitant medication), have been reported from ING113086. The Sponsor concludes that the risk for serious hepatotoxicity may be comparable to other marketed antiretrovirals and that routine safety monitoring in patients receiving DTG is adequate.**

**Does the Agency agree with this interpretation?**

*FDA Response: This is a review issue. The FDA is using an internal review tool (eDISH: Evaluation of Drug Induced Serious Hepatotoxicity) for the analysis and visualization of*

*clinical trial data for the assessment of potential drug-induced liver injury. This tool will assist clinical reviewers in safety analyses associated with the planned NDA submissions. In order to use this tool, we recommend that you provide datasets using the format specified in the attached eDISH-Data Requirements document. Please pay special attention to how clinical narratives should be organized and submitted. If you have any technical questions, please contact Ted Guo of Office of Biostatistics at ted.guo@fda.hhs.gov.*

Discussion: ViiV presented examples of eDISH plots and the datasets will be formatted as recommended.

- 8. In the ISS, the studies in integrase inhibitor naïve (INI-N) subjects [ING112276 (SPRING-1), ING113086 (SPRING-2), ING114467 (SINGLE) and ING111762 (SAILING)] will be considered separately to studies in INI-resistant (INI-R) subjects [ING112961 (VIKING) and ING112574 (VIKING-3)] due to the different doses of DTG being administered (i.e., DTG 50mg once daily versus DTG 50mg twice daily) and the different patient populations being studied. Outputs will be summarized by study and treatment arm. A total will be displayed for DTG once daily for the INI-N, antiretroviral (ART)-N population, and DTG twice daily for the INI-R population only.**
- All other ongoing studies will be considered separately [ING112578, ING114915 (FLAMINGO), ING116070, ING116529 (VIKING-4), ING115502 (investigator INDs, named patient programs outside the US) and ING114916 (expanded access/treatment protocol)]. Please find below potential mock-ups for the INI-N and INI-R summaries.

INI-N Subjects:

| ART-Naive Adults                                               |                                                |                                                                |                                                    |                                                              |                                             | ART-Exp Adults                                                       |                                                         |                                                |
|----------------------------------------------------------------|------------------------------------------------|----------------------------------------------------------------|----------------------------------------------------|--------------------------------------------------------------|---------------------------------------------|----------------------------------------------------------------------|---------------------------------------------------------|------------------------------------------------|
| ING112276<br>SPRING-1                                          |                                                | ING113086<br>SPRING-2                                          |                                                    | ING114467<br>SINGLE                                          |                                             | TOTAL<br>DTG<br>50 mg<br>Once<br>Daily +<br>2 NRTI<br>N=xxx<br>n (%) | ING111762<br>SAILING                                    |                                                |
| DTG<br>50 mg<br>once<br>daily +<br>2<br>NRTI<br>N=xxx<br>n (%) | EFV<br>600 mg<br>+ 2<br>NRTI<br>N=xxx<br>n (%) | DTG<br>50 mg<br>Once<br>Daily<br>+ 2<br>NRTI<br>N=xxx<br>n (%) | RAL<br>400 mg<br>BID +<br>2 NRTI<br>N=xxx<br>n (%) | DTG<br>50 mg +<br>ABC/3TC<br>Once<br>Daily<br>N=xxx<br>n (%) | EFV/TDF/FTC<br>Once Daily<br>N=xxx<br>n (%) |                                                                      | DTG<br>50 mg<br>Once<br>Daily<br>+ BR<br>N=xxx<br>n (%) | RAL<br>400 mg<br>BID +<br>BR<br>N=xxx<br>n (%) |

Note: subjects on 10mg and 25mg will also be included for ING112276 (SPRING-1).

INI-R Subjects:

| ING112961<br>VIKING                                    |                                                          | ING112574<br>VIKING-3                        | Total                                                 |
|--------------------------------------------------------|----------------------------------------------------------|----------------------------------------------|-------------------------------------------------------|
| Cohort I<br>DTG 50 mg once daily<br>plus OBR<br>(N=27) | Cohort II<br>DTG 50 mg twice daily<br>plus OBR<br>(N=24) | DTG 50 mg twice daily<br>plus OBR<br>(N=xxx) | DTG 50 mg<br>twice daily plus<br>OBR Daily<br>(N=xxx) |

**Does the Agency agree with this proposal?**

*FDA Response: We are in general agreement with your proposal. Please present the safety results for naïve subjects separately from the safety results from the treatment experienced population (i.e. INSTI naïve, receiving 50 mg QD). These subjects will likely be less healthy than the ARV naïve population.*

*Please clarify if you are planning to pool safety data from the phase 2b trial (SPRING-1) and the phase 3 trials ((SPRING-2, SINGLE).*

Discussion: ViiV stated they have combined all DTG doses from SPRING-1 (10, 25, 50mg) with the DTG 50mg data from SINGLE & SPRING-2. In addition to the pooled data just described for Phase 2b/3, they have also presented the safety data for these studies separately. DAVP accepted this proposal.

- 9. In addition to safety data described above, the ISS will contain a non-integrated description of SAEs, deaths and pregnancies from all studies for the time period May 2012 through October 26, 2012 (DSUR cut-off). Data will be pulled from the GlaxoSmithKline (GSK) Global Clinical Safety and Pharmacovigilance's (GCSP) Operating Company Event Accession and Notification System (OCEANS) safety database. These data will not have undergone a complete quality assurance check and will be considered preliminary.**

**Does the Agency agree with this proposal?**

*FDA Response: The safety information should contain summary table of events (SAEs, deaths, pregnancies). The SAEs should be summarized by SOC and PT. It is not necessary that the events from the various studies be integrated. If possible, include summary of subjects who withdrew study drug due to AEs.*

Discussion: ViiV stated the ISS will contain a summary table of events (SAEs, deaths and pregnancies) that occur between May and October 2012. They will provide listings of all AEs leading to withdrawal from May 2012 to approximately 4 weeks post NDA submission for the 2 month safety update. DAVP accepted this proposal.

**11. The following proposals apply to the ISE:**

- a. **No pooling of data from the Phase 2 pilot study in integrase inhibitor resistant (INI-R) subjects (ING112961) and the Phase 3 study in INI-R subjects (ING112574). The timing of the primary endpoint for these 2 studies was different: Day 11 was used for ING112961 and Day 8 was used for ING112574. In addition the number of subjects in ING112961 was relatively small compared to the number of subjects in ING112574; therefore, ING112574 would dominate the results if the data were pooled.**
  - **In addition, subjects in ING112574 could be eligible for the study with historical integrase resistance, where subjects had evidence for current raltegravir resistance as a requirement for entry in ING112961.**
  - **The analysis used for the primary endpoint differed in the 2 studies: Time to Loss of Virologic Response (TLOVR) was used for ING112961 and Snapshot was used for ING112574.**

- **A once daily (QD) regimen of dolutegravir (DTG) was used in Cohort I of ING112961; a twice daily (BID) regimen of DTG was used in Cohort II.**

**Does the Agency agree with this proposal?**

*FDA Response: We agree with your proposal to not pool the VIKING and VIKING-3 50 mg BID cohorts. However, resistance and safety data from these studies should be pooled.*

Discussion: ViiV stated the resistance data are presented as shown, (see slide #11 in attached slide set), which provides a summary of treatment-emergent IN genotypic resistance detected at PDVF for VIKING Cohort II and VIKING-3 from the ISE. DAVP agreed that ViiV may present the results as described from the separate studies in their study reports and ISE, but the PDVF and resistance emergence substitutions from these studies will most likely be pooled during DAVP’s analysis.

- b. The studies (ING112961 and ING112574) will be reported separately. Please find below a potential mockup for the proportion HIV-1 RNA <50 copies/mL (c/mL) table.**

| Visit    | ING112961 (VIKING)                                  | ING112574 (VIKING-3)                    |
|----------|-----------------------------------------------------|-----------------------------------------|
|          | TLOVR                                               | Snapshot                                |
|          | Cohort II<br>DTG 50 mg twice daily<br>N=24<br>n (%) | DTG 50 mg twice daily<br>N=xxx<br>n (%) |
| Baseline | xx (xx%)                                            | xx (xx%)                                |
| Week 4   | xx (xx%)                                            | xx (xx%)                                |
| Week 12  | xx (xx%)                                            | xx (xx%)                                |

**Does the Agency agree with this proposal?**

*FDA Response: Please present the Snapshot results for VIKING instead of TLOVR.*

Discussion: ViiV presented slides 12-15 to address the limitations of using the Snapshot algorithm for SPRING-1 and VIKING. Because of these limitations, ViiV proposed to analyze the data by MDF method (see slide for details). In summary, the MDF analysis was similar but not identical to the snapshot analysis method. ViiV’s main concern with implementation of the snapshot algorithm was that these two protocols were written and the studies were initiated prior to the wide usage of the snapshot analysis. With the snapshot analysis, the protocols allowed for background regimen switches due to toxicities which would be counted negatively. For these reasons, ViiV prefers to use TLOVR and MDF analysis. DAVP clarified ViiV did not have to conduct snapshot analysis for the Phase 2b trials (SPRING-1 and VIKING) as efficacy results from these trials will not be included in the labeling. DAVP also recognized the issues associated with switches in the background regimen and would likely conduct its own snapshot analysis (for review purposes) without penalizing for switches in background regimen, if done according to

protocol specification. For Phase 3 trials, ViiV confirmed Snapshot algorithm will be used.

**VIROLOGY**

**18. In the resistant datasets, for PRO/RT mutations, only major mutations will be included, as described by IAS-USA (see Table below). For integrase inhibitor (INI) mutations, only resistant mutations described in the table below will be included.**

|         |                                                                                                                                                                                                                                                                                                     |
|---------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| NRTIs*  | M41L, A62V, K65R, D67N, 69 insert, K70E/R, L74V, V75I, F77L, Y115F, F116Y, Q151M, M184V/I, L210W, T215Y/F, K219Q/E                                                                                                                                                                                  |
| NNRTIs* | L100I, K101E/P, K103N/S, V106A/M, V108I, E138/A/G/K/Q/R, V179L, Y181C/I/V, Y188C/L/H, G190S/A, H221Y, P225H, F227C, M230I/L,                                                                                                                                                                        |
| PIs*    | D30N, V32I, M46I/L, I47A/V, G48V, I50V/L, I54M/L, Q58E, T74P, L76V, V82A/T/F/L/S, N83D, I84V, N88S, L90M                                                                                                                                                                                            |
| INIs**  | H51Y, <b>T66A, T66I, T66K</b> , L68V, L68I, L74I, L74M, L74R, <b>E92Q, E92V</b> , Q95K, T97A, G118R, E138A, E138K, E138T, G140A, G140C, G140S, <b>Y143C, Y143H, Y143R</b> , P145S, S147G, <b>Q148H, Q148K, Q148R</b> , V151I, V151L, S153F, S153Y, <b>N155H</b> , E157Q, G163R, G163K, G193E, R263K |

\* IAS-USA website: [http://www.iasusa.org/resistance\\_mutations/index.html](http://www.iasusa.org/resistance_mutations/index.html) (2011)

\*\* may be modified in case of additional substantive data availability. INI substitutions listed above were defined from <http://hivdb6.stanford.edu> with a score of >45. All other mutations were detected during INI clinical investigation or during in vitro studies with DTG. The mutations bolded are referred to as ‘primary’ mutations, and those unbolded are referred to as ‘secondary’ mutations for this reporting and analysis.

**Does the Agency agree with the type of mutations to be included in the resistant dataset for submission?**

*FDA Response: No, we do not agree. All positions in the RT, IN and PR should be included in the datasets – not just major substitution sites.*

Discussion: ViiV stated they will provide datasets including all positions in the RT, IN and PR mutations as requested. DAVP also asked ViiV to include historical resistance data for subjects who did not have mutations documented at baseline. DAVP referred to the EOP2 meeting discussion when DAVP requested to create a column in the dataset for display of historical resistance information. ViiV proposed to have a follow-up discussion to discuss pre-specified definitions for specific substitutions and additional column headings (i.e., OSS, Historical INSTI substitutions and/or phenotype, INSTI baseline groups ([148+2, 148+1, no 148], TOTDTG, TOTRAL, etc) for inclusion in the resistance datasets. DAVP agreed.

**20. Based on data from ING112961 and ING112574, the Sponsor proposes to describe responses to DTG in labeling by baseline IN genotype for the INI-resistant patient population.**

**Does the Agency agree with this approach?**

*FDA Response: Yes, in general we agree, but reserve the right to modify this criterion depending on the review of the data. Please do analyses by individual baseline INSTI substitutions, specific combinations (most common) of INSTI substitutions, number of baseline INSTI substitutions, and baseline phenotype. Provide a justification for the analyses included in the label.*

Discussion: ViiV agreed to complete analyses by individual baseline INSTI substitutions, specific combinations (most common) of INSTI substitutions, number of baseline INSTI substitutions and baseline phenotype as requested. They also agreed to provide a justification in the NDA for the analyses included in labeling.

## CLINICAL PHARMACOLOGY/BIPHARMACEUTICS

### 32. Module 2.7.1 – Summary of Biopharmaceutic Studies and Associated Analytical Methods for dolutegravir in humans, there are no plans to provide a Biopharm Review Aid.

#### Is it acceptable to the Agency that a Biopharm Review Aid is not provided?

*FDA Response: It is not clear to the agency what specific contents would be included in a Biopharm Review Aid. Please clarify this issue.*

Discussion: ViiV stated that a Biopharm Review Aid was requested by some FDA review divisions but had not been requested by DAVP in the past. DAVP agreed that a Biopharm Review Aid is not required to be submitted as part of the NDA.

### 33. Module 2.7.1 – Summary of Biopharmaceutic Studies and Associated Analytical Methods for dolutegravir in humans.

- a. For Appendix Table 4 (exemplified below – not all studies included) – we propose to present the Bioanalytical Methods Summary in three columns:
  - i. a listing of all validation reports (hyperlinked to the individual report) supporting the submission starting with dolutegravir in plasma then for additional matrices and followed with additional analytes,
  - ii. a listing of studies supported by each validation report, and
  - iii. a brief description of the method and validation parameters for each report.
  
- b. For Appendix Table 5 (exemplified below) – Between-run Accuracy and Precision Quality Control Samples - we propose to present 5 columns that list:
  - i. all studies for which dolutegravir or other analytes were measured in support of this submission beginning with the biopharmaceutic studies,
  - ii. the total number of QC values for each concentration within a study,
  - iii. the overall study precision range,
  - iv. the overall study percent bias range, and
  - v. a listing of the document number for the individual bioanalytical results report, which could be hyperlinked, to provide the reader with the study specific bioanalytical results.

*FDA Response:*

*A) In addition to the information that is already displayed in Table 4, in order to ensure that all the method validation reports and bioanalytical reports have been submitted in the eCTD, Table 4 should also specifically state the title and report number of the validation report as displayed in 5.3.1.4. For methods that involve analysis of plasma samples, please also specify the anticoagulant that the method was validated in. Also, please provide a brief description for each method to aid the clinical pharmacology in identifying and tracking changes in either the method or in the bioanalytical laboratory conducting the analysis (e.g. this is the original method validated by XYZ laboratories, the method is a partial validation by JMZ laboratories of the original method validated*

*by XYZ laboratories). For method validations where no new stability experiments were conducted, please specifically provide the cross reference to the method validation(s) under which the relevant stability experiments were conducted and state whether the same analytical method was used.*

Discussion: ViiV stated they will add Title and anticoagulant to Column 1 of Table 4. To aid DAVP's review in tracking changes in either the method or bioanalytical laboratory, ViiV will also include the GSK site for internal validations and identify the original method. ViiV also clarified that all stability assessments are independently conducted except for whole blood stability.

DAVP stated the purpose of this request was to provide an overview of the history of the method. In response to a question, ViiV stated that each bioanalytical laboratory conducted their own stability experiments with the standards and the analytical method provided by ViiV.

*A table should also be provided that provides the location of the bioanalytical reports in the eCTD. An example of a table for the bioanalytical reports is provided below. Bioanalytical reports should be provided as standalone documents in the eCTD and should not be provided as attachments to the clinical trial reports. Submission of these materials in this manner will assist reviewers in locating and evaluating all the method validation reports and bioanalytical reports that are submitted with the NDA as part of the filing review and the NDA review.*

Discussion: ViiV will add an abbreviated title to the first column of Table 5 and provide the validation report number in a new column after the BAR number (example below). ViiV clarified that all bioanalytical reports will be submitted as stand alone reports and are also included in some clinical study reports within the eCTD.

| <b>Study (Analyte) and Title</b>             | <b>Total number of QC samples</b> | <b>Overall precision (%CV range)</b> | <b>Accuracy (%bias range)</b> | <b>Report Number</b> | <b>Validation report number</b>                              |
|----------------------------------------------|-----------------------------------|--------------------------------------|-------------------------------|----------------------|--------------------------------------------------------------|
| ING111322 (DTG) Repeat dose escalation study | (n=60 at each of 3 levels)        | 4.2% to 7.0%                         | -1.8% to -0.8%                | 2011N126878_00       | RD2007/01425/00<br><br>Supplemental Report<br>2011N112541_00 |

**Example of a table for bioanalytical reports**

| Analyte                                                                                                                                                            | Bioanalytical Report Number                                        | Clinical Trial Number | Method Validation Report Number | Biological Matrix | Anticoagulant (if applicable) | Description of clinical trial                     |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------|-----------------------|---------------------------------|-------------------|-------------------------------|---------------------------------------------------|
| XZY                                                                                                                                                                | <b>IHD001BR-01 (located in 5.3.1.4.1 for the XYZ001-100 trial)</b> | XYZ001-100            | <b>XYZ001MVR-01</b>             | Plasma            | Sodium Heparin                | Single dosing trial using a isohydraline solution |
| Bold text: A hyperlink should be provided to the location of the method validation report or amendments (e.g., Module 5.3.1.4) or the bioanalytical study reports. |                                                                    |                       |                                 |                   |                               |                                                   |

*Complete method validation reports and bioanalytical reports should be submitted for dolutegravir as well as for any analytes that were analyzed in drug-drug interaction trials. At the time of NDA submission, the required stability data, including long term stability data, for dolutegravir as well as for any analytes that were analyzed in drug-drug interaction trials should also be submitted that cover the necessary duration of stability (see B below). If the required stability data, including long term stability data, are not available at the time of NDA submission, the pharmacokinetic data will not be included in the proposed dolutegravir U.S prescribing information.*

Discussion: DAVP agreed on ViiV’s plan to submit the long-term stability data for telaprevir (as part of the telaprevir/dolutegravir DDI trial) within 30 days post-NDA submission. ViiV will confirm the submission timeline. For the boceprevir-dolutegravir drug-drug interaction trial, ViiV was having difficulty obtaining standards for the M+2 boceprevir metabolites; therefore, the boceprevir data will not be in the NDA submission. DAVP stated it was acceptable to submit the dolutegravir PK data only in the NDA submission (b) (4)

- B) Lastly, the clinical pharmacology team requests a more comprehensive summary of bioanalytical information for each bioanalytical report as listed below. This information should be provided as a MS Word document.
1. Please provide a summary of the relevant method validation and bioanalysis items listed (a-w) below.
    - a. Bioanalysis summary for trial (list trial number).
    - b. Title of corresponding method validation report(s) and relevant report number(s).
    - c. Title of corresponding bioanalytical report and relevant report number(s).
    - d. Analyte(s).
    - e. Biological matrix (e.g. plasma, urine)
    - f. Methodology/Platform.
    - g. Duration (Month/Date/Year) from time sample was first drawn to date of last sample analysis (including ISR) for the trial.

- h. For plasma samples, anticoagulant used for:
  - i. Method validation.*
  - ii. Collecting blood samples in the trial.**
- i. Temperature subject samples were stored at the trial site.*
- j. Temperature subject samples were stored at satellite facility (if applicable).*
- k. Temperature subject samples were stored at the bioanalytical laboratory.*
- l. Temperature(s) freeze/thaw stability experiments were conducted (see footnote 1 below).*
- m. Number of validated freeze/thaw cycles for the analyte(s).
  - i. specify the duration (e.g. number of hours) of freezing and thawing for each cycle**
- n. Hyperlink to freeze thaw stability data for the analyte(s) [or attach the data].*
- o. Temperature(s) long term stability experiments were conducted (see footnote 1 below).*
- p. Duration of validated long term stability for the analyte(s).*
- q. Hyperlink to long term stability data for the analyte(s) [or attach the data].*
- r. Total number of analytical runs.*
- s. Number of analytical runs passed.*
- t. Number of analytical runs that failed.
  - i. Please include reasons for the run failure and corrective actions taken, if any**
- u. In analyzing subject samples, were all reference standards and stock solutions for the analyte(s) and internal standard and the calibration curve standards and QC samples for the analyte(s) prepared and used prior to the expiration date(s) or within the established stability period?
  - i. List the expiration dates for each reference standard-if more than one lot of a reference standard was used, please specify which lots were used for specific analytical runs for the respective trial.*
  - ii. If runs were analyzed using expired reference standard, please provide the specific date the stock solutions were prepared and the date the stock solutions were used to prepare the calibration curve standards and QC samples used for the runs. Please also provide the following information: a) provide a hyperlink to the stock solution stability data for the analyte(s) [or attach the data] and b) specify the storage temperatures for the stock solutions, calibration curve standards and QC samples.**
- v. ISR (if performed):
  - i. Percentage of samples reanalyzed (out of the total number of subject samples)*
  - ii. Did 2/3 of the ISR samples meet the acceptance criteria?**
- w. Relevant comments, if any (including issues in shipping samples)*

<sup>1</sup> if the temperatures that the freeze thaw stability and long term stability experiments were conducted do not match the storage temperature(s) throughout the life cycle of

*the samples, please provide a rationale to support the acceptability of the reported concentration data in plasma or other biological matrix.*

Discussion: ViiV stated that providing the requested summary of bioanalytical data in a MS word document would require a significant amount of work. DAVP stated that the requested summary of bioanalytical data was still preferred but was open to alternatives regarding how this information could be provided. One alternative would be to provide hyperlinks to the exact location each listed item could be found. DAVP added that it was important to have information linking the generated stability data to the actual storage conditions for subject samples (e.g. at the trial site or bioanalytical laboratory). ViiV stated that they would be more amenable to providing hyperlinks and would provide a follow-up response with additional details. DAVP also clarified it was not necessary to have a per site breakdown of information regarding the duration from the time a sample was first drawn to the date of last sample analysis for the Phase 2 and 3 trials.

#### ADDITIONAL CLINICAL PHARMACOLOGY COMMENTS (from sponsor questions set)

- 2. For in vitro studies evaluating the cytochrome P450 enzyme induction effects of dolutegravir by determining the change in mRNA level, please provide R3 values for each cytochrome P450 enzyme that was studied or provide the predefined threshold for the increase in mRNA consistent with the recommendations in the February 2012 draft guidance on drug interaction studies.**

Discussion: ViiV stated that for the in vitro enzyme induction assessment, the relative mRNA expression (treated vs control) was compared to the response from a prototypical inducer. The relative response following treatment with dolutegravir was <15% of the prototypical inducer response for each gene (8, 14, and 13% for CYP1A2, CYP2B6, and CYP3A4, respectively). The pre-established threshold for induction was 40% of the positive control value consistent with the September 2006 draft guidance on drug interaction studies as this study was conducted in 2007. Fold increases for all positive controls were consistent with literature values.

The induction potential also was investigated in vivo using midazolam as a sensitive probe substrate. No inductive effects on midazolam metabolism were observed when dolutegravir was dosed for 10 days (beyond steady-state).

DAVP responded that the drug-drug interaction guidance was in transition but if a threshold was used, the threshold should be justified. Additionally, DAVP would further review the in vitro enzyme induction data.

#### STATISTICS

- 36. We plan to submit SAS datasets and SAS programs to the Agency as outlined in the March 8, 2011 DAVP response to January 26, 2011 Company questions. We plan to submit SAS datasets and SAS programs for the ISS and for the following studies:**

- **Pivotal Phase 2b studies:**
  - **ING112961(VIKING) 96 week dataset for Cohort I and 48 week dataset for Cohort II (TLOVR endpoint) (includes the primary efficacy endpoint for Cohort I Weeks 24, 72, and 96 and Cohort II Weeks 24 and 48)**
  - **ING112276 (SPRING-1) 96 week dataset (TLOVR endpoint) (includes the primary efficacy endpoint for Weeks 16, 24, 48, and 96)**
  - **ING112578 IMPAACT/P1093) 24 week dataset for Cohort I, Stage 1 (Snapshot endpoint).**
- **Pivotal Phase 3 studies (Snapshot endpoint for all):**
  - **ING113086 (SPRING-2) 48 week dataset**
  - **ING114467 (SINGLE) 48 week dataset**
  - **ING112574 (VIKING-3) 24 week dataset [includes the primary efficacy endpoint for Day 8 and Week 24]**
  - **ING111762 (SAILING) 24 week dataset.**

**Is this acceptable to the Agency?**

*FDA Response: We would prefer that the snapshot endpoint be computed for all studies, regardless of what the initial protocol specified. Otherwise this is acceptable.*

Discussion: ViiV stated that the SAS programs provided will be non-executable and the SAS datasets provided will be legacy Analysis & Reporting (A&R) datasets, not in CDISC (SDTM or ADAM) format. ViiV stated a sample of nonexecutable SAS programs will be provided for the primary endpoints for the Phase 3 studies so that the review team could assess if they are acceptable. If not acceptable, then executable SAS files will need to be provided for the primary endpoints of the Phase 3 studies. \*

ViiV confirmed that the legacy dataset proposed will be the complete direct translations from the CRFs. ViiV also requested and DAVP agreed to provide updated efficacy dataset specifications.

DAVP also asked to include efficacy specifications for datasets as previously communicated to ViiV. ViiV did not recall receiving such communication was. DAVP stated that the specifications can be provided to ViiV soon after this meeting.

\*Post meeting comment: The statistics review team added that SAS programs are not needed at all.

**37. We do not intend to submit SAS datasets and SAS programs to the Agency for clinical pharmacology studies. We will submit SAS datasets and programs for the population pharmacokinetic analyses (POP PK).**

**Is this acceptable to the Agency?**

*FDA Response: No, SAS datasets and SAS programs for the clinical pharmacology studies should be submitted as part of the New Drug Application. These datasets will enable the agency to independently analyze the pharmacokinetic data from the clinical pharmacology trials.*

ViiV stated they will submit SAS datasets and SAS programs (nonexecutable) for all clinical pharmacology studies as requested. SAS datasets will be legacy A&R datasets, not CDISC datasets. DAVP agreed with the proposal.

**Appendix Table 4 Bioanalytical Methods Summary**

| Validation Report                                                                                                                                                                                                                                              | Clinical Studies Supported                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Method Description and Performance                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p><b>Dolutegravir Human Plasma</b><br/>                     RD2007/01425/0<br/>                     Issued: 15 Jan 2008<br/>                     Supplemental Report<br/>                     2011N112541_00<br/>                     Issued: 07 Feb 2011</p> | <p>ING111207<br/>                     ING111322<br/>                     ING111405<br/>                     ING111521<br/>                     ING111602<br/>                     ING111603<br/>                     ING111604<br/>                     ING111853<br/>                     ING111854<br/>                     ING111856<br/>                     ING112276<br/>                     ING112934<br/>                     ING112941<br/>                     ING112961</p> | <p>Dolutegravir is extracted from 25 µL human plasma by protein precipitation using acetonitrile containing [<sup>2</sup>H<sub>7</sub><sup>15</sup>N]-dolutegravir as an internal standard. Extracts are analyzed by HPLC-MS/MS using a Turbo IonSpray interface and multiple reaction monitoring.<br/>                     Lower limit of quantification (LLQ): 5 ng/mL<br/>                     Validated Range: 5 to 5000 ng/mL<br/>                     QC levels: 5, 20, 400, 4000 and 5000 ng/mL<br/>                     Within-run Precision (%CV): ≤ 14.4%<br/>                     Between-run Precision (%CV): ≤ 3.8%<br/>                     Accuracy (% Bias): -8.4 ≤ bias ≤ -0.7%<br/>                     Stability in Human Plasma: 3 freeze-thaw cycles from -30°C at least 16 months at -30°C at least 24 hours at ambient temperature<br/>                     Processed Extract Stability: At least 3 days at ambient temperature</p>     |
| <p><b>Dolutegravir Human Plasma</b><br/>                     RD2010/00175/0<br/>                     Issued: 27 Oct 2010<br/>                     Supplemental Report<br/>                     2011N112542_00<br/>                     Issued: 07 Feb 2011</p> | <p>ING113068<br/>                     ING113096<br/>                     ING113097<br/>                     ING113125<br/>                     ING113674<br/>                     ING114005<br/>                     ING114819<br/>                     ING116070</p>                                                                                                                                                                                                                   | <p>Dolutegravir is extracted from 25 µL human plasma by protein precipitation using acetonitrile containing [<sup>2</sup>H<sub>7</sub><sup>15</sup>N]-dolutegravir as an internal standard. Extracts are analyzed by HPLC-MS/MS using a Turbo IonSpray interface and multiple reaction monitoring.<br/>                     Lower limit of quantification (LLQ): 20 ng/mL<br/>                     Validated Range: 20 to 20000 ng/mL<br/>                     QC levels: 20, 60, 1600, 16000 and 20000 ng/mL<br/>                     Within-run Precision (%CV): ≤ 4.5%<br/>                     Between-run Precision (%CV): ≤ 2.7%<br/>                     Accuracy (% Bias): -0.3 ≤ bias ≤ 9.6%<br/>                     Stability in Human Plasma: 3 freeze-thaw cycles from -20°C at least 265 days at -20°C at least 24 hours at ambient temperature<br/>                     Processed Extract Stability: At least 3 days at ambient temperature</p> |

**Appendix Table 5 Between-run Accuracy and Precision of Quality Control (QC) Samples**

| Study (Analyte) | Total number of QC samples                                        | Overall precision (%CV range) | Accuracy (%bias range) | Report Number   |
|-----------------|-------------------------------------------------------------------|-------------------------------|------------------------|-----------------|
| ING111322 (DTG) | (n=60 at each of 3 levels)                                        | 4.2% to 7.0%                  | -1.8% to -0.8%         | 2011N126878_00  |
| ING113068 (DTG) | (n=26 at each of 3 levels)                                        | 3.0% to 5.3%                  | 5.3% to 6.9%           | 2011N112681_00  |
| ING113674 (DTG) | (n=44 at each of 3 levels)                                        | 3.5% to 4.4%                  | 0.2% to 3.9%           | RD2010/00558/00 |
| ING112941 (DTG) | (n=24 at each of 3 levels)                                        | 2.6% to 4.0%                  | -4.7% to 1.0%          | RD2009/01353/00 |
| ING111207 (DTG) | (n=44 at each of 3 levels)                                        | 3.0% to 6.7%                  | -3.5% to 0.0%          | 2011N126877_00  |
| ING111405 (DTG) | (n=22 at each of 3 levels)                                        | 2.5% to 4.3%                  | -1.1% to 5.2%          | RD2009/00885/00 |
| ING111521 (DTG) | (n=36 at each of 3 levels)                                        | 2.3% to 3.7%                  | -0.9% to 1.1%          | 2011N126879_00  |
| ING111602 (DTG) | (n=32 at 20 and 400 ng/mL, and n=31 at 4000 ng/mL)                | 3.5% to 5.4%                  | -2.5% to -1.7%         | 2011N126880_00  |
| ING111603 (DTG) | (n=12 at each of 3 levels)                                        | 1.7% to 4.0%                  | 0.5% to 4.0%           | 2011N126881_00  |
| ING111604 (DTG) | (n=12 at each of 3 levels)                                        | 2.0% to 4.1%                  | -1.5% to 1.8%          | 2011N126882_00  |
| ING111762 (DTG) | on going                                                          |                               |                        | 2011N117340_00  |
| ING111853 (DTG) | (n=4 at each of 3 levels)                                         | 2.0% to 5.1%                  | 10.3% to 17.1%         | RD2009/00551/00 |
| ING111854 (DTG) | (n=20 at each of 3 levels)                                        | 3.1% to 7.1%                  | -8.2% to -3.5%         | RD2009/00809/00 |
| ING111855 (DTG) | on going                                                          |                               |                        |                 |
| ING111856 (DTG) | (n=34 at each of 3 levels)                                        | 2.5% to 3.2%                  | -6.4% to 4.2%          | RD2010/00015/00 |
| ING112276 (DTG) | (n=46 at 20, 400, and 4000 ng/mL, n=12 at 6000 ng/mL Dilution QC) | 3.3% to 4.5%                  | -7.5% to -0.1%         | RD2010/00559/00 |

## DATASETS:

### Additional Comments:

4. General comment regarding xpt datasets

For all datasets, in order to significantly reduce dataset file sizes, the allotted character column length/size for each column should be the maximum length used. Lengths/sizes of columns should not arbitrarily be set to 200. For example, if USUBJID has a maximum length of 18, the USUBJID's column size should be set to 18, not 200. An inclusion of a small amount of padding to column width may be acceptable as long as this doesn't result in significant increases in file size.

*We agree with your request for the Phase 2 and 3 studies. Given the large number of Phase 1 studies and given that they are relatively small compared to later phase studies, we propose to not reduce column lengths for the Phase 1 studies.*

Discussion: DAVP accepted this proposal.

6. Content/format of NDA submission modules and TOC:

Module 2.7.3. should contain the summary text and M5.3.5.3 should contain all datasets, appendices of supporting tables and figures, etc.,

*Please refer to the Final Guidance for Industry: Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document (PDF - 98KB), located at:- <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf>*

Discussion: ViiV will follow the content and format as requested. DAVP also stated submission of a 'mock' dataset for the clinical safety and efficacy data would be helpful so that feedback could be provided, if needed, prior to the NDA submission. ViiV mentioned the datasets from the Phase 2b trial (SPRING-1) is already available and these can be provided instead of 'mock' datasets. DAVP agreed.

## ADDITIONAL COMPANY QUESTIONS

1. **PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2013 THROUGH 2017 PDF describes the following:**

- **2.a. All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.**

Discussion: DAVP clarified the list only pertains to pivotal phase 3 trials and the preferred location would be provided to ViiV at a later time. DAVP requested to include the all of the contact information for the sites.

2. **In order to plan and complete necessary submission activities, a rationale for submitting the NDA** (b) (4)

(b) (4) with 9 months drug product (DP) stability data was informally provided on September 17th via email. We would like to receive feedback from the review team regarding our proposal. 12 months DP stability data would be available no earlier than June 2013 and could be provided if the review team was in agreement.

Discussion: DAVP would respond to this question in writing.

### **DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION**

As stated in our June 05, 2012 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic and the date of submission is on or after October 1, 2012, the application will be subject to "The Program" under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission. Discussions and agreements on the content of a complete application will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities. Information on PDUFA V and "The Program" is available at <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>.

### **DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION**

- The content of a complete application was discussed to include:
  - A clinical Pharmacology package describing the pharmacokinetics and the pharmacokinetic/pharmacodynamic relationship of DTG across a broad range of studies in both healthy and HIV-infected subjects,
  - A Phase 2 package, which will include efficacy data as well as enabling dose-ranging data and longer-term efficacy and safety data in antiretroviral therapy-naïve and integrase inhibitor-resistant subjects
  - A Phase 3 package designed to assess DTG across a broad range of treatment experience in HIV-infected patients and to support an unrestricted indication for the treatment of HIV-infected patients. The initial application for the term clinical safety data for approximately 1400 subjects receiving DTG at the recommended dose or higher for 24 weeks or longer.

All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

A preliminary discussion on the need for a REMS was held and it was concluded that based on preliminary review, REMS is unlikely to be required. However, final determination will be made once the NDA has been reviewed.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. We agreed that the following minor application components may be submitted within 30 calendar days after the submission of the original application:
  - Long term stability data for telaprevir (TVR) (ING115697)
- Prominently identify each submission containing your late component(s) with the following wording in bold capital letters at the top of the first page of the submission:

**NDA NUMBER: LATE COMPONENT - QUALITY**

#### **PREA PEDIATRIC STUDY PLAN**

The Food and Drug Administration Safety and Innovation Act of 2012 changes the timeline for submission of a PREA Pediatric Study Plan and includes a timeline for the implementation of these changes. You should review this law and assess if your application will be affected by these changes. If you have any questions, please email the Pediatric Team at [Pedsdrugs@fda.hhs.gov](mailto:Pedsdrugs@fda.hhs.gov).

#### **PRESCRIBING INFORMATION**

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

#### **ISSUES REQUIRING FURTHER DISCUSSION/ACTION ITEMS:**

1. Virology: A follow up teleconference to discuss DAVP's requested VIKING 3 historical resistance data inclusion in the dataset as a column.
2. Clinical Pharmacology: ViiV will provide a proposal regarding the requested bioanalytical data & methods along with hyperlinking details.

3. CMC: DAVP will respond in writing regarding the submission of 9 months vs. 12 months drug product stability data for the  <sup>(b) (4)</sup> NDA.
4. Statistics:
  - ViiV will provide a sample of their nonexecutable SAS programs for the primary endpoints for the Phase 3 studies for the FDA review team to whether these are acceptable. If not acceptable, then executable SAS files will need to be provided for the primary endpoints of the Phase 3 studies.
  - DAVP will provide efficacy specifications for datasets to ViiV.
  - DAVP requested “mock” data sets for safety and efficacy data from the Phase 2 studies. ViiV will instead submit the case report tabulation (CRT) packages which include SAS datasets with both safety and efficacy data for the Phase 2 studies
5. Need for Advisory Committee: DAVP will notify ViiV of the final decision.
6. DAVP will provide ViiV the desired location of the clinical site list in the NDA submission.

#### **ATTACHMENTS AND HANDOUTS**

The preliminary meeting comments sent to the sponsor is attached along with ViiV’s slide set from the meeting.

**Tivicay® (dolutegravir)  
Pre-NDA Meeting**

**NDA 204,790**

**September 20, 2012**



**SHIONOGI**



**Shionogi - ViiV Healthcare LLC**

# Agenda

- **Introduction of Participants – 5 minutes**
- **Key Results of Phase 3 Studies – 25 minutes**
  - **ING113086 (SPRING-2)**
  - **ING114467 (SINGLE)**
  - **ING112574 (VIKING-3)**
- **Discussion of Questions for the Agency – 50 minutes**
- **Summary of Meeting Conclusions and Action Items – 10 minutes**

# Sponsor Meeting Attendees

## GlaxoSmithKline LLC

- Martha Anne Auld, R.Ph. – Senior Director, Regulatory Affairs (RA)
- Lloyd D. Curtis, MA MRCP - Medical Director, Signal Evaluation & Risk Management
- Ella Jaczynska - Vice President, RA
- Jessica Lim, M.A. - Manager, Clinical Statistics
- Sherene Min, M.D., M.P.H. - Physician Integrase Project Leader
- W. Garrett Nichols, M.D., M.S. - Project Leader, Vice President
- Steve Piscitelli, Pharm.D. - Director, Clinical Pharmacology
- Mark Underwood, Ph.D. - Lead Integrase Virologist

## Shionogi & Co., Ltd

- Roger M. Echols, M.D. – Global Medical Lead
- Kazunori Ohno, M.P.H., R.Ph. - Global Project Manager

## ViiV Healthcare

- James Goodrich, Ph.D., M.D. - Vice President, Global Medical Strategy
- Neil Shortman - Vice President, Head of Regulatory



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Shionogi - ViiV Healthcare LLC



# Tivicay Proposed Indication and Dosing

- **Proposed Indication:**

The treatment of HIV-1 infection, used in combination with other approved antiretroviral agents, in treatment-naïve and treatment-experienced adults, and treatment-experienced children aged 12 years ( $\geq 40$  kg) and older.

- **Proposed Dosing Regimen:**

| Patient Population                                                      | Proposed DTG Dose  |
|-------------------------------------------------------------------------|--------------------|
| ART-naïve adults                                                        | 50 mg, once daily  |
| ART-experienced, INI-naïve adults                                       | 50 mg, once daily  |
| ART-experienced, INI-naïve children ( $\geq 12$ years and $\geq 40$ kg) | 50 mg, once daily  |
| ART-experienced (with INI resistance) adults                            | 50 mg, twice daily |



# Clinical Program

## Key Results of Phase 3 Studies

SPRING-2 (ING113086)

SINGLE (ING114467)

VIKING-3 (ING112574)

Sherene Min, MD, MPH

Lloyd Curtis, MA MRCP



**SHIONOGI**



Shionogi - ViiV Healthcare LLC

# Dolutegravir (DTG, 572)

## Phase 3 studies

### Patient population

Treatment naive  
(SPRING-2, ING113086)

Treatment naive  
ABC/3TC FDC enabling study  
(SINGLE, ING114467)

Treatment experienced,  
INI-naive  
(SAILING, ING111762)  
Data available 01Oct2012

Treatment experienced, INI-  
resistant  
(VIKING-3, ING112574)

### Study design

Phase 3 trial:  
ART-naive pts (n=822)  
–DTG vs. **RAL** (+ NRTIs of choice)  
–Non-inferiority design (10% margin)

Phase 3 trial:  
ART-naive pts (n=833)  
– DTG + ABC/3TC vs. **Atripla**  
– Non-inferiority design (10% margin)

Phase 3 trial:  
ART-experienced, INI-naive pts (n=719)  
–DTG vs. **RAL** (+ OBT)  
–Non-inferiority design (12% margin)

Phase 3 trial:  
INI-resistant pts (n=183; 114 with 24wk data)  
–Single cohort, DTG functional mono-rx (7d)  
followed by DTG + OBT



SPRING<sup>2</sup>



SINGLE



SAILING



VIKING-3

**DTG Clinical Efficacy and Virology  
in Treatment Naïve Patients:  
SPRING-2 (ING113086) and SINGLE  
(ING114467)**

Sherene Min, MD, MPH



**SHIONOGI**

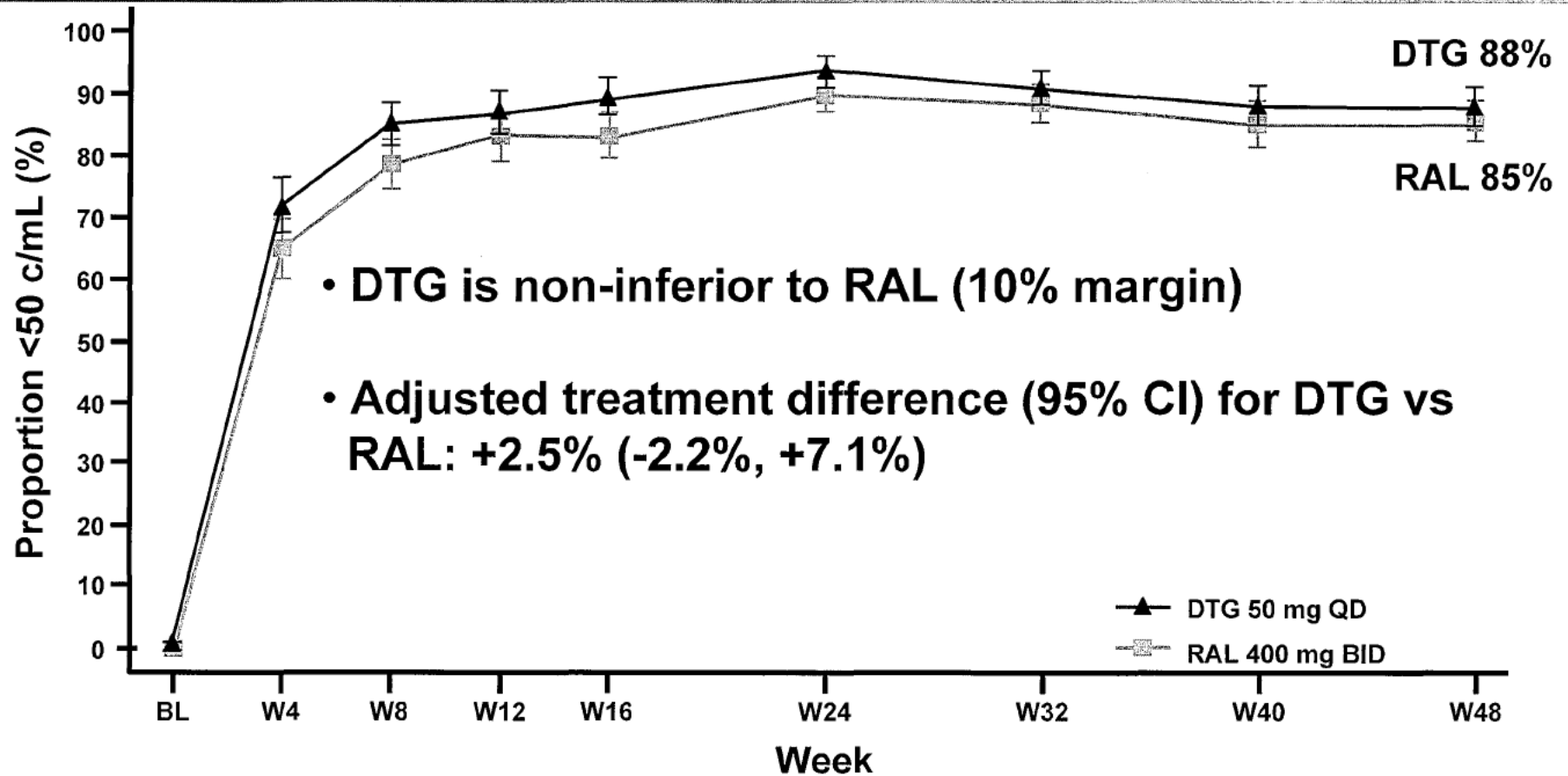


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# SPRING-2 Primary Analysis: Proportion <50 c/mL by FDA Snapshot



SPR 2



Median (IQR) Change From Baseline CD4<sup>+</sup> Cell Count (cells/mm<sup>3</sup>)

|                       | W4           | W24            | W48            |
|-----------------------|--------------|----------------|----------------|
| <b>DTG 50 mg QD</b>   | 87 (26, 149) | 183 (100, 295) | 230 (128, 338) |
| <b>RAL 400 mg BID</b> | 88 (32, 163) | 182 (94, 296)  | 230 (139, 354) |



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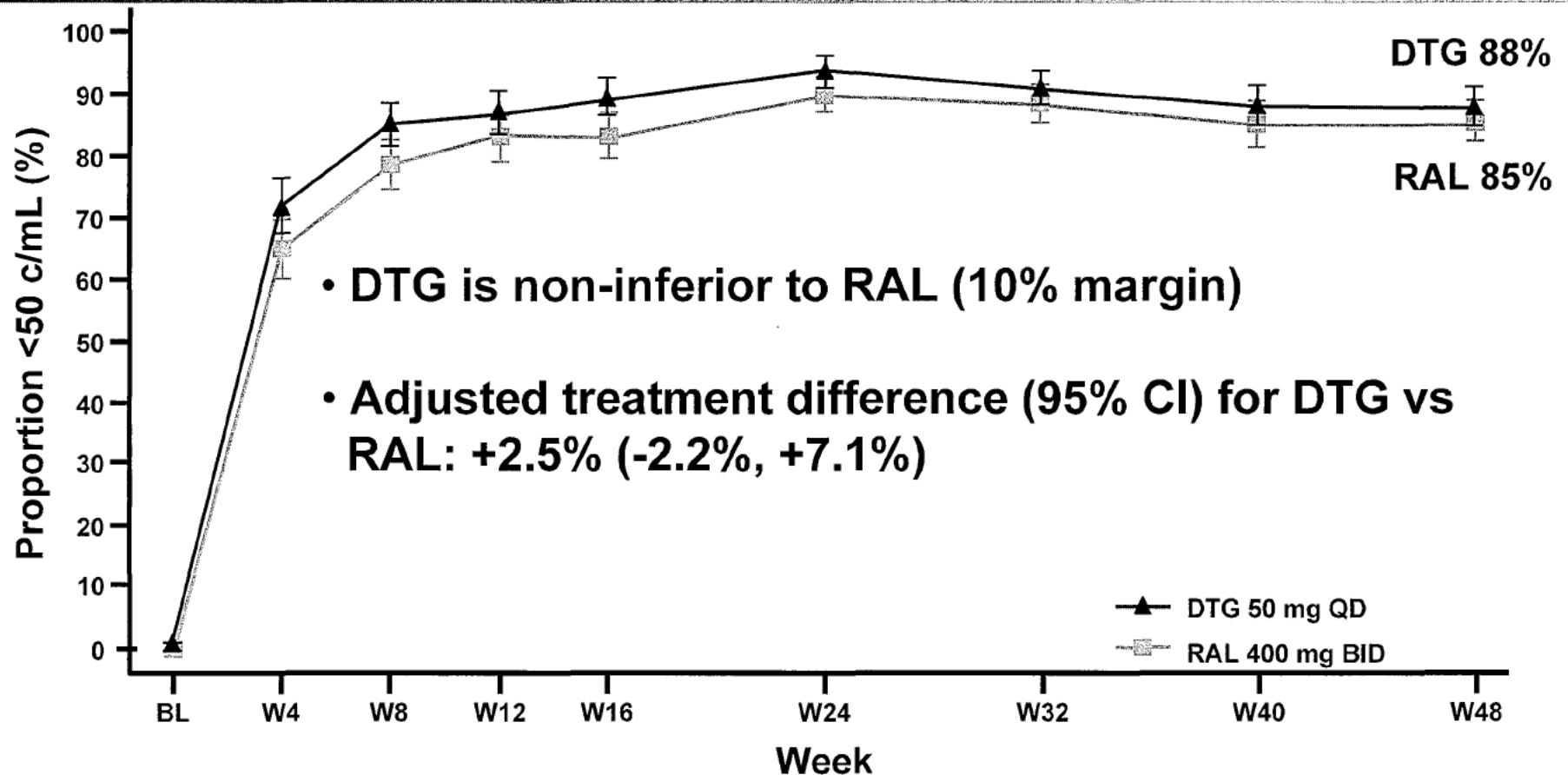
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# SPRING-2 Primary Analysis: Proportion <50 c/mL by FDA Snapshot



SPR 2



Median (IQR) Change From Baseline CD4<sup>+</sup> Cell Count (cells/mm<sup>3</sup>)

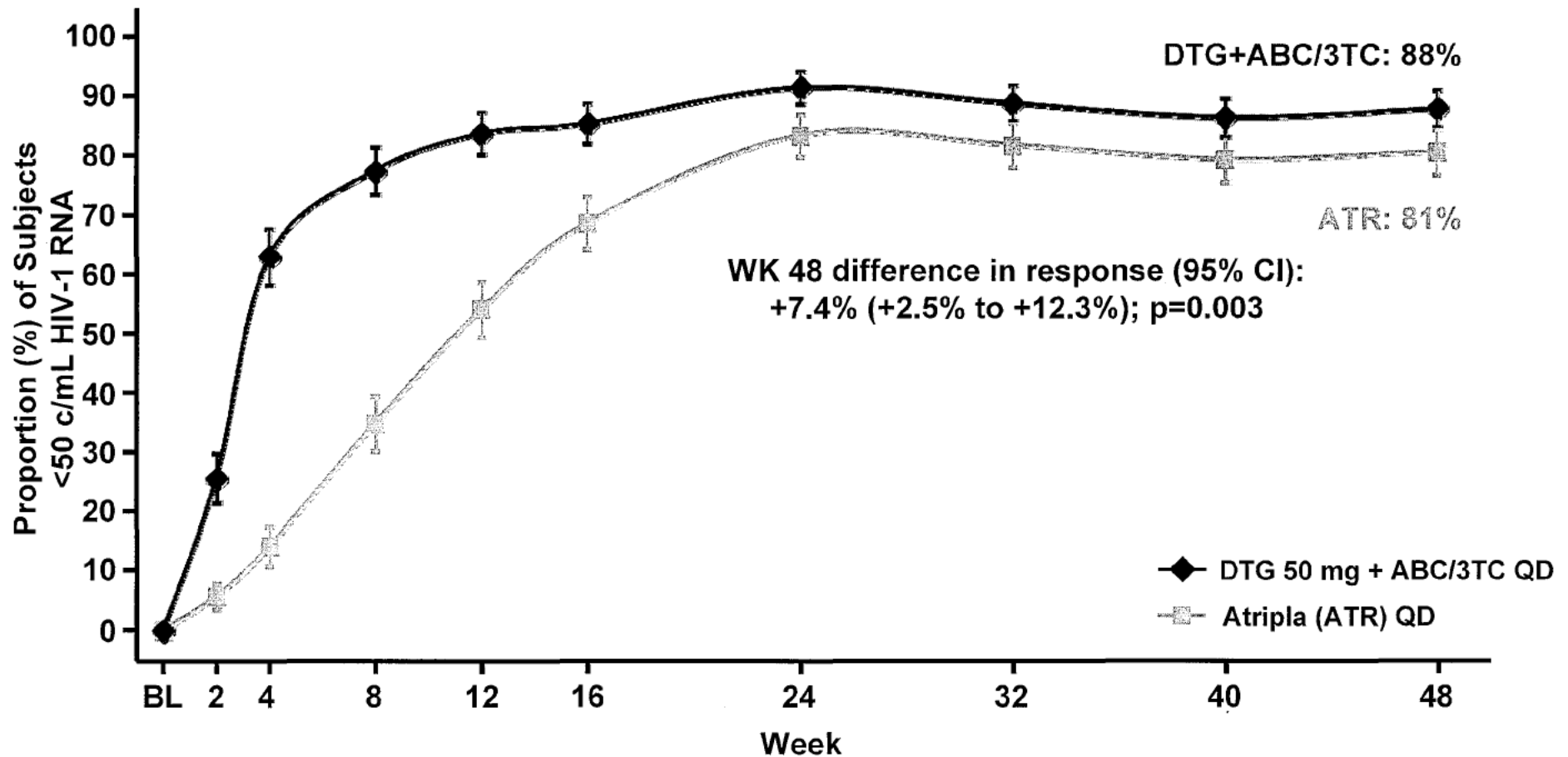
|                       | W4           | W24            | W48            |
|-----------------------|--------------|----------------|----------------|
| <b>DTG 50 mg QD</b>   | 87 (26, 149) | 183 (100, 295) | 230 (128, 338) |
| <b>RAL 400 mg BID</b> | 88 (32, 163) | 182 (94, 296)  | 230 (139, 354) |

# Proportion <50 c/mL: Snapshot Outcomes

| Outcome (snapshot) at Week 48                    | DTG 50 mg QD<br>n=411<br>n (%) | RAL 400 mg BID<br>n=411<br>n (%) |
|--------------------------------------------------|--------------------------------|----------------------------------|
| <b>Virologic success</b>                         | <b>361 (88)</b>                | <b>351 (85)</b>                  |
| <b>Virologic nonresponse</b>                     | <b>20 (5)</b>                  | <b>31 (8)</b>                    |
| Data in window not <50 c/mL                      | 8 (2)                          | 5 (1)                            |
| Discontinued for lack of efficacy                | 5 (1)                          | 13 (3)                           |
| Discontinued for other reason while not <50 c/mL | 2 (<1)                         | 11 (3)                           |
| Change in ART                                    | 5 (1)                          | 2 (<1)                           |
| <b>No virologic data at Week 48</b>              | <b>30 (7)</b>                  | <b>29 (7)</b>                    |
| Discontinued because of AE or death              | 9 (2)                          | 6 (1)                            |
| Discontinued for other reasons                   | 21 (5)                         | 23 (6)                           |



# Proportion (95% CI) of Subjects <50 c/mL (FDA Snapshot)



- DTG 50mg +ABC/3TC QD was statistically superior to Atripla at Week 48 (primary endpoint)
- Subjects receiving DTG +ABC/3TC achieved virologic suppression faster than Atripla, median time to HIV-1 RNA <50c/mL of 28 days (DTG +ABC/3TC) vs 84 days (Atripla), P<0.0001

# Proportion <50 c/mL: Snapshot Outcomes



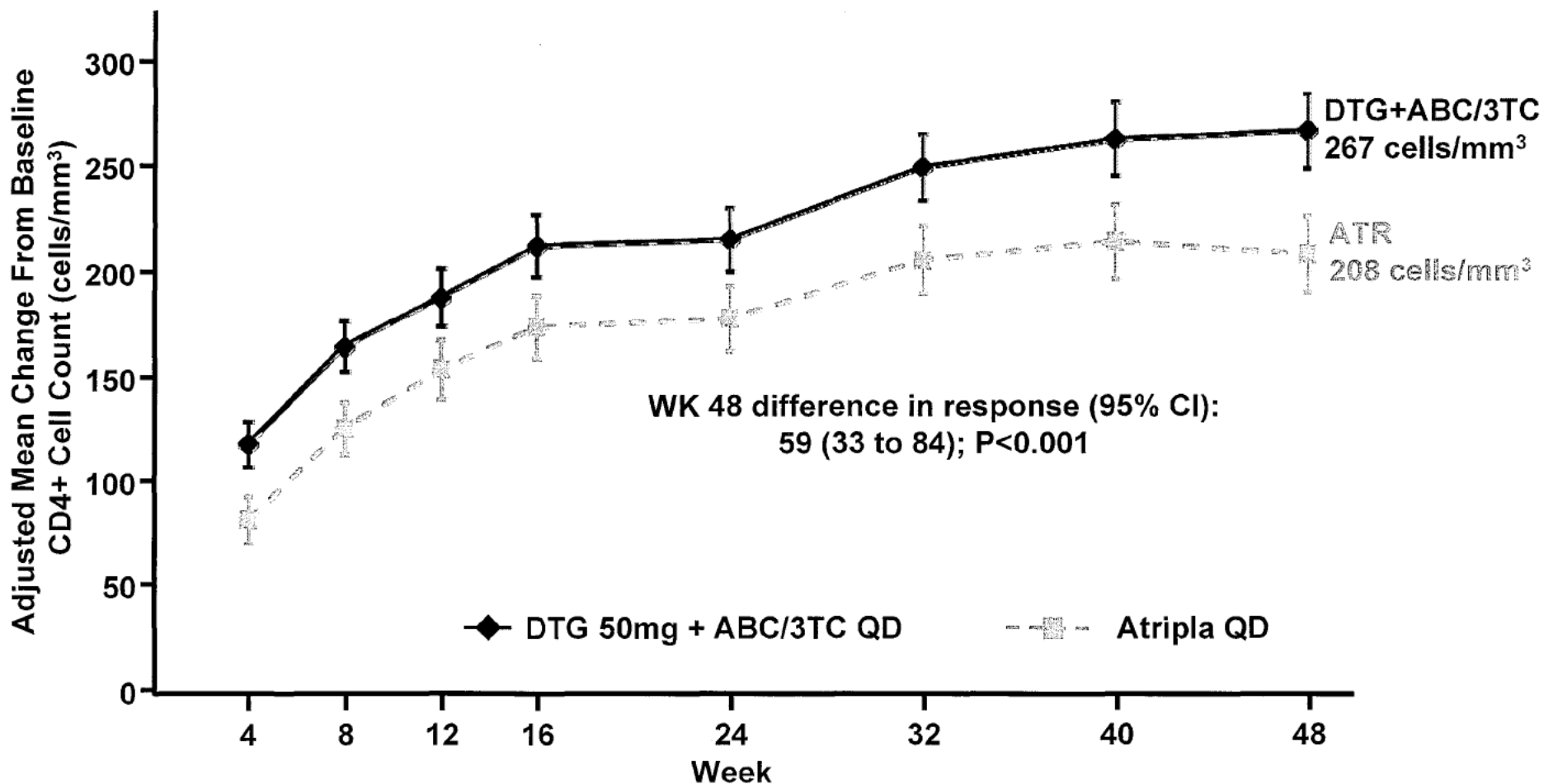
| Outcome (snapshot) at Week 48                    | DTG 50 mg<br>+ABC/3TC QD<br>n=411<br>n (%) | Atripla QD<br>(N=419)<br>n (%) |
|--------------------------------------------------|--------------------------------------------|--------------------------------|
| <b>Virologic success</b>                         | <b>364 (88)</b>                            | <b>338 (81)</b>                |
| <b>Virologic nonresponse</b>                     | <b>21 (5)</b>                              | <b>26 (6)</b>                  |
| Data in window not <50 c/mL                      | 6 (1)                                      | 5 (1)                          |
| Discontinued for lack of efficacy                | 7(2)                                       | 9 (2)                          |
| Discontinued for other reason while not <50 c/mL | 8 (2)                                      | 12 (3)                         |
| <b>No virologic data at Week 48</b>              | <b>29 (7)</b>                              | <b>55 (13)</b>                 |
| Discontinued because of AE or death*             | 9 (2)                                      | 40 (10)                        |
| Discontinued for other reasons                   | 20 (5)                                     | 14 (3)                         |
| Missing data during window but on study          | 0                                          | 1 (<1)                         |

\*Deaths: n=2, both on Atripla: n=1 primary cause of death (sepsis) judged unrelated to study drug but complicated by renal failure judged possibly related to Atripla; n=1 not related to Atripla (pneumonia).



# Absolute Change from Baseline in CD4+ Cell Count

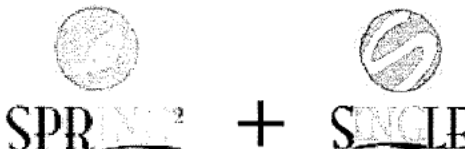
Repeated Measures Mixed Model Analysis



Significant at pre-specified level of 4%

# DTG Resistance Profile in Treatment Naïve Studies

- DTG *in vitro* evidence: difficult to select resistance
  - Single mutations associated with low level resistance (FC <4)
- Pharmacologic barrier is also potentially relevant to findings
  - $C_t$  is above target (PA-IC90) 3-4 days after last dose

| Treatment-emergent resistance in Phase 3 Naïve Studies                             |                                              |                                     |                                               |                                    |
|------------------------------------------------------------------------------------|----------------------------------------------|-------------------------------------|-----------------------------------------------|------------------------------------|
|  | SPRING-2 Week 48                             |                                     | SINGLE Week 48                                |                                    |
|                                                                                    | DTG 50 mg<br>Once Daily<br>+ 2 NRTI<br>N=411 | RAL 400 mg BID<br>+ 2 NRTI<br>N=411 | DTG 50 mg<br>+ ABC/3TC<br>Once Daily<br>N=414 | EFV/TDF/FTC<br>Once Daily<br>N=419 |
| Protocol-defined Virologic Failure                                                 | 20 (5%)                                      | 28 (7%)                             | 18 (4%)                                       | 17 (4%)                            |
| Genotype/phenotype Determinable                                                    |                                              |                                     |                                               |                                    |
| INI-r Mutations Present                                                            | 0                                            | 1/18 (6%)                           | 0                                             | 0                                  |
| NNRTI-r Mutations Present                                                          | -                                            | -                                   | 0                                             | 4 /17 (24%)                        |
| NRTI-r Mutations Present                                                           | 0                                            | 4/19 (21%)                          | 0                                             | 1 /17 (6%)                         |



# DTG Resistance Profile in Treatment Naïve Studies

**DRAFT  
Data**

**To be QCd**

- DTG *in vitro* evidence: difficult to select resistance
  - Single mutations associated with low level resistance (FC <4)
- Pharmacologic barrier is also potentially relevant
  - C<sub>t</sub> is above target (PA-IC90) 3-4 days after last dose

**Treatment-emergent resistance in Phase 3 Naïve Studies**

|  | SPRING-2 Week 48                             |                                     | SINGLE Week 48                                |                                    |
|------------------------------------------------------------------------------------|----------------------------------------------|-------------------------------------|-----------------------------------------------|------------------------------------|
|                                                                                    | DTG 50 mg<br>Once Daily<br>+ 2 NRTI<br>N=411 | RAL 400 mg BID<br>+ 2 NRTI<br>N=411 | DTG 50 mg<br>+ ABC/3TC<br>Once Daily<br>N=414 | EFV/TDF/FTC<br>Once Daily<br>N=419 |
| Protocol-defined Virologic Failure                                                 | 20 (5%)                                      | 28 (7%)                             | 18 (4%)                                       | 17 (4%)                            |
| Genotype/phenotype Determinable<br>(>400 c/mL HIV-1 RNA)                           | 5                                            | 4                                   | 3                                             | 6                                  |
| INI-r Mutations Present                                                            | 0                                            | 1/4 (25%) <sup>a</sup>              | 0                                             | 0                                  |
| NNRTI-r Mutations Present                                                          | -                                            | -                                   | 0                                             | 4 / 6 (67%)                        |
| NRTI-r Mutations Present                                                           | 0                                            | 1/4 (25%) <sup>a</sup>              | 0                                             | 0 / 6 (17%)                        |

<sup>a</sup> T97T/A, E138E/D, V151V/I, N155H + A62A/V, K65K/R, K70K/E, M184V

**DTG Clinical Efficacy and Virology  
in Treatment Experienced, Integrase Resistant  
Patients**

**VIKING-3 (ING112574)**



**SHIONOGI**



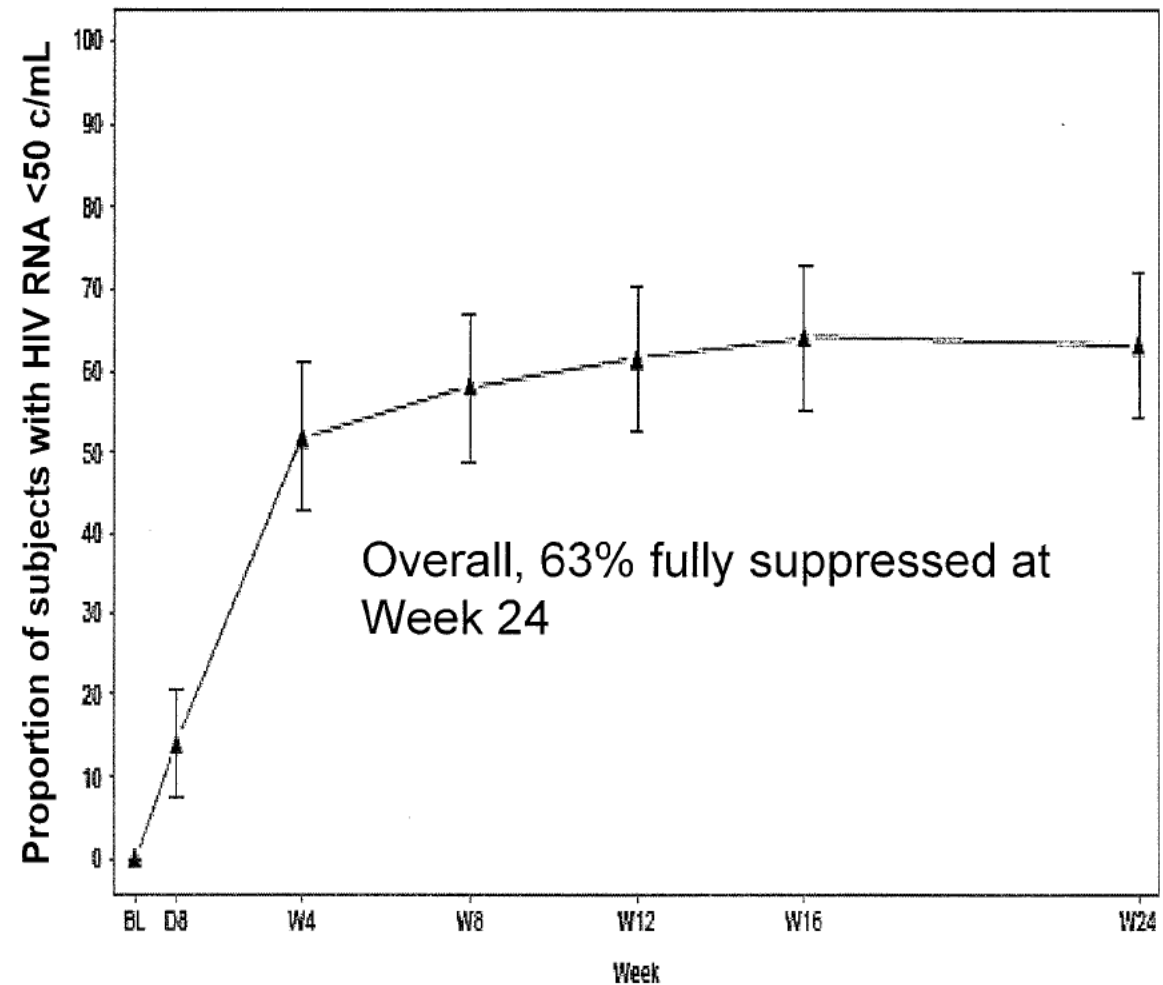
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# VIKING-3 Summary:

## Robust responses in INI-resistant subjects



- Highly ART-experienced population
  - Median 13yrs on ART
- Highly resistant population
  - 79% with  $\geq 2$  NRTI mutations
  - 75% with  $\geq 1$  NNRTI mutations
  - 70% with  $\geq 2$  PI mutations
  - 61% with X4 or dual mixed
- Significant change from baseline in HIV RNA at Day 8 (primary endpoint):
  - $-1.43 \log$  (95% CI  $-1.52$  to  $-1.34$ ,  $p < 0.001$ )
- Tolerability at 50 mg BID dose similar to 50 mg QD dose



# VIKING-3: Day 8 responses by baseline resistance



VIKING-3

| Primary INI mutations at BL                | N   | Mean HIV RNA (log <sub>10</sub> )<br>Change from BL (SD) at<br>Day8 | % > 1log HIV RNA<br>decline or <50c/mL<br>at Day8 |
|--------------------------------------------|-----|---------------------------------------------------------------------|---------------------------------------------------|
| TOTAL                                      | 183 | -1.4 (0.61)                                                         | 82%                                               |
| T66                                        | 1   | -1.9                                                                | 100%                                              |
| Y143                                       | 28  | -1.7 (0.42)                                                         | 96%                                               |
| N155                                       | 33  | -1.4 (0.51)                                                         | 82%                                               |
| Q148 + ≤1 secondary mutation <sup>#</sup>  | 32  | -1.1 (0.51)                                                         | 69%                                               |
| Q148 + ≥2 secondary mutations <sup>#</sup> | 20  | -1.0 (0.81)                                                         | 48%                                               |
| ≥2 primary mutations                       | 8   | -1.4 (0.76)                                                         | 75%                                               |
| No primary mutations                       | 60  | -1.6 (0.55)                                                         | 95%                                               |

<sup>#</sup> Key secondary mutations comprised G140\_ACS, L74I, E138\_AKT



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# Determination of Virologic Correlates to Response

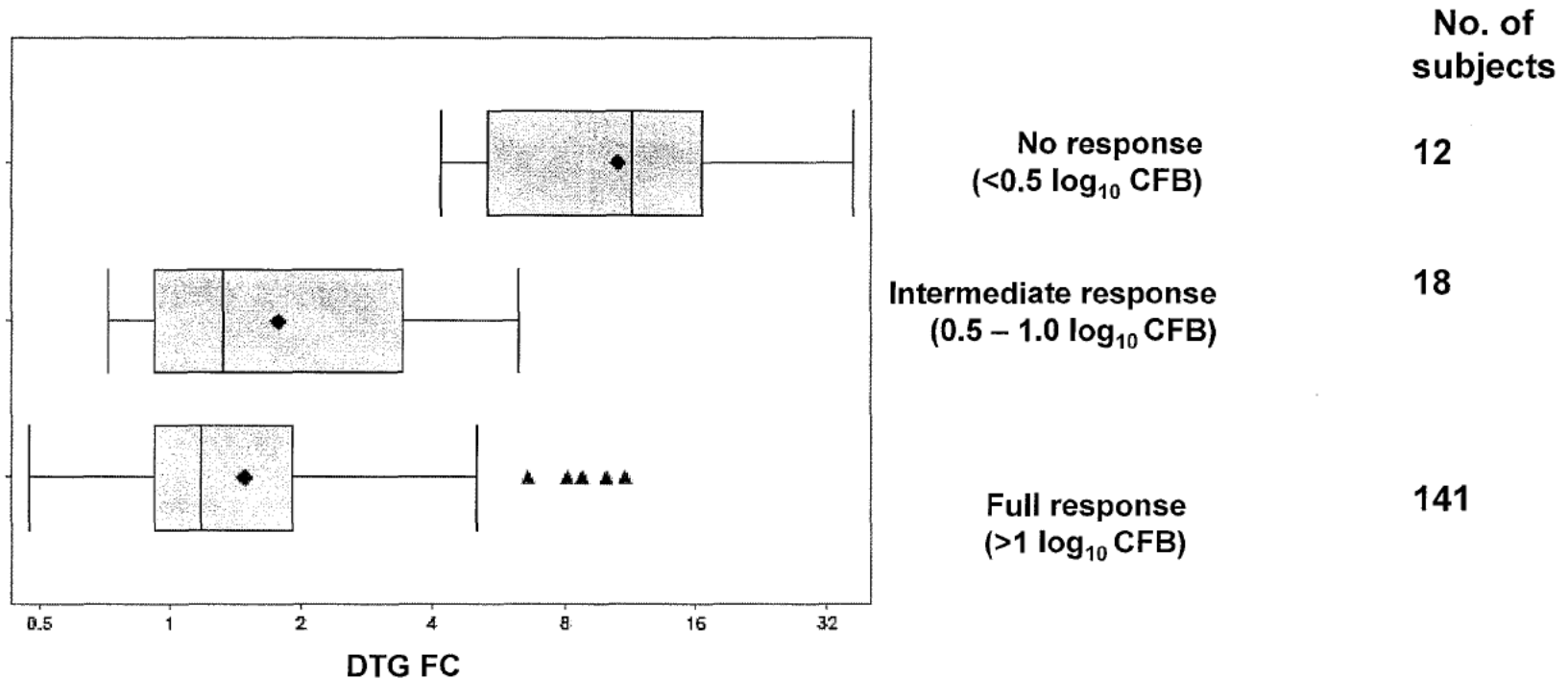


VIKING-3

- As per FDA Guidance for Industry and European Medicines Agency (EMA) guideline, analyses were performed in an attempt to identify the baseline genotypic and phenotypic determinants of virologic success or failure in this population
- Analysis of change from Baseline in plasma HIV-1 RNA at Day 8 by
  - **Phenotypic determinants:** Baseline DTG Fold Change
  - **Genotypic determinants:**  
H51Y, T66A, T66I, T66K, L68V, L68I, L74I, L74M, L74R, E92Q, E92V, Q95K, T97A, G118R, E138A, E138K, E138T, G140A, G140C, G140S, Y143C, Y143H, Y143R, P145S, S147G, Q148H, Q148K, Q148R, V151I, V151L, S153F, S153Y, N155H, E157Q, G163R, G163K, G193E, R263K
- Study Population: Day 8 Virologic Outcome Population (N=177)



# Box Plot of Baseline DTG FC by Day 8 Response Category (Change from Baseline in HIV-1 RNA)



- Subjects with 'no response' at Day 8 had the highest mean DTG FC, followed by those with 'intermediate response', and the lowest mean of DTG FC observed in 'full response'.
- DTG FC spread widely in each group and overlap, indicating no precise phenotypic cutoffs can be derived to differentiate antiviral activity at Day 8.
  - The prediction of long term response at Week 24 with these phenotypic cut-offs was also not accurate. due to few subjects with high DTG FC (>10)

## Day 8 Virologic Response by Derived Mutational Group from Genotypic Analysis

- Three IN mutation groups were derived based on the results from the multivariate analysis.

No Q148: 143/155/66/historical resistant evidence only

Q148+1: Q148\_HKR with one mutation (G140\_ACS, L74I, E138\_AKT)

Q148+≥2: Q148\_HKR with two or three mutations (G140\_ACS, L74I, E138\_AKT)

- Day 8 virologic responses well-predicted by derived mutational group

| DTG 50mg BID<br>Derived Group | Change from Baseline in VL ( $\log_{10}$ c/mL) |       |       |        |      |      | Full Response<br>n (%) |
|-------------------------------|------------------------------------------------|-------|-------|--------|------|------|------------------------|
|                               | N                                              | Mean  | SD    | Median | Min  | Max  |                        |
| No Q148**                     | 122                                            | -1.59 | 0.509 | -1.65  | -3.4 | 0.0  | 112 (92%)              |
| Q148 + 1*                     | 35                                             | -1.18 | 0.520 | -1.10  | -2.6 | -0.1 | 25 (71%)               |
| Q148 + 2*                     | 20                                             | -0.92 | 0.810 | -0.735 | -2.3 | 0.4  | 9 (45%)                |

•L74I/Q138/G140

•\*\*143/155/66/historical resistant evidence only

•Full Response - >1  $\log_{10}$  c/mL decrease from Baseline or <50 c/mL at Day 8

# Week 24 Virologic Response by Derived Mutational Group from Genotypic Analysis



VIKING-3

**Number and % of subjects with HIV-1 RNA <50 c/mL and <400 c/mL at Week 24 (snapshot)  
N=101**

| Derived Group                                              | n  | DTG 50mg BID <50c/mL | DTG 50mg BID <400 c/mL |
|------------------------------------------------------------|----|----------------------|------------------------|
| No Q148<br>(143/155/66/historical resistant evidence only) | 72 | 57 (79%)             | 61 (85%)               |
| Q148 + 1*                                                  | 20 | 9 (45%)              | 10 (50%)               |
| Q148 + 2*^                                                 | 9  | 1 (11%)              | 2 (22%)                |

\* L74I/E138/G140

^Includes subjects with 2 primary mutations re-mapped to Q148 groups

# Summary of Predictors of Response

- Phenotypic cutoffs did not robustly predict response
- Derived genotypic grouping provided best prediction of Day 8 and Week 24 responses and is recommended for treatment guidance

# Overview of Safety

Lloyd Curtis, MA MRCP



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# Select Summary of Adverse Events



SPR <sup>2</sup>

|                                  | <b>DTG 50 mg QD</b><br>n=411<br>n (%)         | <b>RAL 400 mg BID</b><br>n=411<br>n (%)                                                |
|----------------------------------|-----------------------------------------------|----------------------------------------------------------------------------------------|
| <b>AEs Leading to Withdrawal</b> | <b>10 (2)</b>                                 | <b>7 (2)</b>                                                                           |
| <b>Events with &gt;1 subject</b> |                                               |                                                                                        |
| Acute Hepatitis C                | 2 (<1)                                        | 0                                                                                      |
| ALT increased                    | 2 (<1)                                        | 1 (<1)                                                                                 |
| AST increased                    | 1 (<1)                                        | 1 (<1)                                                                                 |
| Nausea                           | 1 (<1)                                        | 1 (<1)                                                                                 |
| <b>Serious Adverse Events</b>    | <b>29 (7)</b>                                 | <b>31 (8)</b>                                                                          |
| <b>Drug related</b>              | <b>3</b>                                      | <b>5</b>                                                                               |
|                                  | Arrhythmia,<br>hypersensitivity,<br>hepatitis | Convulsion (2), aphasia,<br>hypersensitivity <sup>a</sup> , CPK<br>increased, diarrhea |
| <b>Fatal AEs</b>                 | <b>1 (&lt;1)<sup>b</sup></b>                  | <b>1 (&lt;1)<sup>c</sup></b>                                                           |

a. One subject with cytolytic hepatitis, hypersensitivity, influenza, lymphadenitis viral

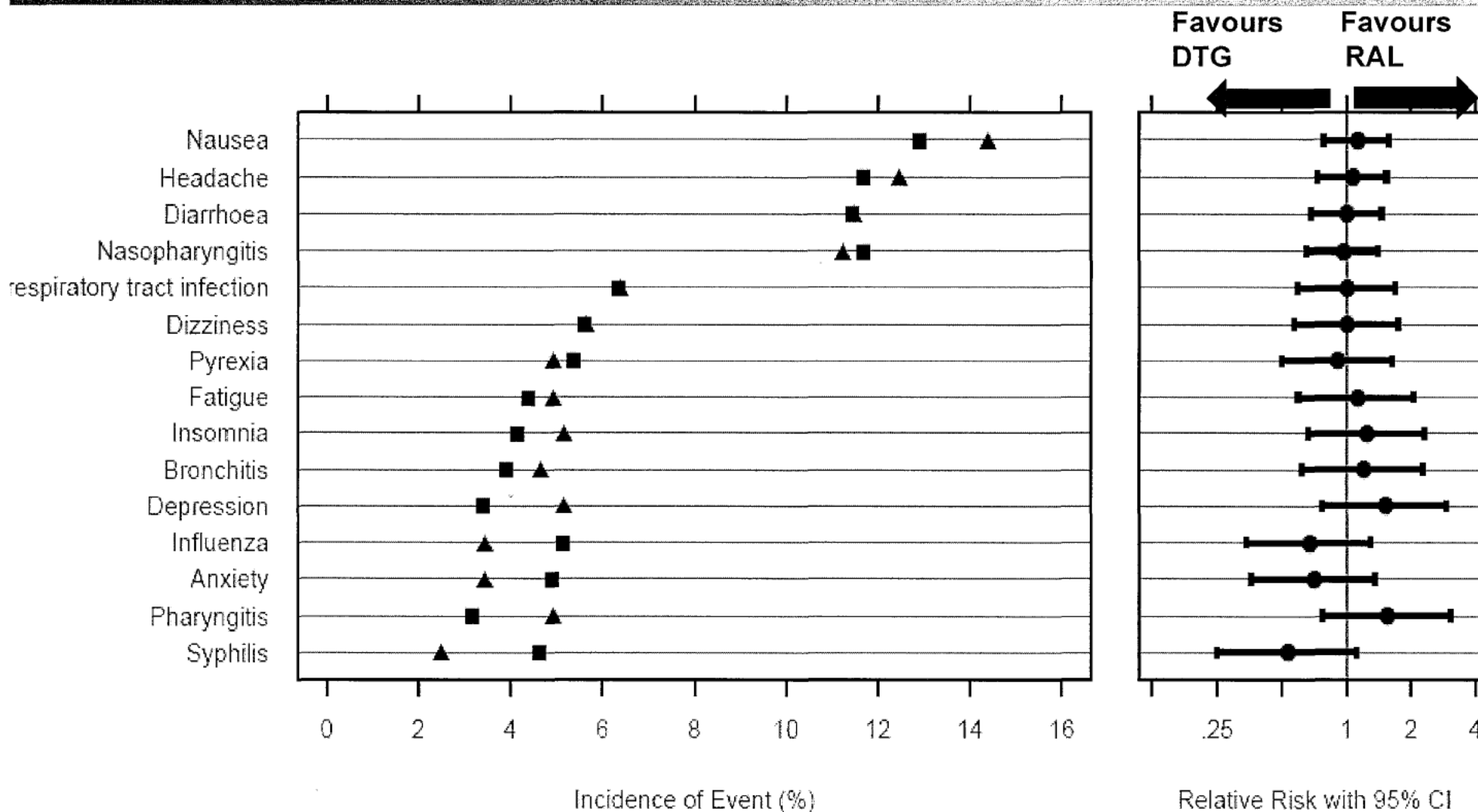
b. Homicide considered not related to DTG;

c. Suicide considered not related to RAL

# DTG Tolerability Comparable to RAL



SPR <sup>2</sup>



▲ DTG 50mg QD, N=411      ■ RAL 400mg BID, N=411



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# Select Summary of Adverse Events



|                                                       | <b>DTG 50mg<br/>+ABC/3TC QD<br/>(N=414) (%)</b> | <b>Atripla QD<br/>(N=419) (%)</b> |
|-------------------------------------------------------|-------------------------------------------------|-----------------------------------|
| <b>Subjects with events leading to withdrawal</b>     | <b>10 (2)</b>                                   | <b>42 (10)</b>                    |
| <b>System Organ Class (at least 2% in either arm)</b> |                                                 |                                   |
| Psychiatric disorders                                 | 2 (<1)                                          | 15 (4)                            |
| Nervous system disorders                              | 0                                               | 13 (3)                            |
| Skin and subcutaneous tissue disorders                | 2 (<1)                                          | 8 (2)                             |
| Gastrointestinal disorders                            | 0                                               | 8 (2)                             |
| General disorders and administration site conditions  | 0                                               | 7 (2)                             |
| <b>Serious Drug-Related – Any Event</b>               | <b>1 (&lt;1)*</b>                               | <b>8 (2)^</b>                     |
| <b>Fatal AEs</b>                                      | <b>0</b>                                        | <b>2(&lt;1)‡</b>                  |

\* DTG+ABC/3TC: 1 drug hypersensitivity    ^ Atripla: 4 psychiatric, 2 HSR, 1 cerebral vascular accident, 1 renal failure

‡ Deaths: n=1 primary cause of death judged unrelated to study drug but complicated by renal failure judged possibly related to ATR, n=1 not related to ATR (pneumonia).

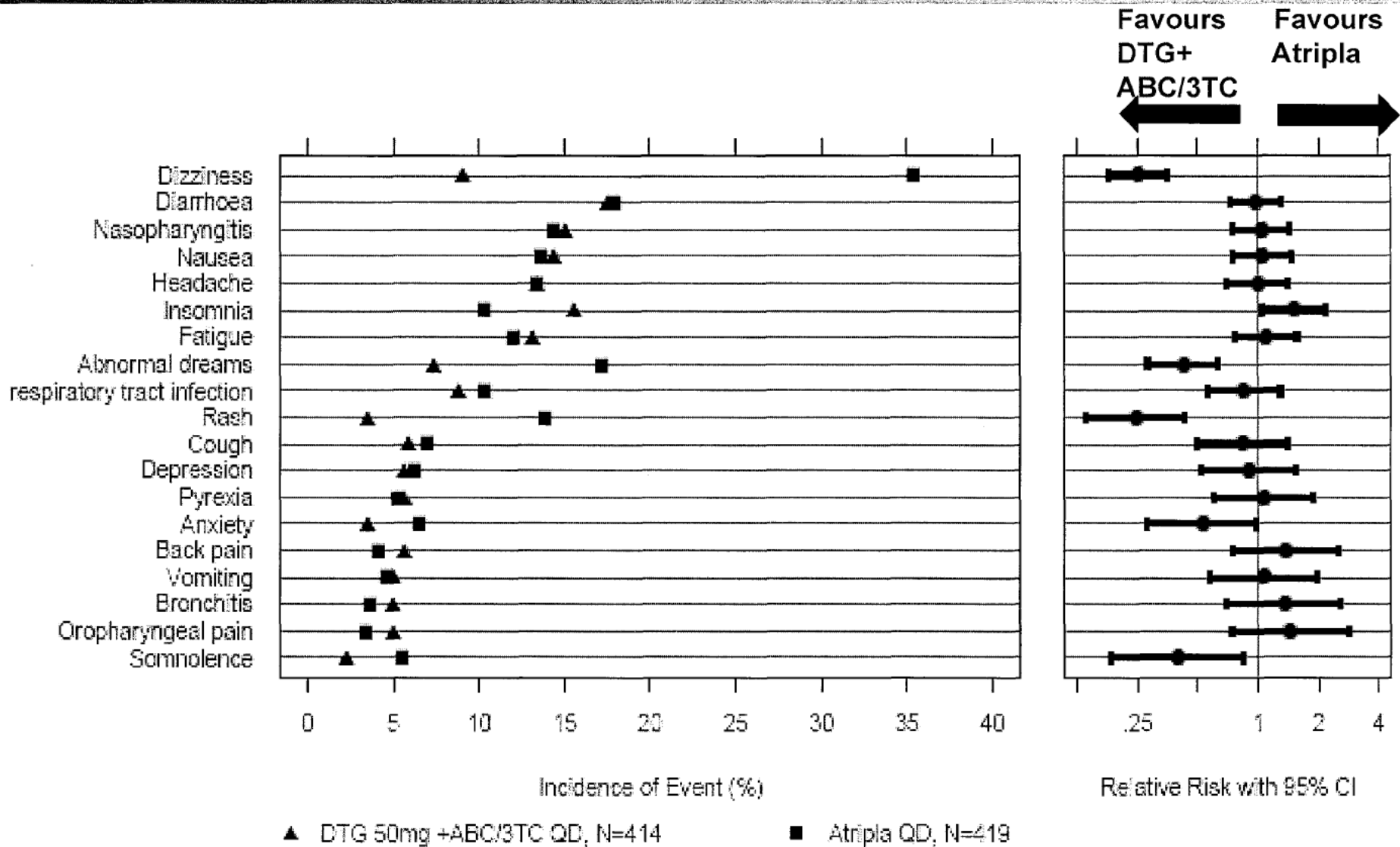


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# DTG + ABC/3TC Tolerability



# Adverse Events: Common ( $\geq 5\%$ )



VIKING-3

| Preferred Term ( $\geq 5\%$ )     | DTG 50mg BID(N=183) |
|-----------------------------------|---------------------|
| <b>ANY EVENT</b>                  | <b>147 (80%)</b>    |
| Diarrhea                          | 25 (14%)            |
| <i>Nausea</i>                     | 17 (9%)             |
| Headache                          | 16 (9%)             |
| Bronchitis                        | 13 (7%)             |
| Cough                             | 13 (7%)             |
| Pyrexia                           | 13 (7%)             |
| Fatigue                           | 12 (7%)             |
| Nasopharyngitis                   | 10 (5%)             |
| <i>Rash</i>                       | 10 (5%)             |
| Injection site reaction           | 9 (5%)              |
| Insomnia                          | 9 (5%)              |
| Upper respiratory tract infection | 9 (5%)              |



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# Select Summary of Adverse Events



|                                                    | DTG 50mg BID (N=183) |
|----------------------------------------------------|----------------------|
| Drug-Related (most common ≥5%)                     | 45 (25%)             |
| Diarrhea                                           | 10 (5%)              |
| Nausea                                             | 10 (5%)              |
| Headache                                           | 9 (5%)               |
| Subjects with AEs leading to withdrawal            | 5 (3%)               |
| Serious – Any Event                                | 27 (15%)             |
| Fatal *                                            | 1 (<1%)              |
| Serious Drug-Related – Any Event                   | 2 (1%)               |
| Pruritus, Rash,                                    | 1 (<1%)              |
| Hyperbilirubinaemia, elevated ALT, drug eruption** | 1 (<1%)              |

\*progressive multifocal leukoencephalopathy (PML), Post-withdrawal

\*\* patient on DRV + ETV



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# Overall Safety Conclusions

- Overall the safety profile for DTG, combined with the efficacy and virology profile, supports a favorable risk/benefit
- The safety profile for DTG is favorable compared to other antiretrovirals.
- Cumulative data suggests a hepatic safety profile for DTG that is comparable to RAL or EFV.
- Cases of hypersensitivity or severe rash with or without systemic involvement have rarely been observed with DTG and the incidence of mild to moderate skin reactions with DTG is comparable to RAL and lower than EFV.
- Overall, the renal profile of DTG is comparable to comparators in Phase 3 studies (i.e., RAL and EFV).
- DTG dose 50 mg twice daily in highly treatment-experienced subjects with advanced HIV disease observed a safety profile comparable to DTG 50 mg once daily in treatment-naïve subjects.



# Risk-benefit assessment and RMP

- Primary risks have been addressed in the safety program
  - Hypersensitivity with hepatic injury is rare effect (also with RAL)
    - Risk minimization to be achieved via warnings and precautions in label
  - Renal safety
    - Likely benign increase in Serum Creatinine to be described in label
- DTG associated with significant benefits, including:
  - In naives, superior efficacy to EFV and comparable to RAL BID
    - Better tolerated than EFV, comparable tolerability to RAL
    - No resistance demonstrated to date in this population
  - In INI-resistant, robust efficacy despite poorly active background
- Pharmacovigilance and risk minimization activities:
  - The draft RMP provided in the briefing document outlined the adverse events of special interest to be monitored
  - For events of interest, labeling and/or routine monitoring in HIV care should be adequate



# Additional Information Regarding Study Report Availability



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## Additional Information Regarding Study Report Availability

| Study Identifier        | Length of Study                                          | Available Data at Initial Submission                 | Data Coming Available During Review           | Estimated Clinical Study Report Availability |
|-------------------------|----------------------------------------------------------|------------------------------------------------------|-----------------------------------------------|----------------------------------------------|
| ING113086<br>(SPRING-2) | 96 weeks                                                 | All subjects through 48 weeks                        | Week 96 Analysis                              | April 2013                                   |
| ING111762 (SAILING)     | 48 weeks                                                 | All subjects through 24 weeks                        | Week 48 Analysis                              | May 2013                                     |
| ING112574<br>(VIKING-3) | 24 and 48 weeks                                          | First ~100 subjects through 24 weeks                 | Week 24 (all) / Week 48 (1 <sup>st</sup> 114) | March 2013                                   |
| ING112578 (P1093)       | 48 weeks, with up to 3-year follow up                    | 10 subjects (Stage 1) from Cohort I through 24 weeks | Week 24 Analysis (Cohort 1, Stage 1&2)        | January 2013                                 |
| ING116070 <sup>a</sup>  | 96 weeks total (primary endpoint at week 16)             | All subjects through 2 weeks                         | Week 16 Analysis                              | February 2013                                |
| ING116529<br>(VIKING-4) | 7 days double blind phase;<br>48 Weeks open label Phase. | Limited safety data only                             | Day 8 (all)                                   | March 2013                                   |

a. Single-arm study of the safety, efficacy and CNS and plasma PK of DTG 50 mg once daily in combination with the ABC/3TC FDC tablet over 96 Weeks in HIV-1-infected, ART-naive adult subjects

# Questions for Discussion



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# Background

**Questions for discussion were submitted on June 21 and August 20, 2012.**

**DAVP preliminary comments were received on September 14, 2012. Questions have been renumbered from June 21 & Aug 20 submissions.**

**Responses to questions that are described as 'review issues' will not be discussed (unless clarification needed).**

**Preliminary Company comments will be provided for DAVP responses and for those comments which require additional information or clarification.**

**Questions / DAVP responses will be abbreviated to decrease the required number of slides.**

**We appreciate the review team's guidance regarding the NDA content.**

# Responses to DAVP Sept 14, 2012 Comments

## Clinical Safety

1. Abbreviated question: We would not provide case report forms for ongoing studies for which there are no available study reports.
  - ***FDA response: Please clarify what you mean by “ongoing studies for which there are no available study reports”. We expect at least an interim study report for all the Phase 3 pivotal trials that will be submitted with the NDA. Thus for these studies, there should be CRFs and case narratives available.***
  - **Company response:**
    - Full study reports, as well as, applicable CRFs and case narratives will be provided for the Phase 3 pivotal trials and supportive Phase 2b studies. In addition, applicable CRFs will be provided for all clinical pharmacology studies.
    - CRFs will not be provided for studies for which no interim analysis has been conducted [ING114916 (EAP), ING115502 (NPP), ING116529 (VIKING-4)].



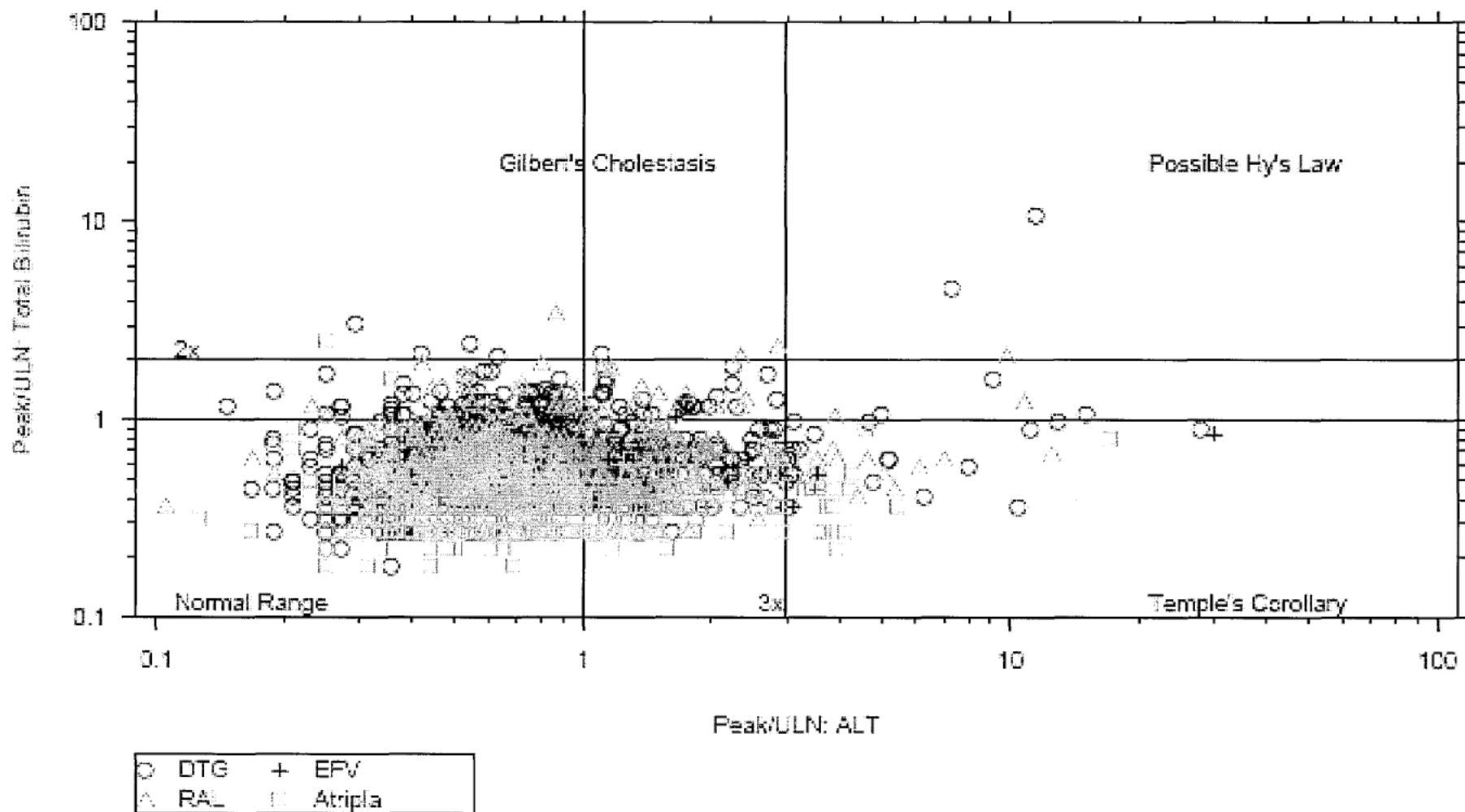
# Responses to DAVP Sept 14, 2012 Comments

## Clinical Safety

6. Two cases of hepatic enzyme elevation from ING113086 (SPRING-2) were reported as IND Safety Reports (INDSRs).
  - ***FDA Response: This is a review issue. The FDA is using an internal review tool (eDISH: Evaluation of Drug Induced Serious Hepatotoxicity) for the analysis and visualization of clinical trial data for the assessment of potential drug-induced liver injury. In order to use this tool, we recommend that you provide datasets using the format specified in the attached eDISH-Data Requirements document. Please pay special attention to how clinical narratives should be organized and submitted.***
  - **Company response:**
    - eDISH plots are currently available. We will reformat the datasets using the format specified in the provided eDISH-Data requirement document.

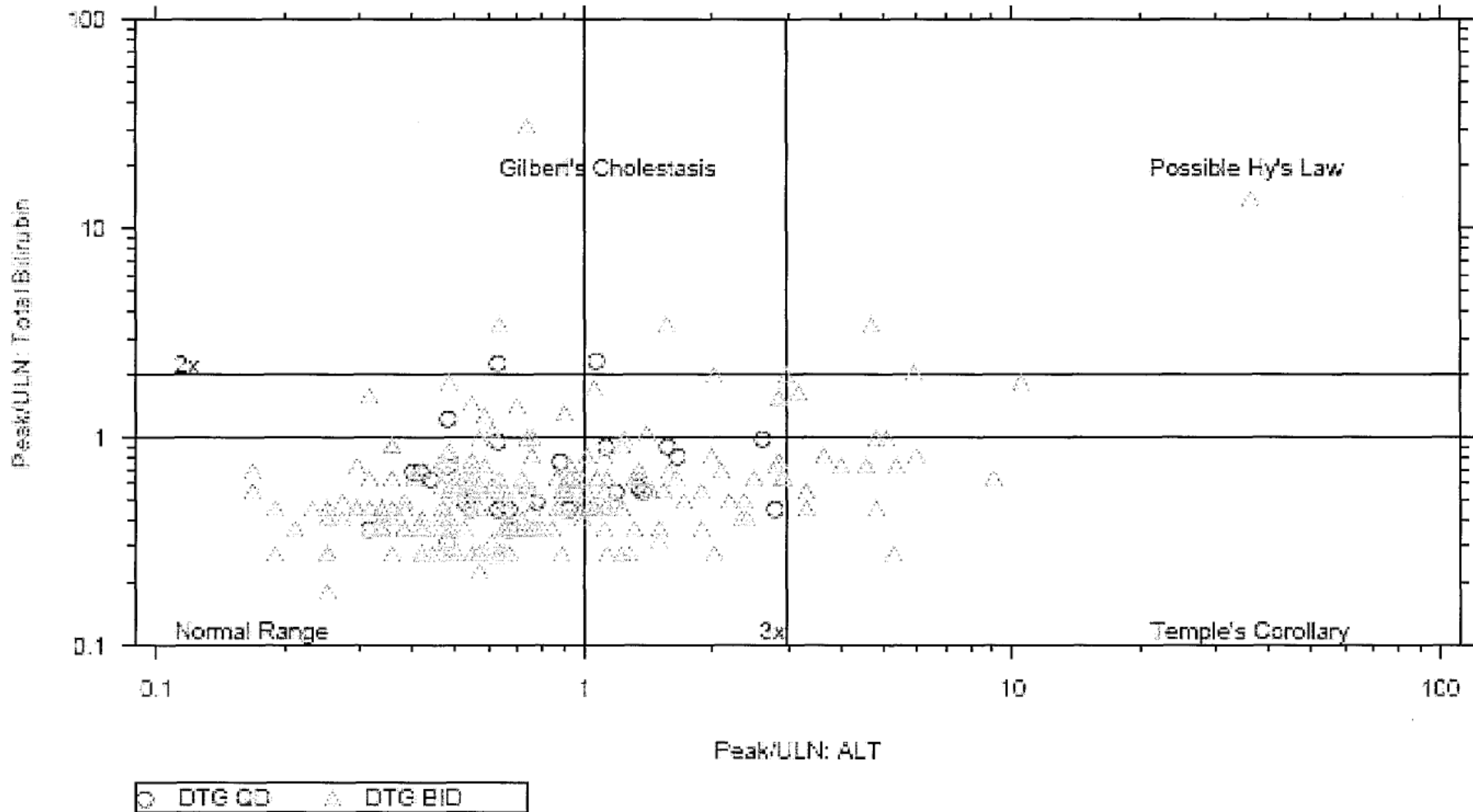
# Liver Safety – eDISH

## Maximum Post-Baseline Total Bilirubin vs Maximum Post-Baseline ALT (/ULN) - ART-naive Population



# Liver Safety – eDISH

## Maximum Post-Baseline Total Bilirubin vs Maximum Post-Baseline ALT (/ULN) – INI-r Population



# Responses to DAVP Sept 14, 2012 Comments

## Clinical Safety, Integrated Summary of Safety (ISS)

### 8. Company proposal for the ISS was provided.

- ***FDA Response: We are in general agreement with your proposal. Please present the safety results for naïve subjects separately from the safety results from the treatment experienced population (i.e. INI naïve, receiving 50 mg QD). These subjects will likely be less healthy than the ARV naïve population.***
- ***Please clarify if you are planning to pool safety data from the phase 2b trial (SPRING-1) and the phase 3 trials (SPRING-2, SINGLE).***
- **Company response:**
  - In the ISS, we have combined all DTG doses from SPRING-1 (10, 25, 50mg) with the DTG 50mg data from SINGLE & SPRING-2. In addition to the pooled data just described for Phase 2b/3, we have also presented the safety data for these studies separately.

# Responses to DAVP Sept 14, 2012 Comments

## ISS Continued

9. In addition to safety data described above, the ISS will contain a non-integrated description of SAEs, deaths and pregnancies from all studies for the time period May 2012 through October 26, 2012 (DSUR cut-off). These data will not have undergone a complete quality assurance check and will be considered preliminary.
- *FDA Response: The safety information should contain summary table of events (SAEs, deaths, pregnancies). The SAEs should be summarized by SOC and PT. It is not necessary that the events from the various studies be integrated. If possible, include summary of subjects who withdrew study drug due to AEs.*
  - **Company response:**
    - The ISS will contain a summary table of events (SAEs, deaths and pregnancies) that occur between May and October 2012. We do plan to provide listings of all AEs leading to withdrawal from May 2012 to approximately 4 weeks post NDA submission for the 2 month safety update. Would this be acceptable to the review team?



# Responses to DAVP Sept 14, 2012 Comments

## Clinical Efficacy, Integrated Summary of Efficacy (ISE)

### 11.a. The Company proposals for the ISE were provided.

No pooling of data from the Phase 2 pilot study in integrase inhibitor resistant (INI-R) subjects (ING112961) and the Phase 3 study in INI-R subjects (ING112574). The timing of the primary endpoint for these 2 studies was different: Day 11 was used for ING112961 and Day 8 was used for ING112574. In addition the number of subjects in ING112961 was relatively small compared to the number of subjects in ING112574; therefore, ING112574 would dominate the results if the data were pooled. [note: additional details were provided]

- ***FDA Response: FDA Response: We agree with your proposal to not pool the VIKING and VIKING-3 50 mg BID cohorts. However, resistance and safety data from these studies should be pooled.***
- **Company response:**
  - Please provide additional details regarding what is meant by “pooling of resistance data”. Currently the resistance data are presented as shown on the next slide which provides a summary of treatment-emergent IN genotypic resistance detected at PDVF for VIKING Cohort II and VIKING-3 from the ISE.
  - Note that safety data are being pooled.



## IN Genotypic Resistance Detected at Time of PDVF but not Detected at Baseline in ART-Experienced, INI-resistant Subjects

|       |                   |                  | ING112961                     | ING112574                      |
|-------|-------------------|------------------|-------------------------------|--------------------------------|
|       |                   |                  | Cohort II<br>DTG 50 mg BID    | ITT-E<br>DTG 50 mg BID         |
| Codon | Baseline Genotype | Genotype at PDVF | (PDVF Genotypic Pop)<br>(N=5) | (PDVF Genotypic Pop)<br>(N=31) |
| ANY   |                   |                  | 3 (60%)                       | 15 (48%)                       |
| 97    | Any change        |                  | 2 (40%)                       | 6 (19%)                        |
|       | T97T              | T97A             |                               | 3 (10%)                        |
|       |                   | T97T/A           | 2 (40%)                       | 3 (10%)                        |
| 138   | Any change        |                  | 2 (40%)                       | 5 (16%)                        |
|       | E138E             | E138A            |                               | 1 (3%)                         |
|       |                   | E138E/K          | 2 (40%)                       | 2 (6%)                         |
|       |                   | E138K            |                               | 2 (6%)                         |
| 148   | Any change        |                  |                               | 4 (13%)                        |
|       | Q148Q             | Q148H            |                               | 1 (3%)                         |
|       |                   | Q148Q/H          |                               | 2 (6%)                         |
|       | Q148R             | Q148Q/R/K        |                               | 1 (3%)                         |
| 92    | Any change        |                  | 2 (40%)                       | 2 (6%)                         |
|       |                   | E92E/Q           | 1 (20%)                       | 2 (6%)                         |
|       |                   | E92E/V           | 1 (20%)                       |                                |
| 140   | Any change        |                  |                               | 2 (6%)                         |
|       | G140G             | G140G/S          |                               | 1 (3%)                         |
|       |                   | G140S            |                               | 1 (3%)                         |
| 155   | N155N             | N155H            | 2 (40%)                       | 2 (6%)                         |
| 157   | E157E             | E157E/Q          |                               | 1 (3%)                         |
| 147   | S147S             | S147G            |                               | 1 (3%)                         |
| 143   | Y143Y             | Y143Y/H          |                               | 1 (3%)                         |



# Responses to DAVP Sept 14, 2012 Comments

## Clinical Efficacy, Integrated Summary of Efficacy (ISE)

11.b. The studies (ING112961 and ING112574) will be reported separately. Please find below a potential mockup for the proportion HIV-1 RNA < 50 copies/mL (c/mL) table.

- ***FDA Response: Please present the Snapshot results for VIKING instead of TLOVR.***
- **Company response:**
  - Please see the following slides which address the limitations of using the Snapshot algorithm for SPRING-1 and VIKING and describe the MDF analyses.
  - Neither Phase 2b study was designed with the Snapshot algorithm in mind.

# Responses to DAVP Sept 14, 2012 Comments

## ING112276 (SPRING-1) by Snapshot - Limitations

- First on-treatment visit was at Week 1 and included a viral load assessment – minimal time to allow for switches based on tolerability
- If Snapshot is implemented, should we penalize for switches after Week 1?
  - 1 (subject 60) switch on DTG 25mg was completed within 1 month of study drug start
- We did perform the MDF analyses which approximates the Snapshot analysis except for switches.

## ING112961 (VIKING) by Snapshot – Limitations

- Small pilot study (N=24-27 per cohort) designed to assess short term responses and confirm a dose for Phase 3
- First on-treatment visit with viral load after re-optimization of background therapy is Day 21 (limited time from Day 11 for switches due to tolerability)
- Longer term response (Week 24 and beyond) was not a primary endpoint
- Investigators were allowed to switch BR with agreement of Medical Monitor after Week 24
- MDF analysis also performed for this study.



# Responses to DAVP Sept 14, 2012 Comments

## SPRING-1 Week 96 Response Rate by MDF

- DTG 10 mg QD: 87% (46/53)
- DTG 25 mg QD: 80% (41/51)
- DTG 50 mg QD: 86% (44/51)
- EFV 600mg QD: 78% (39/50)

- DTG Switches:

| Subject # | Dose      | Treatment Start Date | Switch Date | Original NRTI | NRTI post-switch | Viral Load at Switch |
|-----------|-----------|----------------------|-------------|---------------|------------------|----------------------|
| 92        | DTG 10 mg | 17 Sep 2009          | 07 Sep 2010 | Kivexa        | Truvada          | <50 c/mL             |
| 611       | DTG 25 mg | 02 Sep 2009          | 24 Sep 2009 | Truvada       | Kivexa           | 382 c/mL             |
| 60        | DTG 25 mg | 03 Nov 2009          | 17 Feb 2010 | Epzicom       | Truvada          | <50 c/mL             |
|           |           | 17 Feb 2010          | 21 Mar 2010 | Truvada       | Epzicom          | <50 c/mL             |
| 821       | EFV       | 06 Oct 2009          | 27 Oct 2009 | Kivexa        | Combivir         | 209 c/mL             |



# Responses to DAVP Sept 14, 2012 Comments

## VIKING Response Rate by MDF

- **DTG 50 mg QD, Cohort I: 26% (7/27) Week 96**
  - 1 definite switch, a 2<sup>nd</sup> switch was performed on Day 24
- **DTG 50 mg BID, Cohort II: 67% (16/24) Week 48**
  - ~~no switches~~
  - One additional ART switch on Day 65 (update)



# Responses to DAVP Sept 14, 2012 Comments

## Microbiology/Virology

18. In the resistant datasets, for PRO/RT mutations, only major mutations will be included, as described by IAS-USA (see Table below). For integrase inhibitor (INI) mutations, only resistant mutations described in the table below will be included.

- *FDA Response: No, we do not agree. All positions in the RT, IN and PR should be included in the datasets – not just major substitution sites.*
- **Company response:**
  - We will provide datasets including all positions in the RT, IN and PR mutations as requested.
  - If possible we would appreciate guidance that the pre-specified definitions provided are appropriate for summarizing specific mutations in the resistance data sets. We also can pursue this in follow up activity to this meeting.

# Responses to DAVP Sept 14, 2012 Comments

## Microbiology/Virology

**18. In the resistant datasets, for PRO/RT mutations, only major mutations will be included, as described by IAS-USA (see Table below). For integrase inhibitor (INI) mutations, only resistant mutations described in the table below will be included.**

- ***FDA Response: No, we do not agree. All positions in the RT, IN and PR should be included in the datasets – not just major substitution sites.***
- **Company response (continued):**
  - Thank you for providing the updated Guidance for submitting resistance data. The datasets including all positions will be provided as shown in example table on the next slide based on that guidance. Please confirm this format and the method for calculating of total number of mutation for each region is correct?

## Example Table based on Template for Submitting HIV1 Resistance Data 062212

| PID | VISIT    | TOTPI* | PRV082 | PRN083 | PRI084 | TOTIN** | INQ146 | INS147 | INQ148 |
|-----|----------|--------|--------|--------|--------|---------|--------|--------|--------|
| 001 | Baseline | 0      |        |        |        | 0       |        |        |        |
| 001 | WEEK 48  | 1      |        |        | V      | 1       |        |        | H      |
| 002 | Baseline | 2      | A/T    |        | V      | 1       |        |        | H      |
| 002 | WEEK 48  | 2      | T      |        | V      | 2       |        | G      | H      |
| 003 | Baseline | 2      | A      |        | V      | 0       |        |        |        |
| 004 | Baseline | 0      |        |        |        | 0       |        |        |        |

\*TOTPI based on IAS major mutations D30N,V32I , M46I/L, I47A/V, G48V, I50V/L, I54M/L, Q58E, T74P, L76V, V82A/T/F/L/S, N83D, I84V, N88S,L90M. Similar approach will be used for the calculation of TOTNNRTI and TOTNRTI

\*\*TOTIN H51Y, **T66A**, **T66I**, **T66K**, L68V, L68I, L74I, L74M, L74R, **E92Q**, **E92V**, Q95K, T97A, G118R, E138A, E138K, E138T, G140A, G140C, G140S, **Y143C**, **Y143H**, **Y143R**, P145S, S147G, **Q148H**, **Q148K**, **Q148R**, V151I, V151L, S153F, S153Y, **N155H**, E157Q, G163R, G163K, G193E, R263K as proposed by sponsor

This example highlights how genotype information should be displayed but does not include all column headings or rows.



# Responses to DAVP Sept 14, 2012 Comments

## Microbiology/Virology

**20. Based on data from ING112961 and ING112574, the Sponsor proposes to describe responses to DTG in labeling by baseline IN genotype for the INI-resistant patient population.**

- ***FDA Response: Yes, in general we agree, but reserve the right to modify this criterion depending on the review of the data. Please do analyses by individual baseline INSTI substitutions, specific combinations (most common) of INSTI substitutions, number of baseline INSTI substitutions, and baseline phenotype. Provide a justification for the analyses included in the label.***
- **Company response:**
  - **We agree. We will complete analyses by individual baseline INSTI substitutions, specific combinations (most common) of INSTI substitutions, number of baseline INSTI substitutions and baseline phenotype as requested. In addition we will provide a justification in the NDA for the analyses included in labeling.**

# Responses to DAVP Sept 14, 2012 Comments

## Summary of Biopharmaceutical Studies

**32.Module 2.7.1 – Summary of Biopharmaceutical Studies and Associated Analytical Methods for dolutegravir in humans, there are no plans to provide a Biopharm Review Aid. Is it acceptable to the Agency that a Biopharm Review Aid is not provided?**

- ***FDA Response: It is not clear to the agency what specific contents would be included in a Biopharm Review Aid. Please clarify this issue.***
- **Company response:**
  - A Biopharm Review Aid is requested by some FDA review Divisions; content is driven by Division requests.
  - As a Biopharm Review Aid has not been requested in the past by DAVP and no discussions have occurred regarding its proposed content, our plan is to not provide a Biopharm Review Aid.

# Responses to DAVP Sept 14, 2012 Comments

## Summary of Biopharmaceutical Studies

### 33.Module 2.7.1 – Summary of Biopharmaceutical Studies and Associated Analytical Methods for dolutegravir in humans – the proposed contents of Appendix Tables 4 and 5 were described.

- *FDA Response A: Table 4 should also specifically state the title and report number of the validation report as displayed in 5.3.1.4. For methods that involve analysis of plasma samples, please also specify the anticoagulant that the method was validated in.*
  - *Company response: Title and anticoagulant to be added to Column 1 of Table 4.*
- *Also, please provide a brief description for each method to aid the clinical pharmacology in identifying and tracking changes in either the method or in the bioanalytical laboratory conducting the analysis (e.g. this is the original method validated by XYZ laboratories, the method is a partial validation by JMZ laboratories of the original method validated by XYZ laboratories).*
  - *Company response: GSK site to be specifically added for internal validations and the original method to be identified.*
- *For method validations where no new stability experiments were conducted, please specifically provide the cross reference to the method validation(s) under which the relevant stability experiments were conducted and state whether the same analytical method was used.*
  - *Company response: Except for whole blood stability, all stability assessments are independently conducted.*
- *Continued on next slide*

# Responses to DAVP Sept 14, 2012 Comments

## Summary of Biopharmaceutical Studies

### 33.Module 2.7.1 – Summary of Biopharmaceutical Studies and Associated Analytical Methods for dolutegravir in humans – the proposed contents of Appendix Tables 4 and 5 were described.

- *A table should also be provided that provides the location of the bioanalytical reports in the eCTD. An example of a table for the bioanalytical reports is provided below. Bioanalytical reports should be provided as standalone documents in the eCTD and should not be provided as attachments to the clinical trial reports.*
  - *We will add an abbreviated title to the first column of Table 5 and provide the validation report number in a new column after the BAR number. (example below)*
  - *Reports are stand alone and are also included in some clinical study reports.*
- *Continued on next slide*

| Study (Analyte) and Title                       | Total number of QC samples | Overall precision (%CV range) | Accuracy (%bias range) | Report Number  | Validation report number                                     |
|-------------------------------------------------|----------------------------|-------------------------------|------------------------|----------------|--------------------------------------------------------------|
| ING111322 (DTG)<br>Repeat dose escalation study | (n=60 at each of 3 levels) | 4.2% to 7.0%                  | -1.8% to -0.8%         | 2011N126878_00 | RD2007/01425/00<br><br>Supplemental Report<br>2011N112541_00 |



# Responses to DAVP Sept 14, 2012 Comments

## Summary of Biopharmaceutical Studies

### **33.Module 2.7.1 – Summary of Biopharmaceutical Studies and Associated Analytical Methods for dolutegravir in humans – the proposed contents of Appendix Tables 4 and 5 were described.**

- *Complete method validation reports and bioanalytical reports should be submitted for dolutegravir as well as for any analytes that were analyzed in drug-drug interaction trials. At the time of NDA submission, the required stability data, including long term stability data, for dolutegravir as well as for any analytes that were analyzed in drug-drug interaction trials should also be submitted that cover the necessary duration of stability (see B below). If the required stability data, including long term stability data, are not available at the time of NDA submission, the pharmacokinetic data will not be included in the proposed dolutegravir U.S prescribing information.*
- **Company response part A:**
  - Long term stability data for telaprevir are ongoing. These data can be submitted within 30 days after the submission. Is this acceptable?
  - Completion of the validation for the boceprevir (BCV) assay is awaiting backordered delivery of M+2 metabolites to assess the potential for interference with the method. Thus, BCV (secondary endpoint) data will not be in the submission. Will the DTG data (primary endpoint) from this study be acceptable for inclusion in the label?

# Responses to DAVP Sept 14, 2012 Comments

## Summary of Biopharmaceutical Studies

**33.Module 2.7.1 – Summary of Biopharmaceutical Studies and Associated Analytical Methods for dolutegravir in humans – the proposed contents of Appendix Tables 4 and 5 were described.**

- ***FDA Response B: Lastly, the clinical pharmacology team requests a more comprehensive summary of bioanalytical information for each bioanalytical report as listed below. This information should be provided as a MS Word document.***
  1. ***Please provide a summary of the relevant method validation and bioanalysis items listed (a-w).***
- **Company response part B:**
  - Items a-f, h, and k are provided in the individual study bioanalytical reports
  - Items r-w are provided in the individual bioanalytical reports for later studies or in the study file for earlier studies.
  - Items l-p are provided in the validation documents or their supplements and hyperlinked from Table 4 or Table 5.
  - Is it acceptable not to combine a-w in one document?



# Responses to DAVP Sept 14, 2012 Comments

## Summary of Biopharmaceutical Studies

### **33.Module 2.7.1 – Summary of Biopharmaceutical Studies and Associated Analytical Methods for dolutegravir in humans – the proposed contents of Appendix Tables 4 and 5 were described.**

- *FDA Response B: Lastly, the clinical pharmacology team requests a more comprehensive summary of bioanalytical information for each bioanalytical report as listed below. This information should be provided as a MS Word document.*
  1. *Please provide a summary of the relevant method validation and bioanalysis items listed (a-w).*
- **Company response part B:**
  - **Item g: DTG stability data are available for at least 16 months; all samples were analyzed within that time period. We will summarize these data but not provide on a per site basis for Phase 2 and 3 studies. Is this acceptable?**
  - **Item i: Temperature at the trial sites are available for Phase 1 studies; for Phase 2 – 3 studies, samples were drawn and shipped on dry ice to Quest (satellite facility). Samples were not stored at study sites.**



# Responses to DAVP Sept 14, 2012 Comments

## Statistics

**36. We plan to submit SAS datasets and SAS programs to the Agency as outlined in the March 8, 2011 DAVP response to January 26, 2011 Company questions. We plan to submit SAS datasets and SAS programs for the ISS and for the studies as described.**

- ***FDA Response: We would prefer that the snapshot endpoint be computed for all studies, regardless of what the initial protocol specified. Otherwise this is acceptable.***
- **Company response:**
  - Regarding snapshot, please refer to response for question 11b.
  - Please note that the SAS programs provided will be non-executable. We also want to clarify that the SAS datasets provided will be legacy Analysis & Reporting (A&R) datasets, not in CDISC (SDTM or ADAM) format (as previously agreed as per March 2011 memo).
  - We would also like to request updated efficacy dataset specifications.



# Responses to DAVP Sept 14, 2012 Comments

## Statistics

**37. We do not intend to submit SAS datasets and SAS programs to the Agency for clinical pharmacology studies. We will submit SAS datasets and programs for the population pharmacokinetic analyses (POP PK). Is this acceptable to the Agency?**

- ***FDA Response: No, SAS datasets and SAS programs for the clinical pharmacology studies should be submitted as part of the New Drug Application. These datasets will enable the agency to independently analyze the pharmacokinetic data from the clinical pharmacology trials.***
- **Company response:**
  - We will submit SAS datasets and SAS programs (nonexecutable) for all clinical pharmacology studies as requested.
  - SAS datasets will be legacy A&R datasets, not CDISC datasets.



# Responses to DAVP Sept 14, 2012 Comments

## General and Administrative Questions:

### 42. Proposed eCTD Specifications and File Formats – Specifications:

The proposed specifications and file formats were described.

- ***FDA Response: Your proposal is acceptable; however, the following specifications should also be included:***

- *FDA eCTD Table of Contents Headings and Hierarchy (PDF - 73KB) (updated 7/7/2005)*  
<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163175.pdf>
- *eCTD Backbone File Specification for Modules 2 through 5 3.2.2 (PDF - 726KB) (updated 7/16/2008)*  
<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163556.pdf>
- *the updated version of Study Data Specifications (v2.0 2012-07-20)*  
<http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM312964.pdf>

- **Company response:**

- The specifications will be followed as described above.

# Responses to DAVP Sept 14, 2012 Comments

## General and Administrative Questions:

**46. We propose to submit complete documentation to support marketing approval of dolutegravir tablets in the December 2012 NDA. There are no plans at this time to submit application components during the 30 days following the NDA submission.**

- ***FDA Response: We agree with your plans to submit a complete NDA and do not intend to submit any components during the 30 days following the NDA submission***
  
- **Company response:**
  - **We propose to provide the following item within 30 days of the original submission:**
    - **Long term stability data for telaprevir (TVR) (ING115697).**

# Responses to DAVP Sept 14, 2012 Comments

## Additional Comments:

### Clinical Pharmacology comments

1. Please provide a table that list the dolutegravir formulation that was administered in each clinical trial and state which trials used the Phase 3 or the proposed U.S, marketed formulation. In addition, please provide a summary outlining the formulation development of dolutegravir including whether the Phase 3 formulation is the proposed US marketed formulation in the Summary of Biopharmaceutic Studies and Associated Analytical Methods. If the Phase 3 formulation is not the proposed US marketed formulation, please provide information on the differences between the two formulations and the impact of the differences and whether a bioequivalence trial was conducted. For drug-drug interaction trials, for completeness of information, please also list whether the concomitant medication or medications are the U.S. marketed formulation.
- **Company response:**
    - The information will be provided in m2.7.1.
    - All concomitant medications used in DDI studies were US marketed formulations. This information will be added to m2.7.2.

# Responses to DAVP Sept 14, 2012 Comments

## Additional Comments:

### Clinical Pharmacology comments

2. For in vitro studies evaluating the cytochrome P450 enzyme induction effects of dolutegravir by determining the change in mRNA level, please provide  $R_3$  values for each cytochrome P450 enzyme that was studied or provide the predefined threshold for the increase in mRNA consistent with the recommendations in the February 2012 draft guidance on drug interaction studies.
  - **Company response:**
    - For the in vitro enzyme induction assessment, the relative mRNA expression (treated vs control) was compared to the response from a prototypical inducer. The relative response following treatment with dolutegravir was <15% of the prototypical inducer response for each gene (8, 14, and 13% for CYP1A2, CYP2B6, and CYP3A4, respectively). The pre-established threshold for induction was 40% of the positive control value consistent with the September 2006 draft guidance on drug interaction studies as this study was conducted in 2007. Fold increases for all positive controls were consistent with literature values (RD2007/00074).
    - The induction potential also was investigated in vivo using midazolam as a sensitive probe substrate. No inductive effects were observed (ING111322).

# Responses to DAVP Sept 14, 2012 Comments

## Additional Comments:

### Virology Comments

3. Given the prevalence of subjects with “blipping” at low-level viral loads, we have been looking at the clinical significance of the viral loads that blip >50 copies/mL but <400 copies/mL. After consultation within our Division, we have decided that, at the present time, those subjects who rebounded to >50 copies/mL but did not exceed 400 copies/mL at or before Week 96 will be excluded (censored) from the virologic failure resistance analysis. Note that this will not affect the efficacy snapshot analysis.
- Company response:
    - Thank you for the information. We will add this information in text to m2.7.2.4 regarding SPRING-2 and SINGLE.



# Responses to DAVP Sept 14, 2012 Comments

## Additional Comments:

### Virology Comments #3 continued

Our current guidance states that “Phenotypic and genotypic resistance testing should be performed on baseline and on-treatment failure samples for patients who demonstrate virologic rebound (defined as a 1 log<sub>10</sub> increase in HIV-RNA from nadir value or a confirmed HIV-RNA >400 copies/mL after confirmed suppression to <50 copies/mL). Any changes, including mixtures, in the amino acid coding sequence of the targeted genome region present in on-treatment or follow-up samples, but not in the baseline sample, should be reported as having emerged during therapy.”

- **Company response:**
  - We agree, and will provide emergent resistance data as described in the guidance.



# Responses to DAVP Sept 14, 2012 Comments

## Additional Comments:

### Virology Comments #3 continued

Given that the protocols in your proposed NDA submission followed the PDVF criterion: two consecutive HIV-1 RNA values  $\geq 50$  copies/mL HIV-1 RNA on or after Week 24), which mandated withdrawal from the trial (if confirmed before Week 48) and testing for resistance, we request that you submit the virology resistance data for these subjects with the NDA, but understand that in the FDA analysis, these subjects will likely be excluded from the virology resistance analysis.

- **Company response:**

- We agree, resistance testing as available for samples  $< 400$  copies/mL will be provided in the NDA.

# Responses to DAVP Sept 14, 2012 Comments

## Additional Comments:

### Datasets

#### 4. General comment regarding xpt datasets

For all datasets, in order to significantly reduce dataset file sizes, the allotted character column length/size for each column should be the maximum length used. Lengths/sizes of columns should not arbitrarily be set to 200. For example, if USUBJID has a maximum length of 18, the USUBJID's column size should be set to 18, not 200. An inclusion of a small amount of padding to column width may be acceptable as long as this doesn't result in significant increases in file size.

- **Company response:**

We agree with your request for the Phase 2 and 3 studies. Given the large number of Phase 1 studies and given that they are relatively small compared to later phase studies, we propose to not reduce column lengths for the Phase 1 studies.



# Responses to DAVP Sept 14, 2012 Comments

## Additional Comments:

### Datasets

#### 5. LB xpt dataset comment

- The size of the LB domain is often quite large and can exceed the reviewers' ability to open the file using standard-issue computers. This size issue can be addressed by splitting the large LB dataset into smaller data sets based on the type of laboratory variable. For example, hematology-related laboratory variables for all subjects within a trial would be entered into a 'lbad01' dataset file; liver-related laboratory variables would be entered into 'lbad02' dataset file; chemistry-related laboratory variables would be entered into a 'lbad03' dataset file; and renal-related laboratory variables would be entered into a 'lbad04' dataset file, etc...
- This would reduce the volume of data entered into one analysis dataset file, allowing the review team to navigate the laboratory datasets more efficiently. Sponsor should submit these smaller files in addition to the larger non-split standard LB domain file. The smaller split files should be submitted in a separate Sub-directory/SPLIT which is clearly documented in addition to the larger non-split standard LB domain file in the CRT directory.
- **Company response:**
  - Thank you; we will follow the review team's requests.

# Responses to DAVP Sept 14, 2012 Comments

## Additional Comments:

### Content/format of NDA submission modules and TOC

6. Module 2.7.3. should contain the summary text and M5.3.5.3 should contain all datasets, appendices of supporting tables and figures, etc.,
  - Please refer to the Final Guidance for Industry: Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document (PDF - 98KB), located at:-  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf>
  - Company response:
    - Thank you; we will follow the review team's request.

# Responses to DAVP Sept 14, 2012 Comments

## Additional Comments:

### Content/format of NDA submission modules and TOC

7. The NDA will be reviewed utilizing the CDER Clinical Review Template. Details of the template may be found in the Manual of Policies and Procedures (MAPP 6010.3R)

<http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM236903.pdf>

- To facilitate the review, we request you provide analyses, where applicable, that will address the items as described in the document.
- Company response:
  - Thank you; we will follow the review team's request.

# Additional Company Questions

1. **PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2013 THROUGH 2017 PDF** describes the following:
  - **2.a. All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.**
  - **Please clarify if the list of all clinical sites pertains to Phase 3 pivotal trials, all Phase 2b and 3 studies, or all clinical sites for all clinical trials.**
  - **Please clarify the desired location of the requested list. The list of all manufacturing sites is included as an attachment to the FDA form 356H.**

## Additional Company Questions

2. In order to plan and complete necessary submission activities, a rationale for submitting the NDA [REDACTED] (b) (4) [REDACTED] with 9 months drug product (DP) stability data was informally provided on September 17<sup>th</sup> via email. We would like to receive feedback from the review team regarding our proposal. 12 months DP stability data would be available no earlier than June 2013 and could be provided if the review team was in agreement .
- We are aware that Pre-IND comments were provided on May 21, 2012 and this issue was discussed at the Pre-IND conference call held on May 23, 2012. It was suggested that the Company discuss this issue at the pre-NDA meeting [REDACTED] (b) (4) [REDACTED]. Unfortunately the timing of the pre-NDA meeting (1Q13) would be too late for our team to make critical decisions regarding submission activities.
  - We would appreciate hearing the review team's thoughts on our proposal.



# Summary of Meeting Conclusions and Action Items



**SHIONOGI**



Shionogi - ViiV Healthcare LLC



IND 75382

**MEETING PRELIMINARY COMMENTS**

ViiV Healthcare  
c/o GlaxoSmithKline  
Attention: Martha Anne Auld, R.Ph.  
Senior Director, Infectious Diseases, Regulatory Affairs  
P.O. Box 13398, 5 Moore Drive, Bldg 5.5218  
Research Triangle Park, NC 27709

Dear Ms. Auld:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for GSK1349572 (dolutegravir, DTG).

We also refer to your May 17, 2012, correspondence requesting a Pre-NDA meeting to discuss proposals for the content and format of your New Drug Application (NDA) for DTG and the results of the three Phase 3 studies, [ING113086 (SPRING-2), ING114467 (SINGLE) and ING112574 (VIKING-3)].

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call me at (301) 796-4876 or (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Sohail Mosaddegh, PharmD  
Regulatory Project Manager  
Division of Antiviral Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

ENCLOSURE:  
Preliminary Meeting Comments

## PRELIMINARY MEETING COMMENTS

**Meeting Type:** B  
**Meeting Category:** Pre-NDA

**Meeting Date and Time:** September 20, 2012, 9:00 am to 10:30 am  
**Meeting Location:** 10903 New Hampshire Avenue  
White Oak Building 22, Conference Room: 1417  
Silver Spring, Maryland 20903

**Application Number:** IND 75382  
**Product Name:** GSK1349572 (dolutegravir, DTG)  
**Indication:** treatment of HIV-1 infection  
**Sponsor/Applicant Name:** ViiV Healthcare

### Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for September 20, 2012 from 9:00 am to 10:30 am, at: 10903 New Hampshire Avenue, White Oak Building 22, Conference Room: 1417, Silver Spring, Maryland 20903, between ViiV Healthcare (Viiv) and the Division of Antiviral Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact the RPM to discuss the possibility of including these items for discussion at the meeting.

### BACKGROUND

The purpose of the meeting is to discuss proposals for the content and format of the New Drug Application (NDA) for DTG and the results of the three Phase 3 studies:

1. ING113086 (SPRING-2), a Phase 3, randomized, double blind study of the safety and efficacy of GSK1349572 50 mg once daily to raltegravir 400 mg twice daily both administered with fixed-dose dual nucleoside reverse transcriptase inhibitor therapy over 96 weeks in HIV-1 infected antiretroviral therapy naïve adult subjects
2. ING114467 (SINGLE), a Phase 3, randomized, double-blind study of the safety and efficacy of GSK1349572 plus abacavir-lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1
3. ING112574 (VIKING-3), A Phase III study to demonstrate the antiviral activity and safety of dolutegravir in HIV-1- infected adult subjects with treatment failure on an integrase inhibitor

## DISCUSSION

Your questions are in **bold** font followed by FDA response in *italics*. Please note that your questions have been renumbered and organized to be discipline specific.

### Clinical

#### Clinical Safety

- 1. For ViiV Healthcare (ViiV) sponsored studies, we propose to provide case report forms (CRFs) for patient deaths (& case narratives) and adverse events (AEs) leading to withdrawal (& case narratives for withdrawals for adverse events of special interest) in module 5 with the applicable clinical study reports. We would not provide case report forms for ongoing studies for which there are no available study reports. Exceptions are noted below:**
  - Phase 1 of the Expanded Access Program - ING115502 (investigator INDs, named patient programs outside the US), no case report forms are available [only serious adverse event (SAE) forms are available]**
  - Phase 2 of the Expanded Access Program - ING114916 (Expanded Access/Treatment Protocol) – CRF information is available for SAEs and discontinuations due to dolutegravir related AEs.**

**Does the Agency agree with this approach?**

*FDA response: Please clarify what you mean by “ongoing studies for which there are no available study reports”. We expect at least an interim study report for all the Phase 3 pivotal trials that will be submitted with the NDA. Thus for these studies, there should be CRFs and case narratives available.*

- 2. In general, the submission safety data will include data up to a cut-off date of May 2012 for the majority of studies with exceptions noted below. [Please also note that a Development Safety Update Report (DSUR) with a data cutoff of October 26, 2012 will be submitted in December 2012 for IND 75,382.]**
  - ING111762 (SAILING) 24 week results (cut-off August 17, 2012)**
  - ING116070 [cerebral spinal fluid (CSF) study] Week 2 results (cut-off ~July 2012).**

**Does the Agency agree with this proposal?**

*FDA Response: Yes*

- 3. Does the Agency agree that the safety database of approximately 950 treatment naïve subjects taking DTG for  $\geq 48$  weeks and 350 treatment experienced subjects for  $\geq 24$  weeks is sufficient to support the proposed dosing regimen of DTG 50mg once daily (in combination with other antiretroviral therapy) in integrase inhibitor naïve (INI-N), HIV-1 infected patients?**

*FDA Response: The proposed safety database is sufficient to submit an NDA. However, whether the data supports dosing recommendation is a review issue.*

- 4. Based upon data from studies ING112961 (VIKING) and ING112574 (VIKING-3) described in the Briefing Materials, DTG potentially meets an unmet medical need in INI-resistant (INI-R), highly treatment experienced patient population. Discussions during the July 2010 End of Phase II meeting advised that the safety database of approximately 150 patients taking DTG for  $\geq 24$  weeks was sufficient to support the proposed dosing regimen**

of DTG 50mg twice daily (in combination with other antiretroviral therapy) in INI-R, HIV-1 infected patients.

- Given acceptable efficacy, safety and virologic outcomes, and data on ~140 subjects receiving DTG 50mg twice daily for  $\geq 24$  weeks is included in the submission, does the Agency agree that the safety database is adequate to support dosing recommendations in INI-R, HIV-1 infected patients?

*FDA Response: The number of subjects exposed to 50 mg BID is sufficient to submit an NDA. However, whether the data is adequate to support dosing recommendation is a review issue.*

5. Based on the data presented on the clinical studies to date, the Sponsor believes that the small, non-progressive increases in creatinine are due to likely benign blockade of the renal transporter OCT2 and thus routine safety monitoring of HIV-infected patients is adequate with DTG.

**Does the Agency agree with this interpretation?**

*FDA Response: We cannot provide agreement to your interpretation without first independently reviewing the data.*

6. Two cases of hepatic enzyme elevation from ING113086 (SPRING-2) were reported as IND Safety Reports (INDSRs). However, the overall rates of liver enzyme elevations were comparable for DTG and RAL in ING113086, and were lower for DTG+ABC/3TC versus TDF/FTC/EFV in ING114467 (SINGLE). No additional cases of ALT elevations with concomitant bilirubin elevations, without an alternative explanation or cause (e.g., hepatitis B or C, concomitant medication), have been reported from ING113086. The Sponsor concludes that the risk for serious hepatotoxicity may be comparable to other marketed antiretrovirals and that routine safety monitoring in patients receiving DTG is adequate. **Does the Agency agree with this interpretation?**

*FDA Response: This is a review issue. The FDA is using an internal review tool (eDISH: Evaluation of Drug Induced Serious Hepatotoxicity) for the analysis and visualization of clinical trial data for the assessment of potential drug-induced liver injury. This tool will assist clinical reviewers in safety analyses associated with the planned NDA submissions. In order to use this tool, we recommend that you provide datasets using the format specified in the attached eDISH-Data Requirements document. Please pay special attention to how clinical narratives should be organized and submitted. If you have any technical questions, please contact Ted Guo of Office of Biostatistics at [ted.guo@fda.hhs.gov](mailto:ted.guo@fda.hhs.gov).*

7. The NDA submission will provide an assessment of the benefit versus risk of treatment with DTG. The program safety analysis plan (PSAP) and a risk management assessment document will be useful in describing the overall risk benefit assessment, following review of the safety and efficacy data included in the NDA submission. Based on the safety specification described in the Briefing Materials, we believe that product labeling along with routine pharmacovigilance activities provide adequate materials for risk communication and education of patients and health care professionals about the appropriate use of DTG. No additional risk evaluation and mitigation strategies (REMS) are therefore proposed. (Refer to Section 14, Attachment 4.)

**Does the Agency agree that a formal REMS as described in the Agency's September 2009 draft guidance document is not required for DTG?**

*FDA Response: Based on preliminary review, REMS is unlikely to be required. However, final determination will be made once the NDA has been reviewed.*

**Integrated Summary of Safety (ISS)**

8. In the ISS, the studies in integrase inhibitor naïve (INI-N) subjects [ING112276 (SPRING-1), ING113086 (SPRING-2), ING114467 (SINGLE) and ING111762 (SAILING)] will be considered separately to studies in INI-resistant (INI-R) subjects [ING112961 (VIKING) and ING112574 (VIKING-3)] due to the different doses of DTG being administered (i.e., DTG 50mg once daily versus DTG 50mg twice daily) and the different patient populations being studied. Outputs will be summarized by study and treatment arm. A total will be displayed for DTG once daily for the INI-N, antiretroviral (ART)-N population, and DTG twice daily for the INI-R population only.

- All other ongoing studies will be considered separately [ING112578, ING114915 (FLAMINGO), ING116070, ING116529 (VIKING-4), ING115502 (investigator INDs, named patient programs outside the US) and ING114916 (expanded access/treatment protocol)]. Please find below potential mock-ups for the INI-N and INI-R summaries.

INI-N Subjects:

| ART-Naïve Adults                                            |                                                |                                                                |                                                    |                                                              |                                             | ART-Exp Adults                                       |                                                         |                                                |
|-------------------------------------------------------------|------------------------------------------------|----------------------------------------------------------------|----------------------------------------------------|--------------------------------------------------------------|---------------------------------------------|------------------------------------------------------|---------------------------------------------------------|------------------------------------------------|
| ING112276<br>SPRING-1                                       |                                                | ING113086<br>SPRING-2                                          |                                                    | ING114467<br>SINGLE                                          |                                             | TOTAL<br>DTG                                         | ING111762<br>SAILING                                    |                                                |
| DTG<br>50 mg<br>once<br>daily +<br>2 NRTI<br>N=xxx<br>n (%) | EFV<br>600 mg<br>+ 2<br>NRTI<br>N=xxx<br>n (%) | DTG<br>50 mg<br>Once<br>Daily +<br>2<br>NRTI<br>N=xxx<br>n (%) | RAL<br>400 mg<br>BID + 2<br>NRTI<br>N=xxx<br>n (%) | DTG<br>50 mg +<br>ABC/3TC<br>Once<br>Daily<br>N=xxx<br>n (%) | EFV/TDF/FTC<br>Once Daily<br>N=xxx<br>n (%) | 50 mg<br>Once<br>Daily +<br>2 NRTI<br>N=xxx<br>n (%) | DTG<br>50 mg<br>Once<br>Daily +<br>BR<br>N=xxx<br>n (%) | RAL<br>400 mg<br>BID +<br>BR<br>N=xxx<br>n (%) |

Note: subjects on 10mg and 25mg will also be included for ING112276 (SPRING-1).

INI-R Subjects:

| ING112961<br>VIKING                                    |                                                          | ING112574<br>VIKING-3                        | Total                                                 |
|--------------------------------------------------------|----------------------------------------------------------|----------------------------------------------|-------------------------------------------------------|
| Cohort I<br>DTG 50 mg once daily<br>plus OBR<br>(N=27) | Cohort II<br>DTG 50 mg twice daily<br>plus OBR<br>(N=24) | DTG 50 mg twice daily<br>plus OBR<br>(N=xxx) | DTG 50 mg<br>twice daily plus<br>OBR Daily<br>(N=xxx) |

**Does the Agency agree with this proposal?**

*FDA Response: We are in general agreement with your proposal. Please present the safety results for naïve subjects separately from the safety results from the treatment experienced population (i.e. INI naïve, receiving 50 mg QD). These subjects will likely be less healthy than the ARV naïve population.*

*Please clarify if you are planning to pool safety data from the phase 2b trial (SPRING-1) and the phase 3 trials ((SPRING-2, SINGLE).*

9. In addition to safety data described above, the ISS will contain a non-integrated description of SAEs, deaths and pregnancies from all studies for the time period May 2012 through October 26, 2012 (DSUR cut-off). Data will be pulled from the GlaxoSmithKline (GSK) Global Clinical Safety and Pharmacovigilance’s (GCSP) Operating Company Event

**Accession and Notification System (OCEANS) safety database. These data will not have undergone a complete quality assurance check and will be considered preliminary.**

**Does the Agency agree with this proposal?**

*FDA Response: The safety information should contain summary table of events (SAEs, deaths, pregnancies). The SAEs should be summarized by SOC and PT. It is not necessary that the events from the various studies be integrated. If possible, include summary of subjects who withdrew study drug due to AEs.*

## **Safety Update**

**10. Assuming that the DTG NDA will receive a Priority Review status, we propose the following content for a 2 month safety update. The update will be submitted 60 days post NDA submission and will contain the following:**

**a. Listings and a discussion of all AEs leading to withdrawal. These data will be pulled from available data in study databases by the GSK Clinical Statistics department. These data will not have undergone a complete quality assurance review.**

**i. Data provided will be from May 2012 to approximately 4 weeks post NDA submission, with exceptions noted below:**

- 1. ING111762 – from August 1, 2012 to 4 weeks post NDA submission**
- 2. ING116070 - from ~ July 2012 to ~ 4 weeks post NDA submission.**

**ii. Content will include all AEs leading to withdrawal from the following studies ongoing as of May 2012:**

- 1. Phase 1 studies**
- 2. Phase 2 studies: ING112961, ING112276 and ING112578**
- 3. Phase 3 studies: ING113086, ING114467, ING112574, ING111762 and ING116070**
- 4. Phase 2 of the Expanded Access Program (Treatment Protocol) protocol ING114916.**
- 5. Other ongoing ViiV sponsored studies (e.g., ING116529, ING114915).**

**b. Listings and a brief discussion of SAEs, deaths and pregnancies will be provided. Data will be pulled from the GSK GCSP's OCEANS safety database. These data will not have undergone a complete quality assurance review.**

**i. Data provided will be from October 26, 2012 until approximately 4 weeks post submission, with exceptions noted below: (an update/top up to data provided in the original submission)**

- 1. ING111762 – from August 1, 2012 to 4 weeks post NDA submission**
- 2. ING116070 - from ~ July 2012 to ~ 4 weeks post NDA submission**

**ii. Content will include:**

**1. Available data for deaths, SAEs and pregnancies for the following studies:**

- a. Phase 1 studies – any ongoing Phase 1 clinical pharmacology studies**
- b. Phase 2 studies: ING112961, ING112276 and ING112578**
- c. Phase 3 studies: ING113086, ING114467, ING112574, ING111762 and ING116070**
- d. Phase 1 of the expanded access program [investigator INDs and named patient programs (outside the US) (ING115502)]**

- e. Phase 2 of the Expanded Access Program (Treatment Protocol) (ING114916)
- f. Other ongoing ViiV sponsored studies (e.g., ING116529, ING114915).

Does the Agency agree with this approach?

*FDA Response: Your proposal is acceptable.*

**Clinical Efficacy**

**Integrated Summary of Efficacy (ISE)**

11. The following proposals apply to the ISE:

- a. No pooling of data from the Phase 2 pilot study in integrase inhibitor resistant (INI-R) subjects (ING112961) and the Phase 3 study in INI-R subjects (ING112574). The timing of the primary endpoint for these 2 studies was different: Day 11 was used for ING112961 and Day 8 was used for ING112574. In addition the number of subjects in ING112961 was relatively small compared to the number of subjects in ING112574; therefore, ING112574 would dominate the results if the data were pooled.
  - In addition, subjects in ING112574 could be eligible for the study with historical integrase resistance, where subjects had evidence for current raltegravir resistance as a requirement for entry in ING112961.
  - The analysis used for the primary endpoint differed in the 2 studies: Time to Loss of Virologic Response (TLOVR) was used for ING112961 and Snapshot was used for ING112574.
  - A once daily (QD) regimen of dolutegravir (DTG) was used in Cohort I of ING112961; a twice daily (BID) regimen of DTG was used in Cohort II.

Does the Agency agree with this proposal?

*FDA Response: We agree with your proposal to not pool the VIKING and VIKING-3 50 mg BID cohorts. However, resistance and safety data from these studies should be pooled.*

- b. The studies (ING112961 and ING112574) will be reported separately. Please find below a potential mockup for the proportion HIV-1 RNA <50 copies/mL (c/mL) table.

| Visit    | ING112961 (VIKING)                                  | ING112574 (VIKING-3)                    |
|----------|-----------------------------------------------------|-----------------------------------------|
|          | TLOVR                                               | Snapshot                                |
|          | Cohort II<br>DTG 50 mg twice daily<br>N=24<br>n (%) | DTG 50 mg twice daily<br>N=xxx<br>n (%) |
| Baseline | xx (xx%)                                            | xx (xx%)                                |
| Week 4   | xx (xx%)                                            | xx (xx%)                                |
| Week 12  | xx (xx%)                                            | xx (xx%)                                |

Does the Agency agree with this proposal?

*FDA Response: Please present the Snapshot results for VIKING instead of TLOVR.*

- c. No pooling of data from the Phase 2 study in therapy naïve subjects (ING112276) and the Phase 3 studies in therapy naïve subjects (ING113086 and ING114467) will be done. ING112276 used three different doses (10mg, 25mg and 50mg) of DTG with approximately 50 subjects per arm. The study designs for each study were different. Finally, the primary endpoint analyses were also different (TLOVR was used for ING112276; Snapshot was used for ING113086 and ING114467). (Previous correspondence from DAVP dated December 27, 2011 indicated this proposal was acceptable.)

**Does the Agency agree with this proposal?**

*FDA Response: Yes*

- d. As a reminder, the following items have been previously agreed with review team members (FDA correspondence of December 27, 2011).
- No pooling of data from the Phase 3 studies in INI-N subjects (ING113086 and ING114467) will be done. ING113086 compared DTG 50mg QD versus RAL 400mg BID, both arms received investigator-selected dual nucleoside reverse transcriptase inhibitors (NRTIs). In contrast, ING114467 compared two regimens: DTG plus ABC/3TC versus TDF/FTC/EFV.

**Does the Agency agree with this proposal?**

*FDA Response: Yes*

- e. Data from study ING111762 (therapy experienced, INI-N subjects) will not be pooled with data from other studies, as the patient population (treatment-experienced subjects failing current therapy) and background therapies (up to two drugs from any class other than INIs) are different than the treatment naïve studies. Additionally, background therapy varied from subject to subject based on ability to construct and active background regimen whereas it was more tightly defined in the therapy naïve studies.

**Does the Agency agree with this proposal?**

*FDA Response: Yes*

12. Assuming that data from ING111762 (SAILING) are supportive, does the Agency agree that the Phase III studies [ING113086, ING114467, ING111762 and ING112574] along with supporting studies and information as described in the Briefing Materials provide an adequate basis to support the indication of DTG use in HIV-1 infected adults (treatment naïve, treatment experienced/ INI-N and treatment experienced/INI-R)? (Please note that ING111762 results will be available in October 2012 at which time the data will be shared with the Agency.)

- Does the Agency agree with proposed dose of DTG 50mg QD in treatment-naïve and treatment-experienced/INI-N subjects?
- Does the Agency agree with the proposed dose of DTG 50mg BID in treatment experienced/INI-R subjects?

*FDA Response: At the end of phase 2 meeting we agreed with your proposal to evaluate DTG 50 mg QD in treatment-naïve and treatment-experienced/INI-N subjects, and DTG 50 mg BID in treatment experienced/INI-R subjects. As stated previously you have sufficient information to submit an NDA.*

**Clinical study reports to be included in the Submission**

13. The following clinical study reports will be provided with the NDA submission. Please refer to Attachment 8 [proposed submission Table of Contents (TOC)] for complete details. We do not intend to submit individual line listings on a per patient basis (Patient Profiles).

- a. Ongoing studies (e.g., ING114915, ING114916, ING115502, ING116529 and any collaborative studies) will be described through brief summaries.

| Study number or report Phase                                          | Report duration                                                                                                                                                                                                                                     |
|-----------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Phase I clinical pharmacology reports                                 | All completed studies                                                                                                                                                                                                                               |
| Population pharmacokinetic analyses from Phase 2b and Phase 3 studies | Completed analyses                                                                                                                                                                                                                                  |
| ING112276 (SPRING-1)                                                  | 16, 24, 48 and 96 week reports                                                                                                                                                                                                                      |
| ING112961 (VIKING)                                                    | <ul style="list-style-type: none"><li>• Cohort I 24 week report</li><li>• Combined report for Cohort I 72 week results and Cohort II 24 week results</li><li>• Combined report for Cohort I 96 week results and Cohort II 48 week results</li></ul> |
| ING113086 (SPRING-2)                                                  | 48 week results                                                                                                                                                                                                                                     |
| ING114467 (SINGLE)                                                    | 48 week results                                                                                                                                                                                                                                     |
| ING112574 (VIKING-3)                                                  | Day 8 (entire population) and 24 week (n=114) results                                                                                                                                                                                               |
| ING111762 (SAILING)                                                   | 24 week results                                                                                                                                                                                                                                     |
| ING112578 (P1093)                                                     | Cohort I, Stage 1 24 week results (and pharmacokinetic analyses)                                                                                                                                                                                    |
| Study number or report Phase                                          | Report duration                                                                                                                                                                                                                                     |
| ING116070                                                             | 2 week results (synoptic report)                                                                                                                                                                                                                    |

**Does the Agency agree with this approach?**

FDA Response: Yes

**Pediatrics**

14. The NDA submission will contain a full study report (24 weeks) for Cohort I, Stage 1 including pharmacokinetic analyses from ING112578 (P1093) children aged 12 to 18 years. Depending upon study results, the intent is to seek an indication for use of DTG (at a dose of 50mg once daily) for pediatric patients 12 to 18 years of age and weighing >40 kg. Does the Agency agree that this is a reasonable approach?

*FDA Response: Your proposed approach seems reasonable. However, whether an indication will be granted is a review issue.*

15. For the NDA submission, the intent is to request a deferral of pediatric studies in children 4 weeks to <12 years of age. Study ING112578 (P1093), being conducted by IMPAACT, is ongoing. The protocol is currently being amended and includes allowance of enrollment of patients ≥4 weeks of age (currently written to allow enrollment of patients ≥6 weeks of age).

(b) (4)

**Does the Agency agree with our proposal to request a deferral of pediatric studies in children 4 weeks to <12 years of age?**

*FDA response: Yes*

16. For the NDA submission, the intent is to request a waiver of pediatric studies in children <4 weeks of age (neonates). Because the number of neonates diagnosed with HIV-1 infection is

very small and there are too few pediatric subjects to study in this age group with this disease, we feel that a waiver for pediatric studies in this patient population is warranted/justified. Please reference a request for an amendment to the pediatric Written Request submitted August 14, 2012.

Does the Agency agree with this proposal to request a waiver of pediatric studies in children <4 weeks of age (neonates)?

*FDA Response: We defer our response at this time. A response will be provided to you prior to your NDA submission.*

**Microbiology/Virology**

17. We plan to submit virology datasets as specified in the template updated March 2012 for the following Phase 2b/3 studies in ART-experienced/INI-N subjects and in INI-R subjects:

- ING112961(VIKING) - ART-experienced, INI-R
- ING112574 (VIKING-3) - ART-experienced, INI-R
- ING111762 (SAILING) - ART-experienced, INI-N.

Treatment emergent mutations in studies of treatment naïve population: ING112276 (SPRING-1), ING113086 (SPRING-2), and ING114467 (SINGLE), are less common. In addition, the patient population in these studies did not receive any previous HIV-1 antiretroviral agents. We feel that resistant datasets are not necessary for these studies.

Does Agency agree with the studies to be included in the resistant datasets for submission?

*FDA Response: In addition to the VIKING, VIKING-3 and SAILING virology datasets, resistance data from the treatment-naïve treatment failures of the SPRING-1, SPRING-2 AND SINGLE studies should be included with the NDA. Genotypic and phenotypic data from the treatment failures in the treatment-naïve studies should be submitted in resistant datasets according to the specified template (The most current Guidance for Submitting HIV Resistance Data (June 12, 2012) is attached).*

18. In the resistant datasets, for PRO/RT mutations, only major mutations will be included, as described by IAS-USA (see Table below). For integrase inhibitor (INI) mutations, only resistant mutations described in the table below will be included.

|         |                                                                                                                                                                                                                                                                                                     |
|---------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| NRTIs*  | M41L, A62V, K65R, D67N, 69 insert, K70E/R, L74V, V75I, F77L, Y115F, F116Y, Q151M, M184V/I, L210W, T215Y/F, K219Q/E                                                                                                                                                                                  |
| NNRTIs* | L100I, K101E/P, K103N/S, V106A/M, V108I, E138/A/G/K/Q/R, V179L, Y181C/I/V, Y188C/L/H, G190S/A, H221Y, P225H, F227C, M230I/L,                                                                                                                                                                        |
| PIs*    | D30N,V32I , M46I/L, I47A/V, G48V, I50V/L, I54M/L, Q58E, T74P, L76V, V82A/T/F/L/S, N83D, I84V, N88S,L90M                                                                                                                                                                                             |
| INIs**  | H51Y, <b>T66A, T66I, T66K</b> , L68V, L68I, L74I, L74M, L74R, <b>E92Q, E92V</b> , Q95K, T97A, G118R, E138A, E138K, E138T, G140A, G140C, G140S, <b>Y143C, Y143H, Y143R</b> , P145S, S147G, <b>Q148H, Q148K, Q148R</b> , V151I, V151L, S153F, S153Y, <b>N155H</b> , E157Q, G163R, G163K, G193E, R263K |

\* IAS-USA website: [http://www.iasusa.org/resistance\\_mutations/index.html](http://www.iasusa.org/resistance_mutations/index.html) (2011)

\*\* may be modified in case of additional substantive data availability. INI substitutions listed above were defined from <http://hivdb6.stanford.edu> with a score of >45. All other mutations were detected during INI clinical investigation or during in vitro studies with DTG. The mutations bolded are referred to as ‘primary’ mutations, and those unbolded are referred to as ‘secondary’ mutations for this reporting and analysis.

**Does the Agency agree with the type of mutations to be included in the resistant dataset for submission?**

*FDA Response: No, we do not agree. All positions in the RT, IN and PR should be included in the datasets – not just major substitution sites.*

**19. Does the Agency agree that a sufficient number of subjects with clinically relevant RAL and elvitegravir (EVG) resistance mutations were enrolled in ING112574 to support labeling of DTG to treat a broad population of integrase inhibitor-resistant viruses?**

*FDA Response: In the Viking 3 study, approximately 30% had no primary INSTI substitutions detected at Baseline and a baseline RAL susceptibility of <1.5-fold change. This is a small study with 114 subjects in the ITT population and 35 protocol-defined virologic failures of which 31 had genotypic/phenotypic data. It will be difficult to make broad interpretations of the data when subdividing these small numbers further by baseline substitutions. Therefore, it will be a review issue to determine if a sufficient number of subjects had clinically relevant RAL and EVG resistance substitutions to support labeling of DTG to treat a broad population of integrase strand transfer inhibitor-resistant viruses.*

**20. Based on data from ING112961 and ING112574, the Sponsor proposes to describe responses to DTG in labeling by baseline IN genotype for the INI-resistant patient population.**

**Does the Agency agree with this approach?**

*FDA Response: Yes, in general we agree, but reserve the right to modify this criterion depending on the review of the data. Please do analyses by individual baseline INSTI substitutions, specific combinations (most common) of INSTI substitutions, number of baseline INSTI substitutions, and baseline phenotype. Provide a justification for the analyses included in the label.*

### **Clinical Pharmacology**

**21. An absolute bioavailability study with DTG has not been conducted as an intravenous formulation is not available. However, clinical pharmacology studies have established the predictable nature and low to moderate variability of the systemic exposure. In addition, the metabolic profile has been well characterized and the attributes of high permeability and low systemic clearance result in a low likelihood of presystemic interactions contributing to higher variability. Thus the Sponsor believes that the current information is sufficient to describe the pharmacokinetic profile of DTG; the NDA submission will not contain a human absolute bioavailability study.**

**Does the Agency agree that the NDA can be filed and approved without data on absolute bioavailability of dolutegravir?**

*FDA Response: Yes this is acceptable.*

22. Does the Agency agree with the proposed boundaries of clinically relevant DTG exposures based on the results of ING112276 (SPRING-1), pharmacokinetic/pharmacodynamic (PK/PD) analyses, and safety data described in the Briefing Materials?
23. Does the Agency agree with our recommendations for dosing DTG with inducers of UGT1A1 and CYP3A4, specifically efavirenz, tipranavir/ritonavir and fosamprenavir/ritonavir?
24. Does the Agency agree with our recommendations for co-administration of DTG and etravirine with atazanavir/r?
25. Does the Agency agree with our recommendations for dosing DTG with inhibitors of UGT1A1 and CYP3A4?
26. Does the Agency agree with our recommendations for dosing HIV-infected subjects with mild to moderate hepatic impairment based on PK data obtained in ING113097?
27. Does the Agency agree with our recommendations for dosing HIV-infected subjects with mild, moderate and severe renal impairment based on PK data obtained in ING113125?
28. Does the Agency agree with our recommendation that DTG can be given with food without dose adjustment of DTG and without restriction of food contents?
29. Pharmacokinetic data have been generated in pediatrics in age decreasing cohorts in the IMPAACT study ING112578 (P1093) (described in the briefing document). Are the 24 week PK and safety data from study ING112578 (P1093) sufficient to support an indication for children ages 12-18 years old and weighing  $\geq 40$  kg in the initial prescribing information?

**Study Populations:**

30. Does the Agency agree that sufficient numbers of women (n~245) and African American/African heritage (n~200) subjects received DTG in the Phase 3 INI-naïve (ING113086, ING114467, ING111762) studies to make an assessment of dosing recommendations in these demographic groups?
31. Does the Agency agree that sufficient numbers of subjects with hepatitis B and C received DTG in the phase 3 clinical program to assess safety and provide dosing recommendations for DTG in these co-infected groups?  
*FDA Response: Questions #22 to #29 (Clinical Pharmacology) and #30 to # 31 (Study Populations) will be review issues that will be evaluated as part of the dolutegravir New Drug Application. Population PK and exposure-response safety/efficacy analyses that are submitted with your application should include relevant evaluations for each of these proposed questions.*

**Summary of Biopharmaceutic Studies**

32. Module 2.7.1 – Summary of Biopharmaceutic Studies and Associated Analytical Methods for dolutegravir in humans, there are no plans to provide a Biopharm Review Aid.

**Is it acceptable to the Agency that a Biopharm Review Aid is not provided?**

*FDA Response: It is not clear to the agency what specific contents would be included in a Biopharm Review Aid. Please clarify this issue.*

**33. Module 2.7.1 – Summary of Biopharmaceutical Studies and Associated Analytical Methods for dolutegravir in humans.**

- a. For Appendix Table 4 (exemplified below – not all studies included) – we propose to present the Bioanalytical Methods Summary in three columns:**
  - i. a listing of all validation reports (hyperlinked to the individual report) supporting the submission starting with dolutegravir in plasma then for additional matrices and followed with additional analytes,**
  - ii. a listing of studies supported by each validation report, and**
  - iii. a brief description of the method and validation parameters for each report.**
  
- b. For Appendix Table 5 (exemplified below) – Between-run Accuracy and Precision Quality Control Samples - we propose to present 5 columns that list:**
  - i. all studies for which dolutegravir or other analytes were measured in support of this submission beginning with the biopharmaceutical studies,**
  - ii. the total number of QC values for each concentration within a study,**
  - iii. the overall study precision range,**
  - iv. the overall study percent bias range, and**
  - v. a listing of the document number for the individual bioanalytical results report, which could be hyperlinked, to provide the reader with the study specific bioanalytical results.**

*FDA Response:*

*A) In addition to the information that is already displayed in Table 4, in order to ensure that all the method validation reports and bioanalytical reports have been submitted in the eCTD, Table 4 should also specifically state the title and report number of the validation report as displayed in 5.3.1.4. For methods that involve analysis of plasma samples, please also specify the anticoagulant that the method was validated in. Also, please provide a brief description for each method to aid the clinical pharmacology in identifying and tracking changes in either the method or in the bioanalytical laboratory conducting the analysis (e.g. this is the original method validated by XYZ laboratories, the method is a partial validation by JMZ laboratories of the original method validated by XYZ laboratories). For method validations where no new stability experiments were conducted, please specifically provide the cross reference to the method validation(s) under which the relevant stability experiments were conducted and state whether the same analytical method was used.*

*A table should also be provided that provides the location of the bioanalytical reports in the eCTD. An example of a table for the bioanalytical reports is provided below. Bioanalytical reports should be provided as standalone documents in the eCTD and should not be provided as attachments to the clinical trial reports. Submission of these materials in this manner will assist reviewers in locating and evaluating all the method validation reports and bioanalytical reports that are submitted with the NDA as part of the filing review and the NDA review.*

**Example of a table for bioanalytical reports**

| Analyte                                                                                                                                                                          | Bioanalytical Report Number                                        | Clinical Trial Number | Method Validation Report Number | Biological Matrix | Anticoagulant (if applicable) | Description of clinical trial                     |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------|-----------------------|---------------------------------|-------------------|-------------------------------|---------------------------------------------------|
| XZY                                                                                                                                                                              | <b>IHD001BR-01 (located in 5.3.1.4.1 for the XYZ001-100 trial)</b> | XYZ001-100            | <b>XYZ001MVR-01</b>             | Plasma            | Sodium Heparin                | Single dosing trial using a isohydraline solution |
| <p><b>Bold text:</b> A hyperlink should be provided to the location of the method validation report or amendments (e.g., Module 5.3.1.4) or the bioanalytical study reports.</p> |                                                                    |                       |                                 |                   |                               |                                                   |

*Complete method validation reports and bioanalytical reports should be submitted for dolutegravir as well as for any analytes that were analyzed in drug-drug interaction trials. At the time of NDA submission, the required stability data, including long term stability data, for dolutegravir as well as for any analytes that were analyzed in drug-drug interaction trials should also be submitted that cover the necessary duration of stability (see B below). If the required stability data, including long term stability data, are not available at the time of NDA submission, the pharmacokinetic data will not be included in the proposed dolutegravir U.S prescribing information.*

- B) Lastly, the clinical pharmacology team requests a more comprehensive summary of bioanalytical information for each bioanalytical report as listed below. This information should be provided as a MS Word document.
1. Please provide a summary of the relevant method validation and bioanalysis items listed (a-w) below.
    - a. Bioanalysis summary for trial (list trial number).
    - b. Title of corresponding method validation report(s) and relevant report number(s).
    - c. Title of corresponding bioanalytical report and relevant report number(s).
    - d. Analyte(s).
    - e. Biological matrix (e.g. plasma, urine)
    - f. Methodology/Platform.
    - g. Duration (Month/Date/Year) from time sample was first drawn to date of last sample analysis (including ISR) for the trial.
    - h. For plasma samples, anticoagulant used for:
      - i. Method validation.
      - ii. Collecting blood samples in the trial.
    - i. Temperature subject samples were stored at the trial site.
    - j. Temperature subject samples were stored at satellite facility (if applicable).
    - k. Temperature subject samples were stored at the bioanalytical laboratory.
    - l. Temperature(s) freeze/thaw stability experiments were conducted (see footnote 1 below).
    - m. Number of validated freeze/thaw cycles for the analyte(s).
      - i. specify the duration (e.g. number of hours) of freezing and thawing for each cycle
    - n. Hyperlink to freeze thaw stability data for the analyte(s) [or attach the data].

- o. *Temperature(s) long term stability experiments were conducted (see footnote 1 below).*
- p. *Duration of validated long term stability for the analyte(s).*
- q. *Hyperlink to long term stability data for the analyte(s) [or attach the data].*
- r. *Total number of analytical runs.*
- s. *Number of analytical runs passed.*
- t. *Number of analytical runs that failed.*
  - i. *Please include reasons for the run failure and corrective actions taken, if any*
- u. *In analyzing subject samples, were all reference standards and stock solutions for the analyte(s) and internal standard and the calibration curve standards and QC samples for the analyte(s) prepared and used prior to the expiration date(s) or within the established stability period?*
  - i. *List the expiration dates for each reference standard-if more than one lot of a reference standard was used, please specify which lots were used for specific analytical runs for the respective trial.*
  - ii. *If runs were analyzed using expired reference standard, please provide the specific date the stock solutions were prepared and the date the stock solutions were used to prepare the calibration curve standards and QC samples used for the runs. Please also provide the following information: a) provide a hyperlink to the stock solution stability data for the analyte(s) [or attach the data] and b) specify the storage temperatures for the stock solutions, calibration curve standards and QC samples.*
- v. *ISR (if performed):*
  - i. *Percentage of samples reanalyzed (out of the total number of subject samples)*
  - ii. *Did 2/3 of the ISR samples meet the acceptance criteria?*
- w. *Relevant comments, if any (including issues in shipping samples)*

<sup>1</sup> *if the temperatures that the freeze thaw stability and long term stability experiments were conducted do not match the storage temperature(s) throughout the life cycle of the samples, please provide a rationale to support the acceptability of the reported concentration data in plasma or other biological matrix.*

**Appendix Table 4 Bioanalytical Methods Summary**

| Validation Report                                                                                                                                                 | Clinical Studies Supported                                                                                                                                                                             | Method Description and Performance                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p><b>Dolutegravir Human Plasma</b></p> <p>RD2007/01425/0<br/>0<br/>Issued: 15 Jan 2008</p> <p>Supplemental Report<br/>2011N112541_00<br/>Issued: 07 Feb 2011</p> | <p>ING111207<br/>ING111322<br/>ING111405<br/>ING111521<br/>ING111602<br/>ING111603<br/>ING111604<br/>ING111853<br/>ING111854<br/>ING111856<br/>ING112276<br/>ING112934<br/>ING112941<br/>ING112961</p> | <p>Dolutegravir is extracted from 25 µL human plasma by protein precipitation using acetonitrile containing [<sup>2</sup>H<sub>7</sub><sup>15</sup>N]-dolutegravir as an internal standard. Extracts are analyzed by HPLC-MS/MS using a Turbo IonSpray interface and multiple reaction monitoring.</p> <p>Lower limit of quantification (LLQ): 5 ng/mL<br/>Validated Range: 5 to 5000 ng/mL<br/>QC levels: 5, 20, 400, 4000 and 5000 ng/mL<br/>Within-run Precision (%CV): ≤ 14.4%<br/>Between-run Precision (%CV): ≤ 3.8%<br/>Accuracy (% Bias): -8.4 ≤ bias ≤ -0.7%<br/>Stability in Human Plasma: 3 freeze-thaw cycles from -30°C<br/>at least 16 months at -30°C<br/>at least 24 hours at ambient temperature<br/>Processed Extract Stability: At least 3 days at ambient temperature</p> |

| Validation Report                                                                                                                                | Clinical Studies Supported                                                                                         | Method Description and Performance                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|--------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p><b>Dolutegravir Human Plasma</b></p> <p>RD2010/00175/00 Issued: 27 Oct 2010</p> <p>Supplemental Report 2011N112542_00 Issued: 07 Feb 2011</p> | <p>ING113068<br/>ING113096<br/>ING113097<br/>ING113125<br/>ING113674<br/>ING114005<br/>ING114819<br/>ING116070</p> | <p>Dolutegravir is extracted from 25 µL human plasma by protein precipitation using acetonitrile containing [<sup>2</sup>H<sub>7</sub> <sup>15</sup>N]-dolutegravir as an internal standard. Extracts are analyzed by HPLC-MS/MS using a Turbo IonSpray interface and multiple reaction monitoring.</p> <p>Lower limit of quantification (LLQ): 20 ng/mL<br/>Validated Range: 20 to 20000 ng/mL<br/>QC levels: 20, 60, 1600, 16000 and 20000 ng/mL<br/>Within-run Precision (%CV): ≤ 4.5%<br/>Between-run Precision (%CV): ≤ 2.7%<br/>Accuracy (% Bias): -0.3 ≤ bias ≤ 9.6%<br/>Stability in Human Plasma: 3 freeze-thaw cycles from -20°C<br/>at least 265 days at -20°C<br/>at least 24 hours at ambient temperature<br/>Processed Extract Stability: At least 3 days at ambient temperature</p> |

**Appendix Table 5 Between-run Accuracy and Precision of Quality Control (QC) Samples**

| Study (Analyte) | Total number of QC samples                                        | Overall precision (%CV range) | Accuracy (%bias range) | Report Number   |
|-----------------|-------------------------------------------------------------------|-------------------------------|------------------------|-----------------|
| ING111322 (DTG) | (n=60 at each of 3 levels)                                        | 4.2% to 7.0%                  | -1.8% to -0.8%         | 2011N126878_00  |
| ING113068 (DTG) | (n=26 at each of 3 levels)                                        | 3.0% to 5.3%                  | 5.3% to 6.9%           | 2011N112681_00  |
| ING113674 (DTG) | (n=44 at each of 3 levels)                                        | 3.5% to 4.4%                  | 0.2% to 3.9%           | RD2010/00558/00 |
| ING112941 (DTG) | (n=24 at each of 3 levels)                                        | 2.6% to 4.0%                  | -4.7% to 1.0%          | RD2009/01353/00 |
| ING111207 (DTG) | (n=44 at each of 3 levels)                                        | 3.0% to 6.7%                  | -3.5% to 0.0%          | 2011N126877_00  |
| ING111405 (DTG) | (n=22 at each of 3 levels)                                        | 2.5% to 4.3%                  | -1.1% to 5.2%          | RD2009/00885/00 |
| ING111521 (DTG) | (n=36 at each of 3 levels)                                        | 2.3% to 3.7%                  | -0.9% to 1.1%          | 2011N126879_00  |
| ING111602 (DTG) | (n=32 at 20 and 400 ng/mL, and n=31 at 4000 ng/mL)                | 3.5% to 5.4%                  | -2.5% to -1.7%         | 2011N126880_00  |
| ING111603 (DTG) | (n=12 at each of 3 levels)                                        | 1.7% to 4.0%                  | 0.5% to 4.0%           | 2011N126881_00  |
| ING111604 (DTG) | (n=12 at each of 3 levels)                                        | 2.0% to 4.1%                  | -1.5% to 1.8%          | 2011N126882_00  |
| ING111762 (DTG) | on going                                                          |                               |                        | 2011N117340_00  |
| ING111853 (DTG) | (n=4 at each of 3 levels)                                         | 2.0% to 5.1%                  | 10.3% to 17.1%         | RD2009/00551/00 |
| ING111854 (DTG) | (n=20 at each of 3 levels)                                        | 3.1% to 7.1%                  | -8.2% to -3.5%         | RD2009/00809/00 |
| ING111855 (DTG) | on going                                                          |                               |                        |                 |
| ING111856 (DTG) | (n=34 at each of 3 levels)                                        | 2.5% to 3.2%                  | -6.4% to 4.2%          | RD2010/00015/00 |
| ING112276 (DTG) | (n=46 at 20, 400, and 4000 ng/mL, n=12 at 6000 ng/mL Dilution QC) | 3.3% to 4.5%                  | -7.5% to -0.1%         | RD2010/00559/00 |

Does the Agency agree with this proposal?

34. It is our understanding that summaries of virology / microbiology data from in vitro and in vivo studies (reports typically located in m4.2.1.1) should be included with the information in m2.7.2.4 (Special Studies) and the corresponding reports should be submitted in m5.3.5.4 (Other Study Reports) rather than in m4.2.1.1 (in accordance with guidance from ICH M4 Q&A, Nov, 2003). In module 2.6.2, we propose to not include any summary information for virology reports (primary pharmacology). Instead, we will include a cross-reference to the appropriate clinical sections. Does the Agency agree with the proposed content of module 4 (m4.2.1.1) being moved to module 5 (m5.3.5.4) as described in the draft TOC (Attachment 1)?

*FDA Response: We agree.*

#### Nonclinical

35. A comprehensive package of nonclinical studies were conducted with DTG in accordance with the ICH M3 (R) Guidelines and will be available at the time of submission [details provided in draft Table of Contents (August 2012); Attachment 8]. In addition, results of two carcinogenicity studies (rat and mouse) will be included in the initial NDA.

Does the Division agree that no further nonclinical studies are required to support the registration of DTG tablets?

*FDA Response: Yes, pending review of final study reports.*

#### Statistics

36. We plan to submit SAS datasets and SAS programs to the Agency as outlined in the March 8, 2011 DAVP response to January 26, 2011 Company questions. We plan to submit SAS datasets and SAS programs for the ISS and for the following studies:

- Pivotal Phase 2b studies:
  - ING112961(VIKING) 96 week dataset for Cohort I and 48 week dataset for Cohort II (TLOVR endpoint) (includes the primary efficacy endpoint for Cohort I Weeks 24, 72, and 96 and Cohort II Weeks 24 and 48)
  - ING112276 (SPRING-1) 96 week dataset (TLOVR endpoint) (includes the primary efficacy endpoint for Weeks 16, 24, 48, and 96)
  - ING112578 IMPAACT/P1093) 24 week dataset for Cohort I, Stage 1 (Snapshot endpoint).
- Pivotal Phase 3 studies (Snapshot endpoint for all):
  - ING113086 (SPRING-2) 48 week dataset
  - ING114467 (SINGLE) 48 week dataset
  - ING112574 (VIKING-3) 24 week dataset [includes the primary efficacy endpoint for Day 8 and Week 24]
  - ING111762 (SAILING) 24 week dataset.

Is this acceptable to the Agency?

*FDA Response: We would prefer that the snapshot endpoint be computed for all studies, regardless of what the initial protocol specified. Otherwise this is acceptable.*

Can the Agency please provide an updated specification for the HIV efficacy datasets discussed in the 8 March 2011 memorandum (Attachment 4)?

37. We do not intend to submit SAS datasets and SAS programs to the Agency for clinical pharmacology studies. We will submit SAS datasets and programs for the population pharmacokinetic analyses (POP PK).

Is this acceptable to the Agency?

*FDA Response: No, SAS datasets and SAS programs for the clinical pharmacology studies should be submitted as part of the New Drug Application. These datasets will enable the agency to independently analyze the pharmacokinetic data from the clinical pharmacology trials.*

38. Study ING112578 IMPAACT/P1093 will have SAS datasets, SAS programs, annotated CRFs and a codebook of variables/codes as a basis for the case report tabulation (CRT) package. IMPAACT does not have the capability to link to the CRFs.

Is this acceptable to the Agency?

*FDA response: yes*

39. Studies (b) (4) are collaborative studies conducted by external investigators and supported by ViiV; these studies are being conducted under an investigator held IND/INDs. Our plans are to provide abbreviated study reports for these studies. We do not plan to provide datasets for these studies.

(b) (4)

Is this acceptable to the Agency?

*FDA Response: yes*

#### Regulatory: Prescription Drug User Fee Act V (PDUFA V)

40. It is our understanding that PDUFA V will likely be reauthorized and in place by October 1, 2012, prior to submission of the dolutegravir (DTG) New Drug Application (NDA). From materials available in the fall of 2011, it appeared PDUFA V allowed for a pilot program for new chemical entity (NCE) NDAs (and original BLAs) which would initiate the review period after the 60 day filing review period. More recently available information indicates that this program under PDUFA V would apply to all NCE NDAs and original BLAs. In order to assist with our planning, we have the following questions:

- a. Is the Agency aware if the PDUFA V program initiating the review after the 60-day filing review period is proposed as a pilot program or if it will apply to all NCE NDAs?

- b. **If PDUFA V contains a pilot program with respect to initiation of the review clock after the 60-day filing review period, does the Agency anticipate that the DTG NDA will be included in the pilot program?**
- c. **If the PDUFA V reauthorization requires that the review clock begin after the 60-day filing review period and the DTG NDA receives a Priority Review classification, would the Agency share its views regarding the expected review period for the NDA? We are working to a six (6) month review period (60 days plus 4 months).**

*FDA Response: PDUFA V included a review model for NME NDAs and original BLAs known as "the Program." All NME NDAs and original BLAs received between October 1, 2012 and September 30, 2017 will be reviewed under the Program. Under the program the review period for priority reviews will be 6 months from the filing date, with the filing date being 60 days from the receipt date. The standard review clock will be 10 months from the filing date.*

**General and Administrative Questions:**

**41. Proposal for electronic Common Technical Document (eCTD)**

- **The NDA will be submitted via the Electronic Submissions Gateway in eCTD format according to the June 2008 - Final Guidance for Industry: Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications.**
- **We commit to submit any amendments (or responses to FDA's requests during the review cycle) with an eCTD backbone file, with the supporting data located at the appropriate level of granularity, appropriate meta-data.**

**Does the Agency agree with the above proposals regarding eCTD submissions?**

*FDA Response: Your proposal is acceptable*

**42. Proposed eCTD Specifications and File Formats – Specifications: The specifications and file formats that we propose to use are as follows:**

- **ICH eCTD Specification version 3.2.2 (2008-07-16)**
- **US FDA eCTD Backbone Files Specification for Module 1 Version 1.3 (2006-12-13)**
- **US FDA Implementation of Study Tagging File Specification 2.6.1**
- **Portable Document Format Specifications (v3.1 / 2012-1-20).**
- **Study Data Specifications (v1.6 2011-06-22)**

**Does the Agency agree with the above proposed eCTD specifications?**

*FDA Response: Your proposal is acceptable; however, the following specifications should also be included:*

- *FDA eCTD Table of Contents Headings and Hierarchy (PDF - 73KB) (updated 7/7/2005)*  
<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissions/Requirements/ElectronicSubmissions/UCM163175.pdf>

- *eCTD Backbone File Specification for Modules 2 through 5 3.2.2 (PDF - 726KB) (updated 7/16/2008)*  
<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissions/Requirements/ElectronicSubmissions/UCM163556.pdf>
- *the updated version of Study Data Specifications (v2.0 2012-07-20)*  
<http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM312964.pdf>

**43. Forty-eight (48) week results for ING113086 and ING114467 and 24 week results for ING111762, ING112574 and ING112578 (Cohort I, Stage I) will be submitted in the New Drug Application (NDA). It is anticipated that traditional approval will be granted for all patient populations (treatment naïve, treatment experienced/INI-N and treatment experienced/INI-R).**

**Does the Agency agree?**

*FDA Response: Yes, if and when the NDA is approved, it will be a traditional approval. Week 96 data for ARV naïve and a minimum of 48 week data for treatment experienced population will be required (as PMR) to be submitted at future date(s).*

**44. Based upon the information provided in Attachment 5 of the Briefing Materials (rationale for priority review), would the Agency share its thoughts regarding the possibility of the dolutegravir NDA submission receiving a Priority review status?**

**Does the Agency agree?**

*FDA Response: We agree there is an unmet medical need for patients with INI-R virus as their effective treatment options are limited. Therefore, your NDA will be considered for a priority review. However, the decision to grant priority review status will be determined at the time of NDA filing.*

**45. Given the safety and efficacy data described for DTG to date and the rationale provided in the Briefing Materials (Attachment 6), we anticipate that an Advisory Committee meeting does not need to be held to discuss the data package.**

**Does the Agency agree?**

*FDA Response: Thank you for providing your rationale for why an Advisory Committee meeting is not needed for this NDA. This is still being discussed with senior management and a determination will be made no later than NDA filing.*

**46. We propose to submit complete documentation to support marketing approval of dolutegravir tablets in the December 2012 NDA. There are no plans at this time to submit application components during the 30 days following the NDA submission.**

*FDA Response: We agree with your plans to submit a complete NDA and do not intend to submit any components during the 30 days following the NDA submission.*

**Additional Comments:**

**Clinical Pharmacology comments**

1. Please provide a table that list the dolutegravir formulation that was administered in each

clinical trial and state which trials used the Phase 3 or the proposed U.S, marketed formulation. In addition, please provide a summary outlining the formulation development of dolutegravir including whether the Phase 3 formulation is the proposed US marketed formulation in the Summary of Biopharmaceutic Studies and Associated Analytical Methods. If the Phase 3 formulation is not the proposed US marketed formulation, please provide information on the differences between the two formulations and the impact of the differences and whether a bioequivalence trial was conducted. For drug-drug interaction trials, for completeness of information, please also list whether the concomitant medication or medications are the U.S. marketed formulation.

2. For in vitro studies evaluating the cytochrome P450 enzyme induction effects of dolutegravir by determining the change in mRNA level, please provide  $R_3$  values for each cytochrome P450 enzyme that was studied or provide the predefined threshold for the increase in mRNA consistent with the recommendations in the February 2012 draft guidance on drug interaction studies.

### **Virology Comments**

3. Given the prevalence of subjects with “blipping” at low-level viral loads, we have been looking at the clinical significance of the viral loads that blip  $>50$  copies/mL but  $<400$  copies/mL. After consultation within our Division, we have decided that, at the present time, those subjects who rebounded to  $>50$  copies/mL but did not exceed 400 copies/mL at or before Week 96 will be excluded (censored) from the virologic failure resistance analysis. Note that this will not affect the efficacy snapshot analysis.

Our current guidance states that “Phenotypic and genotypic resistance testing should be performed on baseline and on-treatment failure samples for patients who demonstrate virologic rebound (defined as a 1  $\log_{10}$  increase in HIV-RNA from nadir value or a confirmed HIV-RNA  $>400$  copies/mL after confirmed suppression to  $<50$  copies/mL). Any changes, including mixtures, in the amino acid coding sequence of the targeted genome region present in on-treatment or follow-up samples, but not in the baseline sample, should be reported as having emerged during therapy.”

Given that the protocols in your proposed NDA submission followed the PDVF criterion: two consecutive HIV-1 RNA values  $\geq 50$  copies/mL HIV-1 RNA on or after Week 24), which mandated withdrawal from the trial (if confirmed before Week 48) and testing for resistance, we request that you submit the virology resistance data for these subjects with the NDA, but understand that in the FDA analysis, these subjects will likely be excluded from the virology resistance analysis.

### **Datasets**

4. General comment regarding xpt datasets

For all datasets, in order to significantly reduce dataset file sizes, the allotted character column length/size for each column should be the maximum length used. Lengths/sizes of columns should not arbitrarily be set to 200. For example, if USUBJID has a maximum length of 18, the USUBJID's column size should be set to 18, not 200. An inclusion of a small amount of padding to column width may be acceptable as long as this doesn't result in significant increases in file size.

5. LB xpt dataset comment

- The size of the LB domain is often quite large and can exceed the reviewers' ability to open the file using standard-issue computers. This size issue can be addressed by splitting the large LB dataset into smaller data sets based on the type of laboratory variable. For example, hematology-related laboratory variables for all subjects within a trial would be entered into a 'lbad01' dataset file; liver-related laboratory variables would be entered into 'lbad02' dataset file; chemistry-related laboratory variables would be entered into a 'lbad03' dataset file; and renal-related laboratory variables would be entered into a 'lbad04' dataset file, etc...
- This would reduce the volume of data entered into one analysis dataset file, allowing the review team to navigate the laboratory datasets more efficiently. Sponsor should submit these smaller files in addition to the larger non-split standard LB domain file. The smaller split files should be submitted in a separate Sub-directory/SPLIT which is clearly documented in addition to the larger non-split standard LB domain file in the CRT directory.

**Content/format of NDA submission modules and TOC**

6. Module 2.7.3. should contain the summary text and M5.3.5.3 should contain all datasets, appendices of supporting tables and figures, etc.,
- Please refer to the Final Guidance for Industry: Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document (PDF - 98KB), located at:-  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf>
7. The NDA will be reviewed utilizing the CDER Clinical Review Template. Details of the template may be found in the Manual of Policies and Procedures (MAPP 6010.3R)  
<http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM236903.pdf>

To facilitate the review, we request you provide analyses, where applicable, that will address the items as described in the document.

## **DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION**

As stated in our June 05, 2012 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic and the date of submission is on or after October 1, 2012, the application will be subject to “The Program” under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission. Discussions and agreements on the content of a complete application will be summarized at the conclusion of the meeting and reflected in FDA’s meeting minutes.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities. Information on PDUFA V and “The Program” is available at <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>.

## **PREA PEDIATRIC STUDY PLAN**

The Food and Drug Administration Safety and Innovation Act of 2012 changes the timeline for submission of a PREA Pediatric Study Plan and includes a timeline for the implementation of these changes. You should review this law and assess if your application will be affected by these changes. If you have any questions, please email the Pediatric Team at [Pedsdrugs@fda.hhs.gov](mailto:Pedsdrugs@fda.hhs.gov).

## **PRESCRIBING INFORMATION**

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

## **ABUSE POTENTIAL ASSESSMENT**

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, “Guidance for Industry Assessment of Abuse Potential of Drugs”, available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

## **MANUFACTURING FACILITIES**

To facilitate our inspectional process, the Office of Manufacturing and Product Quality in CDER's Office of Compliance requests that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

| Site Name | Site Address | Federal<br>Establishment<br>Indicator<br>(FEI) or<br>Registration<br>Number<br>(CFN) | Drug<br>Master<br>File<br>Number<br>(if applicable) | Manufacturing Step(s)<br>or Type of Testing<br>[Establishment function] |
|-----------|--------------|--------------------------------------------------------------------------------------|-----------------------------------------------------|-------------------------------------------------------------------------|
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| 2.        |              |                                                                                      |                                                     |                                                                         |

Corresponding names and titles of onsite contact:

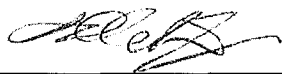
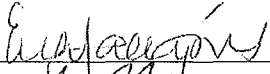
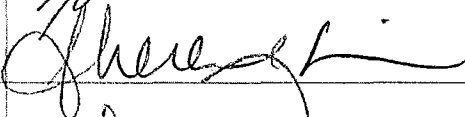
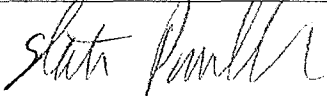
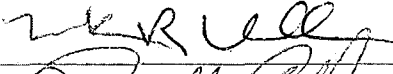
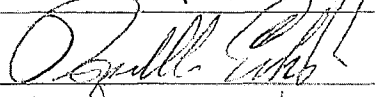
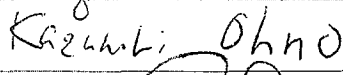
| Site Name | Site Address | Onsite Contact<br>(Person, Title) | Phone and<br>Fax number | Email address |
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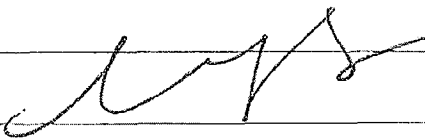
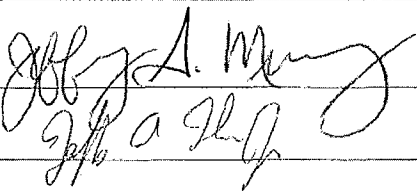
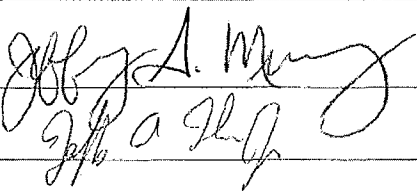
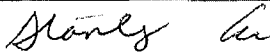
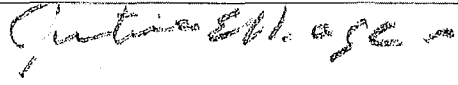
**ViiV/GSK and DAVP MEETING ATTENDEES**

**Date:** 09/20/2012 **Time:** 9:00 am – 10:30 am

**Place:** WO Bldg.22, room 1417

**Firm:** ViiV/GSK Re: IND 75382 pre-NDA meeting

| NAME                                                                            | SIGNATURE                                                                            | REPRESENTING        |
|---------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|---------------------|
| Martha Anne Auld, RPh, Senior Director, Regulatory Affairs (RA)                 |    | GlaxoSmithKline LLC |
| Lloyd D. Curtis, MA MRCP, Medical Director, Signal Evaluation & Risk Management |    | GlaxoSmithKline LLC |
| Ella Jaczynska, Vice President, RA                                              |    | GlaxoSmithKline LLC |
| Jessica Lim, MA, Manager, Clinical Statistics                                   |    | GlaxoSmithKline LLC |
| Sherene Min, MD, Physician Integrase Project Leader                             |    | GlaxoSmithKline LLC |
| W. Garrett Nichols, MD, MS, Project Leader, Vice President                      |    | GlaxoSmithKline LLC |
| Steve Piscitelli, PharmD, Director, Clinical Pharmacology                       |   | GlaxoSmithKline LLC |
| Mark Underwood, PhD, Lead Integrase Virologist                                  |  | GlaxoSmithKline LLC |
| Roger M. Echols, MD, Global Medical Lead                                        |  | Shionogi & Co., Ltd |
| Kazunori Ohno, MPH, RPh, Global Project Manager                                 |  | Shionogi & Co., Ltd |
| James Goodrich, PhD, MD, Vice President, Global Medical Strategy                |  | ViiV Healthcare     |
| Neil Shortman - Vice President, Head of Regulatory                              |  | ViiV Healthcare     |
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| Andrew Yu, PhD, Chemist                                                                        |                                                                                      | DAVP |
| Debra Birnkrant, MD, Director                                                                  |    | DAVP |
| Edward M Cox, MD, MPH, Director, Office of Antimicrobial Products                              |                                                                                      | DAVP |
| Greg Soon, PhD, Statistical Team Lead                                                          |    | DAVP |
| Hanan Ghantous, PhD, DABT, Pharmacology/ Toxicology Team Lead                                  |                                                                                      | DAVP |
| Jeffrey Murray, MD, MPH, Deputy Director                                                       |    | DAVP |
| Jeffrey Florian, PhD, Pharmacometrics Reviewer                                                 |    | DAVP |
| Julian O'Rear, PhD, Virology Team Lead                                                         |                                                                                      | DAVP |
| Karen Winestock, Chief, Project Management Staff, DAVP                                         |    | DAVP |
| Kendall Marcus, MD, Associate Director of Safety                                               |                                                                                      | DAVP |
| Kim Struble, PharmD, Medical Team Lead                                                         |                                                                                      | DAVP |
| Lisa Naeger, PhD, Virology Reviewer                                                            |  | DAVP |
| Mammah Sia Borbor, MS, MBA, Regulatory Project Manager                                         |                                                                                      | DAVP |
| Mark Seaton, PhD, Pharmacology/Toxicology Reviewer, DAVP                                       |                                                                                      | DAVP |
| Sohail Mosaddegh, PharmD, Regulatory Project Manager                                           |                                                                                      | DAVP |
| Stanley Au, PharmD, Clinical Pharmacology Reviewer                                             |  | DAVP |
| Stephen Miller, PhD, CMC-Lead, ONDQA                                                           |                                                                                      | DAVP |
| Thomas Hammerstrom, PhD, Biometrics Reviewer                                                   |                                                                                      | DAVP |
| Yodit Belew, MD, Clinical Reviewer                                                             |                                                                                      | DAVP |
| Antoine El Hage, PhD, Office of Scientific Investigations, Office of Compliance                |  | DAVP |
| John Farley, M.D., M.P.H., Deputy Director, OAP                                                |                                                                                      | DAVP |
| David Roeder, M.S., Associate Director for Regulatory Affairs                                  |                                                                                      | DAVP |
| Mary Dempsey, Risk Management Coordinator, Division Of Risk Management, Office Of Surveillance |                                                                                      | DAVP |

|                                                                                                                      |                      |      |
|----------------------------------------------------------------------------------------------------------------------|----------------------|------|
| And Epidemiology (OSE)                                                                                               |                      |      |
| Denise DiGiulio, R.Ph., Compliance Officer, Division of Manufacturing and Product Quality, CDER Office of Compliance |                      | DAVP |
| Morgan Walker Pharm.D, MBA, safety Evaluator, Division of Medication Error Prevention and Analysis, OSE              | <i>Morgan Walker</i> | DAVP |
| Susan Thompson, MD, Team Leader, Office of Scientific Investigations, Office of Compliance                           |                      | DAVP |
| Jeannie David, PharmD, Project Manager, Office of New Drug Quality Assessment                                        |                      | DAVP |
| Amalia Himaya, Acting Chief, Project Management Staff, DAVP                                                          |                      | DAVP |
| <i>Yizhang Ph.D. Pharmacometrics Fellow</i>                                                                          | <i>Yizhang</i>       | DAVP |
| <i>Wendy Carter DD MD</i>                                                                                            | <i>Wendy Carter</i>  | DAVP |
| <i>Shirley Seo</i>                                                                                                   | <i>Shirley Seo</i>   | DAVP |
| <i>Cham Mullick MD</i>                                                                                               | <i>Cham Mullick</i>  | DAVP |
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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JEFFREY S MURRAY  
10/12/2012



IND 75382

**MEETING MINUTES**

ViiV Healthcare Company  
Attention: Sherry L. Watson  
Director, CMC Pre-Approval, Global Regulatory Affairs  
5 Moore Drive  
Research Triangle Park, NC 27709

Dear Ms. Watson:

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

We also refer to the telecon between representatives of your firm and the FDA on July 10, 2012. The purpose of this Chemistry, Manufacturing and Controls **(CMC) Type B pre-NDA** meeting was to discuss the proposed content for the CMC section of the planned NDA.

A copy of the official minutes of the telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Jeannie David, Regulatory Project Manager, at (301) 796-4247.

Sincerely,

*{See appended electronic signature page}*

Rapti D. Madurawe, Ph.D.  
Branch Chief, Branch V  
Division of New Drug Quality Assessment II  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes  
GSK Documents

## MEMORANDUM OF MEETING MINUTES

**Meeting Type:** Type B  
**Meeting Category:** CMC pre-NDA

**Meeting Date and Time:** July 10, 2012, 1:30 - 2:30 PM EST  
**Meeting Location:** Teleconference

**Application Number:** IND 75382  
**Product Name:** (dolutegravir sodium) Tablets  
**Indication:** Treatment of HIV-1 Infection  
**Sponsor/Applicant Name:** ViiV Healthcare Company (ViiV)/GlaxoSmithKline (GSK)

**Meeting Chair:** Stephen P. Miller, Ph.D.  
**Meeting Recorder:** Jeannie David, M.S.

### FDA ATTENDEES

Fuqiang Liu, Ph.D., Review Chemist, Office of New Drug Quality Assessment (ONDQA)  
Andrew Yu, Ph.D., Review Chemist, ONDQA  
Houda Mahayni, Ph.D., Biopharmaceutics Reviewer, ONDQA  
Tapash Ghosh, Ph.D., Acting Biopharmaceutics Lead, ONDQA  
Stanley Au, Ph.D., Clinical Pharmacology Reviewer, Office of Clinical Pharmacology  
Yodit Belew, M.D., Medical Officer, Division of Antiviral Products (DAVP)  
Hanan Ghantous, Ph.D., Pharmacology/Toxicology Team Leader, DAVP  
Stephen P. Miller, Ph.D., CMC Lead, ONDQA  
Jeannie David, M.S., Regulatory Health Project Manager, ONDQA

### SPONSOR ATTENDEES

Neil Shortman, Vice President, Regulatory, ViiV Healthcare  
Naoko Fujioka, Ph.D., CMC Leader, Shionogi  
Hideyuki Kitamura, Ph.D., Section Head, Chemical Development, Shionogi  
Hiroyuki Suzuki, Chemical Development, Shionogi  
Yoshihisa Goto, Analytical Development, Shionogi  
Kumiko Miyamura, Analytical Development, Shionogi  
Susan Witham, Vice President, Regulatory Affairs, Shionogi  
John Hughes, MPD Leader, Medicine and Process Delivery, GSK  
Frank Demartin, Sr. Scientific Investigator, API Chemistry and Analysis, GSK  
Matthew Sharp, Ph.D., SM Director, API Chemistry and Analysis, GSK  
Ken Campbell, SM Director, Formulation, Process and Analysis, GSK  
Catherine Barnes, Ph.D., Sr. Scientist, Particle Generation, Control & Engineering, GSK  
Catherine Legg, Sr. Investigator, Formulation, Process and Analysis, GSK  
Manish Gupta, SM Manager, PD Management US, GSK  
Richie Everitt, Sr. Investigator, Shared Project Technical Services, PACE, GSK  
Sherry Watson, Director, CMC New Submissions, GSK  
Heather Peterson, Project Manager, CMC New Submissions, GSK  
Steve Piscitelli, Director, Clinical Development, GSK

## 1.0 BACKGROUND

ViiV Healthcare Company/GlaxoSmithKline requested a Type B pre-NDA Chemistry, Manufacturing and Controls (CMC) meeting request, dated May 2, 2012, to review the proposed content for the CMC section of the planned NDA, for (dolutegravir sodium) Tablets, GSK1349572 HIV Integrase Inhibitor. Previously, a Type B End-of-Phase 2 CMC meeting was held on July 26, 2010. For the CMC pre-NDA meeting, ViiV/GSK submitted a CMC briefing package, dated and received on June 8, 2012. The FDA provided preliminary comments to questions in the CMC pre-NDA briefing package on July 6, 2012. GSK provided their responses to the FDA preliminary comments in an email with documents on July 9, 2012 (attached). The teleconference proceeded as scheduled on July 10, 2012. GSK also provided a post-meeting update to Table 3, page 27 of the briefing package by email, per request from the Agency during the meeting. The FDA preliminary responses and official meeting minutes are provided below.

## 2. DISCUSSION

### Drug Substance

#### Question 1:

**There is no risk of genotoxic impurities in the drug substance. Starting material and intermediate specifications, historical batch data, and spiking and purging studies ensure that no potential genotoxic impurities are present in dolutegravir sodium drug substance. Genotoxic impurities will be controlled by specifications of the intermediates or by control of the manufacturing process.**

#### FDA Summary Response Regarding Control of Genotoxic Impurities:

*We agree that the information summarized in this meeting package shows that genotoxic impurities are being assessed and controlled in an appropriate manner for Phase III development. However, the approach to control that is suitable for commercial manufacture will need to be determined during the NDA review, based on the information available at that time for each of these compounds.*

*We believe that the NDA information could be strengthened by inclusion of the following:*

*a) Spiking studies [REDACTED] (b) (4)*

*b) Additional analytical results [REDACTED] (b) (4) on batches made by the intended commercial manufacturing process*

*c) Clarification in the NDA of whether verification of control [REDACTED] (b) (4) for the commercial process.*

#### Meeting Discussion:

GSK discussed the comments provided in their email dated July 9, 2012, attached. There was discussion [REDACTED] (b) (4) in a) above, as well as design of spiking studies. FDA

suggested that the spiking studies could apply to all potential genotoxic impurities throughout the manufacturing process.

FDA requested as a post-meeting action that GSK update Table 3, p. 27 in the briefing package with a footnote (b) (4) and that some batches were at commercial scale. GSK agreed to provide this by email, which the FDA will document as a Post-Meeting Comment and attachment to these minutes. (See also, FDA Additional Points for Discussion, item 1.)

GSK clarified that at least 5 of the batches presented in the briefing package were produced with the intended commercial process at commercial scale. This information was not available at the time the FDA preliminary responses were sent.

(b) (4)

(b) (4) Does the Agency agree with the above proposed control strategy (b) (4) ?

**FDA Response**

No, FDA does not agree (b) (4)  
*The risk for this impurity is not fully understood with the information available at this stage of development.*

**Meeting Discussion:**

GSK explained (b) (4)

FDA suggested that GSK could provide a statement with the scientific arguments to the NDA. FDA stated that the final decision on the proposed control strategy will be part of the NDA review.

(b) (4)

(b) (4) Does the Agency agree with the above proposed control strategy (b) (4) ?

**FDA Response**

No, FDA does not agree [REDACTED] (b) (4).

[REDACTED] The risk for this impurity is not fully understood  
with the information available at this stage of development. [REDACTED] (b) (4)

[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]

**Meeting Discussion:**

GSK stated that they have additional studies [REDACTED] (b) (4)

[REDACTED]

[REDACTED] FDA encouraged GSK to include this information in the NDA.

FDA stated that the final decision on the proposed control strategy will be part of the  
NDA review.

[REDACTED] (b) (4)

(b) (4) Does the Agency agree with the above proposed control strategy [REDACTED] (b) (4)  
[REDACTED] ?

**FDA Response**

No, FDA does not agree [REDACTED] (b) (4)

[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]

**Meeting Discussion:**

See meeting discussion in 1b).

[REDACTED] (b) (4)

(b) (4) Does the Agency agree with the above proposed control strategy (b) (4)?

**FDA Response**

No, FDA does not agree (b) (4).  
The risk for this impurity is not fully understood with the information available at this stage of development.

**Meeting Discussion:**

GSK explained (b) (4)  
FDA suggested that GSK (b) (4)  
mention in the NDA how close the batches are to the intended commercial process at the commercial scale.

(b) (4)

(b) (4) Does the Agency agree with the above proposed control strategy (b) (4)?

**FDA Response**

No, FDA does not agree (b) (4)

**Meeting Discussion:**

See meeting discussion in 1b).

**Question 2:**

Based on an understanding of the synthesis, and in consideration of regulatory guidance, the proposed specification tests and specification limits provide appropriate control of the quality of dolutegravir sodium. Does the Agency agree with the proposed specification tests?

**FDA Response**

*The Agency agrees with the proposed specification tests at this point, pending your response to the comments on Question 1. However, final specification will be a review issue based on the totality of the NDA submission.*

**Meeting Discussion:**

There was no meeting discussion on this topic.

**Drug Product:**

**Question 3:**

**Based on an understanding of the manufacturing of Dolutegravir Tablets, 50 mg and in consideration of regulatory guidance, the proposed specification tests and specification limits provide appropriate control of the quality of Dolutegravir Tablets, 50 mg. Does the Agency agree with the proposed specification tests?**

**FDA Response**

*The Agency agrees with the proposed specification tests and specification limits for the product at this point. However, final specification will be a review issue based on the totality of the CMC information in the NDA submission. For tests not proposed for the specification, please include the justification, with any necessary data, in the NDA submission.*

**Meeting Discussion:**

There was no meeting discussion on this topic.

**Question 4:**

**A discriminating dissolution method has been developed. Does the Agency agree that the proposed dissolution method and specification limit is appropriate for release of commercial product and stability testing?**

**FDA Response**

*The dissolution method seems acceptable. However, the dissolution acceptance criterion of  $Q = (b)(4)$  at  $(b)(4)$  is not supported by dissolution data generated on the clinical and stability lots. The data submitted from the thirteen lots (clinical and stability) support an acceptance criterion of  $(b)(4)$  at 20 minutes:  $(b)(4)$*

*This recommendation is not considered final, as FDA will not make final decision on the acceptance criterion at the IND stage.*

**Meeting Discussion:**

GSK requested re-consideration of  $Q = (b)(4)$  at  $(b)(4)$  based on two sets of data. The first set is the thirteen lots (clinical and stability). The second set is based on Biopharmaceutics data (GastroPlus and the Developability Classification System (DCS)),

and two pharmacokinetics (PK) studies. These data demonstrated that Dolutegravir rate of absorption is not impacted by the rate of dissolution or solubility. Furthermore, the two PK studies showed that plasma exposures of Dolutegravir were similar (b) (4). Therefore, our proposed acceptance criterion has a clinical relevance.

FDA clarified that the FDA guidance referenced in the handout attached to GSK email dated July 9, 2012 is not an official FDA guidance. See GSK email attached. Also, the referenced DCS has limitations and assumptions meant to address product development rather than it being used a regulatory classification system. Additionally, it is a clinical decision to conclude that the two PK studies provide plasma exposures of dolutegravir that are similar (b) (4).

[REDACTED]

GSK acknowledged that the referenced FDA guidance is a presentation delivered at the American Society of Pharmaceutical Scientists (AAPS) Annual meeting and the DCS has its limitations, and accepted FDA's original response to Question 4.

**Question 5:**

**Does the Agency agree that based on the stability data presented, statistical analysis would be considered unnecessary, and therefore a statistician's package is not required within R.3?**

**FDA Response**

*A statistical analysis is not required, but is often helpful. Please note that we require 12 months of long term stability at the time of NDA submission.*

**Meeting Discussion:**

There was no meeting discussion on this topic.

**General/Regional:**

**Question 6:**

**Does the Agency agree with the proposal for submission of batch records in the NDA?**

**FDA Response**

Yes.

**Meeting Discussion:**

There was no meeting discussion on this topic.

**FDA Additional Points for Discussion**

1) Please clarify [REDACTED] <sup>(b) (4)</sup> This information may be useful for putting the current analytical results (Table 3, p 27) in context.

**Meeting Discussion:**

See GSK email dated July 9, 2012, attached. GSK further clarified that [REDACTED] <sup>(b) (4)</sup> will be part of the commercial process.

2) The current formulation contains 52.6 mg dolutegravir sodium which is equivalent to 50 mg of the free acid. The USP recommends are that the labeled strength be expressed in terms of the parent acid or base for drug products formulated with a salt unless justified otherwise as described in USP<1121>. In consideration of this USP policy which becomes effective May 1, 2013, we would anticipate that the product would be named Trademark (dolutegravir) Tablets, with a note on the container labels and prescribing information that is similar to, 'each tablet contains dolutegravir sodium equivalent to 50 mg of dolutegravir.'

**Meeting Discussion:**

See GSK email dated July 9, 2012, attached. There was no meeting discussion on this topic.

**2.0 ADDITIONAL MEETING DISCUSSION**

1) GSK stated that they plan to submit the NDA in mid- to late December.

2) GSK agreed to provide in the NDA a discussion [REDACTED] <sup>(b) (4)</sup>

**3.0 POST-MEETING COMMENTS**

On July 18, 2012, GSK provided by email an update to Table 3, page 27 of the briefing package, per FDA request (see Question 1, Meeting Discussion of FDA Summary Response). The revised table from the July 18, 2012, email is attached below.

**4.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION**

All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application

Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

#### **4.0 ISSUES REQUIRING FURTHER DISCUSSION**

There were no issues requiring further discussion.

#### **5.0 ACTION ITEMS**

There are no action items beyond those captured in the discussion above.

#### **6.0 ATTACHMENTS AND HANDOUTS**

**From:** Sherry Watson  
**To:** David, Jeannie C  
**Cc:** Heather Peterson; Cuff, Althea  
**Subject:** RE: IND 75,382 Dolutegravir Tablets - upcoming pre-NDA meeting  
**Date:** Monday, July 09, 2012 2:02:56 PM  
**Attachments:** Pre-NDA Dissolution Discussion.pptx  
572\_crystallization\_steps.doc

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Jeannie,

Thank you for providing the FDA preliminary feedback. This information was very helpful to us. For the teleconference tomorrow, we would like to only further discuss responses to questions 1 (sub-bullets a-e and general point a) regarding the spiking studies) and 4. We do not need to further discuss the other questions. We are also providing information to address some of the comments that FDA raised in the response.

#### Question 1

For general point b), All analytical batch data on genotoxin levels provided in Table 3 of the briefing document represent intermediates manufactured at R&D and commercial sites and are representative of the commercial process and commercial scale. Furthermore, at least 5 of these batches were manufactured by the actual commercial process at commercial scale. All analytical methods were validated.

For general point c) A Change Management process is in place (b) (4)

(b) (4) All planned changes will be reviewed and the potential impact (b) (4) determined prior to commencement of the change via a documented risk assessment process. This includes verification of genotoxin control using the ppm-level methods. This confirmation will be included in the NDA.

#### Question 4

GSK want to thank FDA for providing comment on our dissolution method and specification. This is extremely useful at this stage of development and it is appreciated.

As is noted in the dissolution development report (appendix to the Pre-NDA Briefing Document) we have proposed a dissolution specification based on clinical and stability batches as well as consideration of pharmacokinetic data from two PK studies. Our intent was to follow FDA guidance (AAPS Annual Meeting, New Orleans, La, November 18, 2010\*) in linking the setting of the dissolution specification with in vivo data to ensure clinical relevance. In consideration of the PK data GSK would like to better understand FDA's recommendation for a Q= (b) (4) at (b) (4) (b) (4)

*\*Two slides (see attached) have been provided to illustrate how the FDA proposal for setting clinically relevant dissolution specifications has been applied to Dolutegravir Tablets, 50 mg. The Dolutegravir information is as previously provided in the briefing document and is presented alongside the FDA slides for ease of review.*

#### FDA Additional Points for Discussion

1) Please clarify (b) (4) This information may be useful for putting the current analytical results (Table 3, p 27) in context.

A table which outlines the (b) (4) details (b) (4) is provided (see attached). This table should provide further details for putting the current analytical results in Table 3, page 27 in context.

2). FDA's comments on labelling text will be considered for the NDA submission.

In addition, we acknowledge FDA's comment regarding PDUFA V. Information on the manufacturing sites will also be included in the NDA as requested.

Best regards,  
Sherry

**From:** David, Jeannie C [mailto:Jeannie.David@fda.hhs.gov]  
**Sent:** Friday, July 06, 2012 4:16 PM  
**To:** Sherry Watson  
**Cc:** Heather Peterson; Cuff, Althea  
**Subject:** RE: IND 75,382 Dolutegravir Tablets - upcoming pre-NDA meeting

Dear Sherry,

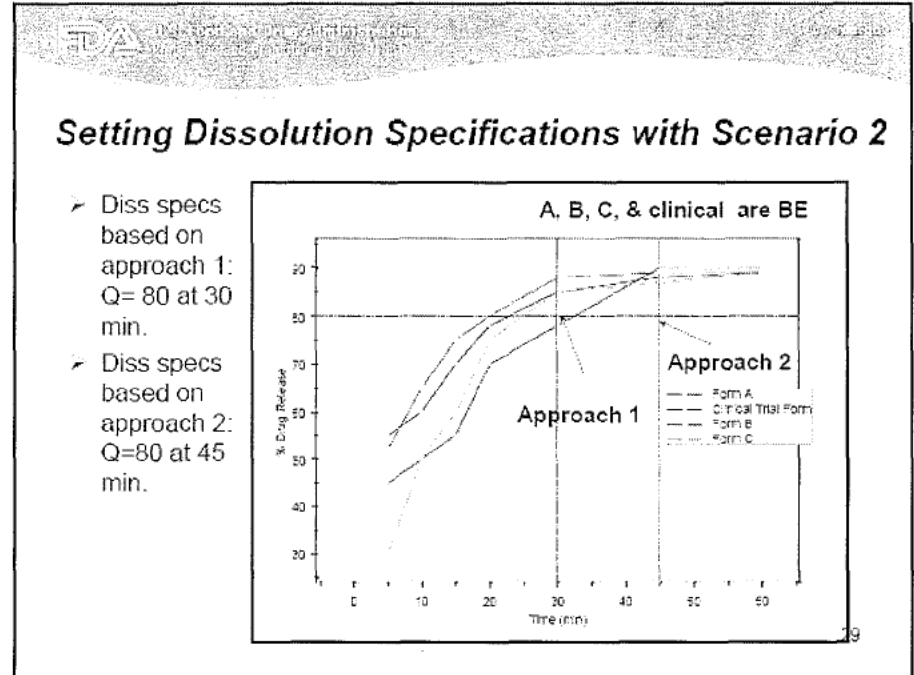
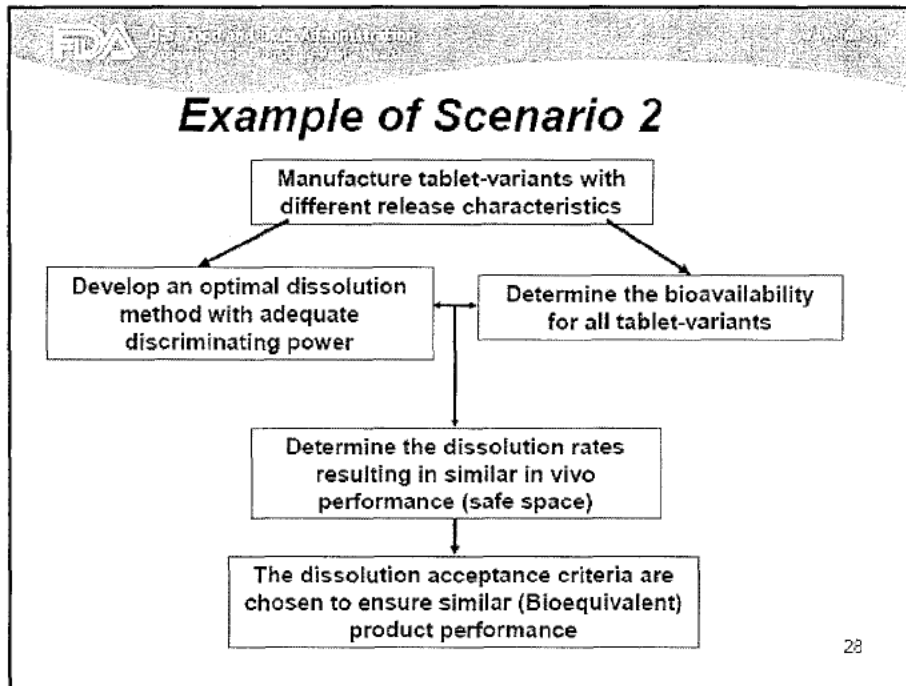
Please find attached are the FDA Preliminary Responses in preparation for our CMC pre-NDA teleconference on July 10, 2012.

After review of the responses, I would appreciate if you can let me know whether or not ViiV/GSK would like to proceed with the scheduled meeting. If the meeting is to proceed, please indicate which questions/responses on which ViiV/GSK would like to focus during our discussions.

If you have any questions, please let me know.

Best regards,

# FDA Guidance



**Reference:** Performance based specifications, AAPS Annual Meeting, New Orleans, LA Nov 2010

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JEANNIE C DAVID  
07/25/2012

STEPHEN MILLER  
07/25/2012  
For R. Madurawe



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

IND 75,382

ViiV Healthcare  
c/o GlaxoSmithKline  
Attention: Martha Anne Moore, R.Ph.  
Senior Director, Global Regulatory Affairs  
Five Moore Drive, P.O. Box 13398  
Research Triangle Park, NC 27709

Dear Ms. Moore:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for GSK1349572.

We also refer to the teleconference between representatives of your firm and the FDA on February 11, 2011. The purpose of the meeting was to establish agreement with the FDA on the study design, sample size, and duration of follow-up for draft protocol ING112574, a Phase 3 protocol evaluating the safety and efficacy of GSK1349572 given as 50 mg twice daily as part of a treatment regimen in HIV-1 infected, antiretroviral therapy (ART)-experienced adults with raltegravir (RAL) or elvitegravir (ELV) resistance.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Amalia Himaya, Regulatory Project Manager, at 301-796-3391 or the Division's main number at 301-796-1500.

Sincerely,

*{See appended electronic signature page}*

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

Enclosures - Meeting Minutes  
Viiv's Slides



**FOOD AND DRUG ADMINISTRATION**  
**CENTER FOR DRUG EVALUATION AND RESEARCH**

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**MEMORANDUM OF MEETING MINUTES**

**MEETING DATE:** February 11, 2011  
**TIME:** 1:20 PM-1:45 PM EST  
**MEETING TYPE:** Type B  
**MEETING CATEGORY:** Pre Phase 3  
**APPLICATION:** IND 75,382  
**DRUG NAME:** GSK1349572  
**INDICATION:** Treatment of HIV-1 infection  
**SPONSOR NAME:** ViiV Healthcare  
**MEETING CHAIR:** Kimberly Struble, Pharm.D.  
**MEETING RECORDER:** Amalia Himaya

**FDA ATTENDEES:**

1. Debra Birnkrant, M.D., Division Director, Division of Antiviral Products (DAVP)
2. Jeffrey Murray, M.D., M.P.H., Deputy Director, Division of Antiviral Products (DAVP)
3. Kimberly Struble, Pharm.D., Medical Team Leader, DAVP
4. Yodit Belew, M.D., Medical Officer, DAVP
5. Mark Seaton, Ph.D., Pharmacology/Toxicology Reviewer, DAVP
6. Julian O'Rear, Ph.D., Virology Team Leader, DAVP
7. Karen Winestock, Chief Project Management Staff, DAVP
8. Amalia Himaya, Regulatory Project Manager, DAVP
9. Stanley Au, Pharm.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology 4 (DCP4)
10. Kevin Krudys, Ph.D., Pharmacometrics Reviewer, Division of Pharmacometrics
11. Fraser Smith, Ph.D., Acting Biometrics Team Leader, Division of Biometrics IV (DBIV)
12. Wen Zeng, Ph.D., Biometrics Reviewer, DBIV

**SPONSOR ATTENDEES:**

*GlaxoSmithKline*

1. Mounir Ait-Khaled, Ph.D., Direct, Center for Clinical Study Excellence (CSSE), Operation and Science Lead for ING112574
2. Robert Cuffe, Ph.D., Project Statistician, Infectious Diseases Medicines Development Center (ID MDC)
3. Jenny Huang, M.S., Study Statistician for ING112574
4. Sherene Min, M.D., M.P.H., Physician Project Leader, ID MDC
5. Martha Anne A. Moore, R.Ph., Senior Director, Global Regulatory Affairs
6. W. Garrett Nichols, M.D., M.S., Project Leader, ID MDC
7. Stephen Piscitelli, Pharm.D., Director, Clinical Pharmacology, ID MDC
8. Cindy Vavro, Ph.D., Virologist, ID MDC

9. Jane M. Yeo, Ph.D., Director, ID MDC, Clinical Investigation Leader for ING112574

*Shionogi*

10. Tamio Fujiwara, Ph.D., Project Leader, Pharmaceutical Development Division, Shionogi & Company, Ltd.

11. James Adams, M.S., Director, Regulatory Affairs, Shionogi USA, Inc.

*ViiV Healthcare*

12. James M. Goodrich, M.D., Ph.D., Vice President Global Medical Strategy

13. Neil Shortman, Vice President, Head of Regulatory

**BACKGROUND:**

ViiV Healthcare (ViiV) is developing GSK1349572, an HIV integrase inhibitor for the treatment of HIV-1 infection in adults and pediatric subjects in combination with other approved antiretroviral agents. The drug development program of GSK1349572 includes the ongoing Phase 2b pilot trial (VIKING, ING112961) in adult subjects with evidence of raltegravir (RAL) genotypic and phenotypic resistance associated with virological failure of a RAL containing regimen. ViiV believes the preliminary results of ING112961 support the design of a Phase 3 trial ING112574, which evaluates GSK1349572 in an adult population with integrase inhibitor (INI)-resistant virus. ViiV is planning to request a priority review for the initial NDA package based on the inclusion of ING112574.

On December 23, 2010, ViiV requested a type B meeting and included the briefing document to discuss draft protocol ING112574. FDA provided preliminary comments on February 4, 2011 and ViiV provided the slides for discussion via electronic mail on February 10, 2011 which includes responses to the FDA preliminary meeting comments. Official submission of the slides was received on February 14, 2011. In the preliminary comments sent to ViiV, FDA agreed with ViiV's proposals in questions 2, 10, 12, and 13. ViiV also accepted FDA's preliminary response to questions 3, 6, and 8. In the meeting, FDA accepted ViiV's response to question 11; therefore, the meeting focused on questions 1, 4, 5, 7, and 9 as well as FDA's additional comments 14a and 14b.

**MEETING OBJECTIVES:**

To establish agreement with the FDA on the study design, sample size, and duration of follow-up for draft protocol ING112574.

**DISCUSSION POINTS:**

ViiV's questions are in bold, FDA's preliminary comments are in italic, and the February 11, 2011 teleconference discussion is in regular font. The slides are enclosed and referenced containing ViiV's response to FDA's preliminary comments.

- 1. Based on the limitations on study designs for treatment-experienced populations, does the Division agree with the current proposed study design to assess the efficacy of GSK1349572 in the treatment experienced, integrase inhibitor-experienced patients?**

FDA response:

*Your study design is generally acceptable but we propose the following:*

- *Include sufficient numbers of subjects who have baseline virus with high-level phenotypic resistance ( $\geq 10$  fold-change in susceptibility to GSK1349572) to assess their response to the 50 mg BID dose.*

Meeting Discussion:

FDA considered the response provided by ViiV (Slide 1) acceptable. FDA again emphasized the label will reflect the data from the studied population. ViiV will try to make every effort to ensure there is a wide range of susceptibilities in baseline isolates, as recommended by FDA.

FDA response:

- *Collect plasma samples at an intermediate time point (e.g., Day 3 or 4) during the functional monotherapy phase for HIV-1 RNA quantification in order to determine whether virologic rebound occurs.*

Meeting Discussion:

FDA disagreed with ViiV's response (Slides 2 and 3). FDA stated the proposed dose may show a 1 log response at Day 4 similar to that observed for the 50 mg dose in the monotherapy data presented in Slide 3 for some INSTI failures while others may have little to no response. This difference may not be detectable at Day 8, as rebound will not be discriminated from a poor response, or, at the end of the study as 8 days of monotherapy may enrich resistant virus sufficiently to affect durability in the responders. Thus, the proposed trial may miss efficacy in some populations that could be identified with baseline genotype or phenotype associated with a strong initial response. FDA stated this was not a hold issue. ViiV will provide to FDA a justification why Day 3 or Day 4 should not be included in the protocol.

- 4. Does the Division agree that acceptable short-term and long-term virologic response data from ~150 subjects (~100 from ING112574 and 47 from ING112961) is sufficient to support an indication for use of GSK1349572 in patients with resistance to existing integrase inhibitors (i.e., raltegravir and elvitegravir)?**

FDA response:

*Please refer to the July 2010 End-of-Phase 2 meeting. The adequacy of the efficacy data from N~120 subjects will depend on the outcome of the study, including genotypic substitutions studied, the effectiveness of the selected dose as well the safety and tolerability of the dose studied. The indication of GSK1349572 will be limited to the type of subjects enrolled (i.e. as it relates to the specific substitutions).*

Meeting Discussion:

FDA considered the response provided by ViiV (Slide 6) acceptable and acknowledged the projected subject enrollment of 150 to 200 subjects in ING112574 [REDACTED] (b) (4)

5. **Does the Division agree that a pre-specified, single, statistical test of a simple hypothesis concerning the activity of GSK1349572 during the functional monotherapy phase is not necessary to support this indication?**

FDA response:

*A pre-specified statistical test at the end of monotherapy phase is necessary to demonstrate the activity of GSK1349572 against HIV virus. Due to the single arm design proposed, we cannot determine if the treatment improvement (if any) at Week 24 is due to the longer duration of GSK1349572 treatment or the new optimized OBR treatment.*

*Please clearly define the primary and secondary efficacy endpoints in the protocol. A formal hypothesis with a stated primary efficacy endpoint is necessary in the design of a protocol before enrolling any subject.*

Meeting Discussion:

FDA considered the response provided by ViiV (Slides 7-9) acceptable. For the estimate of effective size, ViiV clarified it is expected to have at least  $1.5 \log_{10}$  drop during the monotherapy phase with a standard deviation of approximately  $0.5 \log_{10}$ .

7. **Does the Division agree with the inclusion of a patient population combining subjects with evidence of genotypic and/or phenotypic INI resistance at Screening (population sequencing) and those with only evidence of documented historical resistance prior to study?**

FDA response:

*We agree with your proposed plan. In addition, for subjects with evidence of documented historical resistance, we are requesting you confirm the presence and quantify the frequency of INSTI resistance variants as minor species at Baseline and at Day 8 using an ultra-deep nucleotide sequence analysis or similar methodology.*

Meeting Discussion:

ViiV provided a response in Slides 11 and 12. FDA agreed with GSK's plan to conduct deep sequencing of baseline samples. FDA requested GSK to reconsider collecting and analyzing Day 8 samples for deep sequencing as comparison of the Day 8 sequence data with baseline data provide an opportunity to see how different INSTI resistant variants replicate relative to each other in the presence of GSK1349572. Given the potency of GSK1349572, FDA expected few subjects to have sufficient viral load at Day 8 for deep sequence analysis. ViiV responded this analysis would not be included in ING112574 protocol.

9. **With regards to application of the snapshot algorithm to ING112574, does the Division agree that switches for tolerability that take place between Day 8 (background regimen optimization and first on-treatment visit) and Week 4 (i.e. first on-treatment visit subsequent to the BR optimization) prior to investigator knowledge of the HIV-1 RNA not be treated as failures?**

FDA response:

*Please follow the FDA's Snapshot algorithm method which states "OBT substitutions (in class or across class) permitted per protocol for documented toxicity reasons are permitted on or before the first trial visit without penalty."*

*We note your protocol allows a one-time, in-class switching of background regimen for reasons of toxicity. Please note we generally discourage any switching of background regimen. The snapshot algorithm will count such patients as 'failures'. Other types of analyses can be conducted, perhaps allowing cross-class switches in analyses presented in publications, etc. However, for FDA labeling purposes, the more strict snapshot should be used. Therefore, investigators could be informed that not all analyses in their particular subject counting result as failures if they switched and follow-up was maintained. We also encourage you to clarify to investigators that the "failure" categorization is only for snapshot analysis purposes and that patients should not be discontinued from study for protocol allowed switches.*

*We don't believe that there is one "correct" analysis. All analyses only approximate truth. We are only striving for efficiency and consistency across multiple applications. This should not prohibit the presentation of slightly different analyses at meetings or publications. Differences can be described in footnotes.*

Meeting Discussion:

ViiV asked for clarification (Slide 15) and FDA confirmed the Day 8 visit, at which patients optimize their OBT, is treated as "first on-treatment visit" for the purposes of snapshot algorithm.

14. *FDA Additional Comments:*

*Clinical*

- a. *Please include documentation of historical INI-resistance for patients who are enrolled into the study based on historical resistance data. In addition, the information should also be included into the dataset (i.e. xpt) so that the information is available for analysis.*

Meeting Discussion:

ViiV responded (Slide 21) that the details on how the data will be captured will be provided at a later date, but requested clarification on what type of dataset FDA is expecting. ViiV is concerned there will be no uniformity on the presentation of data collected as these will be from a variety of resources. FDA clarified that the dataset (.xpt) should have a column for entering historical resistance information which, after collection, should be translated into a variable and entered into the 'historical resistance' column of the dataset. FDA responded this can be further discussed as the trial progresses when additional information is available such as how many subjects were enrolled based solely on historical resistance data and lacked resistance testing at baseline. The sponsor could send the mock-up data before final submission for review. ViiV plans to discuss further internally how to best present the collated data.

### *Virology*

- b. *Since genotypic and phenotypic resistance tests are limited in detecting resistant subpopulations (genotypic mutations do not always correlate with phenotypic resistance), both tests should be conducted at Screening, and an overall susceptibility score (OSS) should be used to determine the availability of one fully active drug in OBR and to guide the selection of OBR.*

### Meeting Discussion:

ViiV provided a response in Slide 22 and clarified the algorithm for Screening Monogram Net assessment result includes subjects who are genotypic and phenotypic resistant. FDA stated that if a subject's virus is found to be resistant to a particular drug in either the phenotypic or genotypic assay, the subject's virus should be considered resistant to the drug in the overall susceptibility score (OSS). ViiV stated that baseline genotypic and phenotypic data will be provided in the resistance datasets.

### **DECISIONS (AGREEMENTS) REACHED:**

1. The label will only reflect the data from the studied population as ViiV predicts enrollment of sufficient number of subjects with high-level phenotypic resistance will be challenging. (Question 1)
2. Approximately 100 subjects from protocol ING112574 will be included in the initial NDA submission followed by additional enrollment totalling 150 to 200 subjects [REDACTED] (b) (4) [REDACTED] (Question 4)
3. The primary endpoint will be "change from baseline in plasma HIV-1 RNA at Day 8." The proportion of responders at Week 24 would be moved to a secondary endpoint. (Question 5)
4. Although FDA recommended inclusion of deep sequence analysis on Day 8 samples, ViiV will not include this analysis in the protocol. (Question 7)
5. Day 8 visit is treated as "first on-treatment visit" for the purposes of snapshot algorithm analysis. (Question 9)
6. Baseline genotypic and phenotypic data will be provided in the resistance datasets. In addition, if a subject's virus is found to be resistant to a particular drug in either the phenotypic or genotypic assay, the subject's virus will be considered resistant to the drug in the overall susceptibility score (OSS). (FDA Additional Comment 14b)

### **ISSUES REQUIRING FURTHER DISCUSSION:**

1. Whether Day 3 or Day 4 plasma sample collection should be included in the protocol. (Question 1)
2. Presentation of historical resistance dataset from INI-resistance subjects. (FDA Additional Comment 14a)

### **ACTION ITEMS:**

ViiV will provide a justification why Day 3 or Day 4 plasma sample collection should not be included in the protocol. (Question 1)

### **ATTACHMENTS/HANDOUTS:**

Attachment: ViiV's Slide Presentation

# Response to 02/04/11 FDA Comments on Draft Protocol ING112574

## Question 1

### FDA Comment:

Your study design is generally acceptable but we propose the following:

- Include sufficient numbers of subjects who have baseline virus with high level phenotypic resistance ( $\geq 10$  fold-change in susceptibility to GSK1349572) to assess their response to the 50 mg BID dose.

### Company Response:

- The population of INI-resistant patients is different in Cohort I and II of ING112961; it appears there are fewer subjects with high FC. This may be the result of earlier discontinuation of RAL (such that secondary mutations did not accumulate).
- Enrolment in ING112574 will be open to all, but it is difficult to guarantee who will present for enrolment.
- We are specifically limiting the number of subjects with historical resistance.
- We recognize that any description/indication in label will only reflect the population studied.



# Response to 02/04/11 FDA Comments on Draft Protocol ING112574

## Question 1

### FDA Comment:

Your study design is generally acceptable but we propose the following:

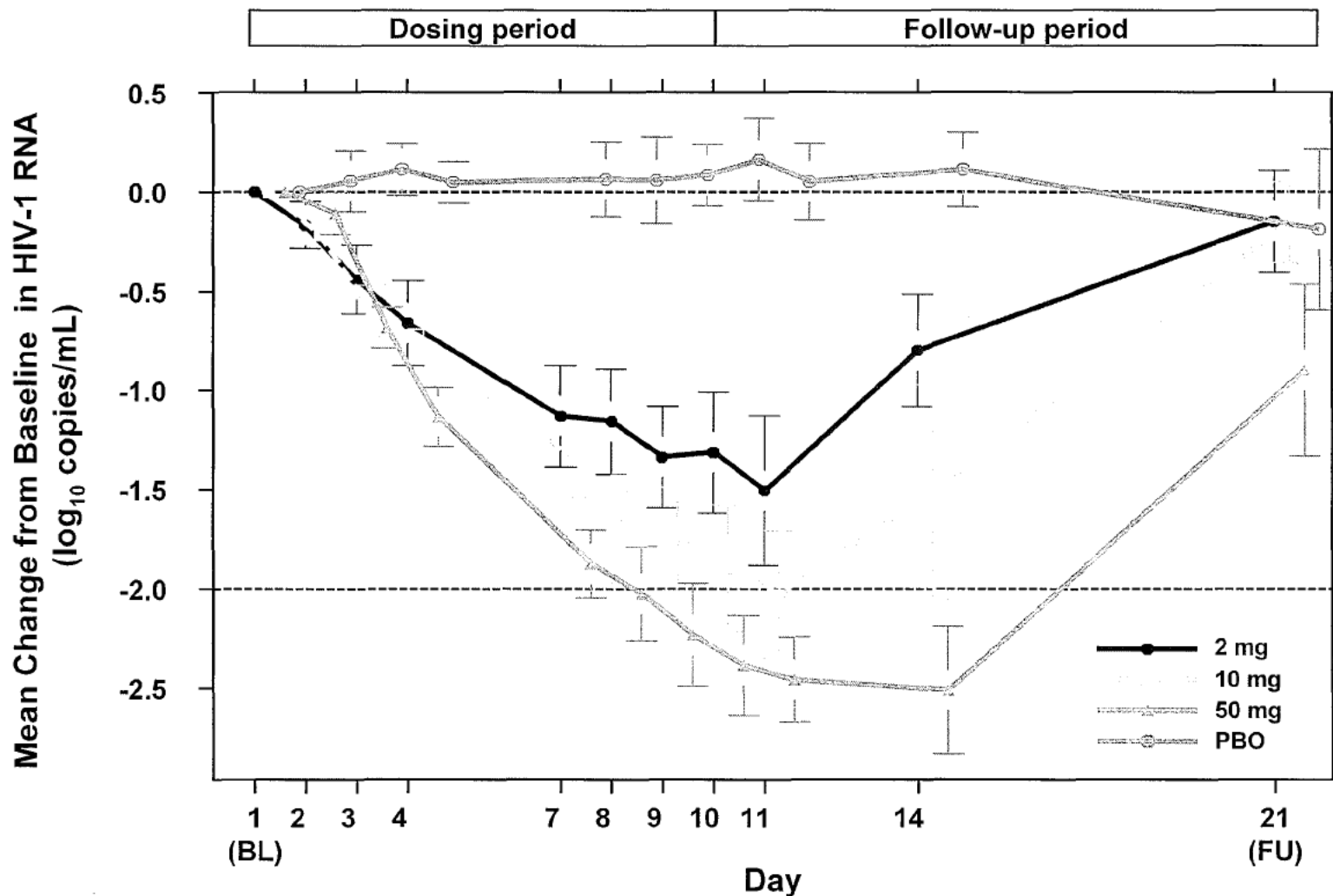
- Collect plasma samples at an intermediate time point (e.g., Day 3 or 4) during the functional monotherapy phase for HIV-1 RNA quantification in order to determine whether virologic rebound occurs.

### Company Response:

- Please clarify how the information at D3-4 would be used
  - We are concerned that variability in HIV-1 RNA PCR may impact early look.
- Even in best circumstances (i.e., POC study), the rate of decline at D3-4 is 0.5 to 1 log decline (see next slide)
- We do not have data from a relevant population with which to compare D3-4 responses.
- In Ph3, requirement for 2 visits in 1 week could hamper recruitment in a challenging population.
- Day 8 is early assessment of virologic response and would determine continuation in the study.



# ING111521 Response Rates: INI naïve population



# Response to 02/04/11 FDA Comments on Draft Protocol ING112574

## Question 2

### FDA Comment:

Based on the PK/PD and virology data, we agree with the 50 mg BID dose selection for ING112574.

Company Response: Thank you.



# Response to 02/04/11 FDA Comments on Draft Protocol ING112574

## Question 3

### FDA Comment:

The initial labeling for GSK134572 will contain descriptive information on the 50 mg BID dosing regimen for treatment experienced (INI-experienced) HIV-infected adult patients. The content shall describe subjects enrolled into the studies (ING2574 and ING1296) in regards to mutations, substitutions, FC susceptibility at baseline and Week 24, as well as antiviral effect of GSK134572 assessed as proportion of subjects with viral load <50 copies/mL at Week 24. The information should also include description of adverse events. We agree a post NDA submission (as a post marketing requirement) is likely necessary for further safety (and possibly efficacy) characterization of the 50 mg BID dosing regimen.

Company Response: Thank you. Please see response to Question 4.



# Response to 02/04/11 FDA Comments on Draft Protocol ING112574

## Question 4

### FDA Comment:

Please refer to the July 2010 End-of-Phase 2 meeting, the adequacy of the efficacy data from N~120 subjects will depend on the outcome of the study, including genotypic substitutions studied, the effectiveness of the selected dose as well the safety and tolerability of the dose studied. The indication of GSK1349572 will be limited to the type of subjects enrolled (i.e. as it relates to the specific substitutions).

### Company Response:

The current intent is to provide data on approximately the first 100 subjects from protocol ING112574 in the initial NDA submission. Recruitment to the protocol will continue; safety and efficacy data will be provided from an additional set of subjects (50-100) at a later time point as a post marketing commitment. We anticipate a total of 150 to 200 subjects from ING112574 [REDACTED] (b) (4)



# Response to 02/04/11 FDA Comments on Draft Protocol ING112574

## Question 5

### **FDA Comment:**

**A pre-specified statistical test at the end of monotherapy phase is necessary to demonstrate the activity of GSK1349572 against HIV virus. Due to the single arm design proposed, we cannot determine if the treatment improvement (if any) at Week 24 is due to the longer duration of GSK1349572 treatment or the new optimized OBR treatment.**

**Please clearly define the primary and secondary efficacy endpoints in the protocol. A formal hypothesis with a stated primary efficacy endpoint is necessary in the design of a protocol before enrolling any subject.**

### **Company Response:**

- We agree that a demonstration of activity is a necessary first step before the characterization of response can take place. Therefore, even though the primary objectives of the protocol will not change, we propose to change the primary endpoint (Section 6.3.2) to be the change from**

# Response to 02/04/11 FDA Comments on Draft Protocol ING112574

## Question 5 continued

### Company Response:

baseline in plasma HIV-1 RNA at Day 8. The proportion of responders at Week 24 would be moved to a secondary endpoint. The prespecified test of the primary endpoint will provide statistical proof for evidence of short-term activity of 572 during the functional monotherapy phase, before exploratory analyses are conducted to characterize (as much as the design allows) the Day 8 and Week 24 antiviral responses, their relationships with baseline (or historical) resistance, and the safety and tolerability profile of GSK1349572 50mg BID.

The key points of the planned test of the primary endpoint are listed below.

# Response to 02/04/11 FDA Comments on Draft Protocol ING112574

## Question 5 continued

### Company Response:

The null hypothesis is that there is no change from baseline in the mean plasma HIV-1 RNA at Day 8. The alternative hypothesis is that the change from baseline in mean plasma HIV-1 RNA at Day 8 is at least  $0.7 \log_{10}$  copies/mL. The test will be a one-sample t-test conducted at the 5% level of significance (two-sided). The analysis will use the full intent-to-treat exposed population. The dataset for the analysis will be a “last observation carried forward, discontinuation equals baseline” dataset.



# Response to 02/04/11 FDA Comments on Draft Protocol ING112574

## Question 6

### **FDA Comment:**

**As per FDA policy and based on the preliminary results from ING112961, inclusion of the data from ING112574 in your initial NDA submission will likely qualify your NDA for a priority review. Data from the Pre-NDA package will provide additional information for determination for priority review. However, we will make the final determinations for priority review in our filing meeting. If your application is fileable and qualifies for a priority review, you will be notified in writing 60 days after receipt of your NDA.**

**Company Response: Thank you.**



# Response to 02/04/11 FDA Comments on Draft Protocol ING112574

## Question 7

### FDA Comment:

**We agree with your proposed plan. In addition, for subjects with evidence of documented historical resistance, we are requesting you confirm the presence and quantify the frequency of INSTI resistance variants as minor species at Baseline and at Day 8 using an ultra-deep nucleotide sequence analysis or similar methodology.**

### Company Response:

**Thank you for your comments. We agree with the your request for minor species analysis at Baseline for subjects with documented historic IN resistance and no INSTI associated mutations at Screen.**

**While we agree that INSTI genotype and phenotype generated at Day 8 for all subjects with sufficient HIV-1 RNA would be useful, we do not feel that minor species analysis at Day 8 would provide additional clinically informative data.**



# Response to 02/04/11 FDA Comments on Draft Protocol ING112574

## Question 7 continued

### Company Response:

Differences between minority species analysis at Day 1 and Day 8 may be more reflective of selective HIV-1 RNA suppression or variability within the assay (as opposed to predicting subsequent virologic response). This information would not benefit in the case of treatment successes and depending on the time of virologic failure may provide little understanding to that clinical event as well.

# Response to 02/04/11 FDA Comments on Draft Protocol ING112574

## Question 8

### FDA Comment:

We agree with your proposed safety monitoring plan. Please provide the Informed Consent Form once available.

### Company Response:

Thank you. We will provide the Informed Consent template as soon as it is available.



# Response to 02/04/11 FDA Comments on Draft Protocol ING112574

## Question 9

### **FDA Comment:**

**Please follow the FDA’s Snapshot algorithm method which states “OBT substitutions (in class or across class) permitted per protocol for documented toxicity reasons are permitted on or before the first trial visit without penalty.”**

**We note your protocol allows a one-time, in-class switching of background regimen for reasons of toxicity. Please note we generally discourage any switching of background regimen. The snapshot algorithm will count such patients as ‘failures’. Other types of analyses can be conducted, perhaps allowing cross-class switches in analyses presented in publications, etc. However, for FDA labeling purposes, the more strict snapshot should be used. Therefore, investigators could be informed that not all analyses in their particular subject counting result as failures if they switched and follow-up was maintained. We also encourage you to clarify to investigators that the “failure” categorization is only for snapshot analysis purposes and that patients should not be discontinued from study for protocol allowed switches.**



# Response to 02/04/11 FDA Comments on Draft Protocol ING112574

## Question 9 continued

### FDA Comment:

We don't believe that there is one "correct" analysis. All analyses only approximate truth. We are only striving for efficiency and consistency across multiple applications. This should not prohibit the presentation of slightly different analyses at meetings or publications. Differences can be described in footnotes.

### Company Response:

We wish to clarify that the Day 8 visit, at which patients optimize their OBT, is to be treated as the "first on-treatment visit" for the purposes of the snapshot algorithm.

# Response to 02/04/11 FDA Comments on Draft Protocol ING112574

## Question 10

### FDA Comment:

We agree with your proposed sparse PK sampling and the population PK analysis plan.

Company Response: Thank you.

# Response to 02/04/11 FDA Comments on Draft Protocol ING112574

## Question 11

### FDA Comment:

We recommend the following modifications for the proposed background ART regimens in Section 5.2 of the protocol:

- In addition to excluding use of TPV/RTV, all subjects with Q148H + 2 Q148 associated mutations should not be administered fosamprenavir (with or without ritonavir) during the optimized phase and fosamprenavir (with or without ritonavir) should also not be allowed during the functional monotherapy phase.
- Subjects receiving antiretroviral medications that potentially induce GSK1349572 metabolism should not be administered additional medications (antiretroviral or non-antiretroviral) that potentially induce GSK1349572 metabolism.

# Response to 02/04/11 FDA Comments on Draft Protocol ING112574

## Question 11 Continued

### FDA Comment:

- The results of the etravirine drug-drug interaction data with LPV/RTV and DRV/RTV in combination with GSK1349572 can not be extrapolated to a complex 3 way drug-drug interaction with nevirapine or efavirenz with LPV/RTV or DRV/RTV + GSK1349572, and there are no human drug-drug interaction data to determine whether the 3 way drug-drug interaction will result in a further lowering of GSK1349572 concentrations. Given the lack of DDI data and the unlikelihood the highly-treatment experienced population eligible for this trial will need efavirenz or nevirapine to form an active regimen, DAVP recommends prohibiting the use of nevirapine and efavirenz in the trial.

# Response to 02/04/11 FDA Comments on Draft Protocol ING112574

## Question 11 Continued

### Company Response:

- Fosamprenavir and fosamprenavir/ritonavir will be added to TPV/RTV as drugs that will be prohibited for subjects with Q148H +  $\geq 2$  Q148 associated mutations. In subjects without Q148H +  $\geq 2$  Q148 associated mutations, these drugs will not be allowed during the monotherapy phase but will be allowed during the optimized phase.
- Additional drugs that induce the metabolism of GSK1349572 are prohibited and are outlined in Section 5.7.2 of the protocol.
- We agree to prohibit the use of nevirapine and efavirenz during the study. We propose that subjects who are receiving these drugs as part of their failing regimen may discontinue them 15 days before the monotherapy phase.

# Response to 02/04/11 FDA Comments on Draft Protocol ING112574

## Question 12

**FDA Comment:**

**We agree with your proposed patient management virologic failure criteria.**

**Company Response: Thank you.**

## Question 13

**FDA Comment:**

**We agree with your proposed resistance testing plan.**

**Company Response: Thank you.**

# Response to 02/04/11 FDA Comments on Draft Protocol ING112574

## FDA Addition Comments 14

### Clinical

- a. Please include documentation of historical INI-resistance for patients who are enrolled into the study based on historical resistance data. In addition, the information should also be included into the dataset (i.e. xpt) so that the information is available for analysis.

### Company Response:

**We will respond at a later date with details on how this data will be captured.**

# Response to 02/04/11 FDA Comments on Draft Protocol ING112574

## FDA Addition Comments 14

### Virology

- b. Since genotypic and phenotypic resistance tests are limited in detecting resistant subpopulations (genotypic mutations do not always correlate with phenotypic resistance), both tests should be conducted at Screening, and an overall susceptibility score (OSS) should be used to determine the availability of one fully active drug in OBR and to guide the selection of OBR.

### Company Response:

The protocol inclusion criterion #6 will be modified to address this request as follows:

- Subject must be able to receive at least one fully active drug in the OBR from Day 8 onwards based on the subject's Screening Monogram Net assessment result.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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DEBRA B BIRNKRANT  
03/03/2011



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Silver Spring, MD 20993

IND 75,382

ViiV Healthcare  
c/o GlaxoSmithKline  
Attention: Martha Anne Moore, R.Ph.  
Senior Director, Global Regulatory Affairs  
P.O. Box 13398  
Five Moore Drive  
Research Triangle Park, NC 27709

Dear Ms. Moore:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for GSK 1349572.

We also refer to the teleconference between representatives of your firm and the FDA on September 8, 2010. The purpose of the meeting was to establish agreement with the FDA on your study design, study population and sample size for draft protocol P1093, a Phase II protocol in pediatric subjects with HIV-1 infection.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Amalia Himaya, Regulatory Project Manager, at 301-796-3391 or the Division's main number at 301-796-1500.

Sincerely,

*{See appended electronic signature page}*

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

Enclosures - Meeting Minutes



**FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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**MEMORANDUM OF MEETING MINUTES**

**MEETING DATE:** September 8, 2010  
**TIME:** 10:00AM-11:00AM EST  
**MEETING TYPE:** Type B  
**MEETING CATEGORY:** PrePhase 3  
**APPLICATION:** IND 75,382  
**DRUG NAME:** GSK1349572  
**INDICATION:** Treatment of HIV-1 infection  
**SPONSOR NAME:** ViiV Healthcare  
**MEETING CHAIR:** Kimberly Struble, Pharm.D.  
**MEETING RECORDER:** Amalia Himaya

**FDA ATTENDEES:**

1. Debra Birnkrant, M.D., Division Director, Division of Antiviral Products (DAVP)
2. Jeffrey Murray, M.D., M.P.H., Deputy Director, Division of Antiviral Products (DAVP)
3. Kimberly Struble, Pharm.D., Medical Team Leader, DAVP
4. Yodit Belew, M.D., Medical Officer, DAVP
5. Mark Seaton, Ph.D., Pharmacology/Toxicology Reviewer, DAVP
6. Julian O'Rear, Ph.D., Virology Team Leader, DAVP
7. Karen Winestock, Chief Project Management Staff, DAVP
8. Amalia Himaya, Regulatory Project Manager, DAVP
9. Sarah Robertson, Pharm.D. Clinical Pharmacology Team Leader, Division of Clinical Pharmacology 4 (DCP4)
10. Stanley Au, Pharm.D., Clinical Pharmacology Reviewer, DCP4
11. Kevin Krudys, Ph.D., Pharmacometrics Reviewer, Division of Pharmacometrics
12. Wen Zeng, Ph.D., Biometrics Reviewer, Division of Biometrics IV (DBIV)

**SPONSOR ATTENDEES:**

*GlaxoSmithKline*

1. Alicia Carrod, M.S., Senior Statistician, Infectious Diseases Development Center (ID MDC)
2. Lloyd D. Curtis, MA MRCP, Medical Director Signal Evaluation & Risk Management, GCSP
3. Sherene Min, M.D., M.P.H., Physician Integrase Project Leader, ID MDC
4. Martha Anne A. Moore, R.Ph., Senior Director, Global Regulatory Affairs
5. W. Garrett Nichols, M.D., M.S., Project Leader, ID MDC
6. Stephen Piscitelli, Pharm.D., Director, Clinical Pharmacology, ID MDC
7. Ivy H. Song, Ph.D., Principal Clinical Pharmacokineticist, Clinical Pharmacology Modeling and Simulation
8. Deb Steimers, B.S., Center for Clinical Study Excellence, ID MDC
9. Cindy Vavro, Ph.D., Pediatric Integrase Virologist, ID MD

*Shionogi*

15. Tamio Fujiwara, Ph.D., HIV Integrase Inhibitor Project Leader, Pharmaceutical Development Division, Shionogi & Company, Ltd.
16. James Adams, Regulatory Affairs, Shionogi USA, Inc.

*ViiV Healthcare*

17. James M. Goodrich, Ph.D., M.D., Vice President Global Medical Strategy
18. Neil Shortman, Vice President, Head of Regulatory.

**BACKGROUND:**

ViiV Healthcare (ViiV) is developing GSK1349572, an HIV integrase inhibitor for the treatment of HIV-1 infection in adults and pediatric subjects in combination with other approved antiretroviral agents. Data from protocol P1093 will be used, along with an additional pediatric study in infants, to satisfy the Pediatric Written Request issued on March 3, 2010. To ensure ViiV's pediatric development program adequately addresses the terms of the WR, ViiV Healthcare provided to the FDA the draft, Phase II protocol P1093 for use of GSK1349572 in pediatric subjects. P1093 screening is anticipated to begin in the 4Q10 in subjects ages 6 weeks to < 19 years of age. The trial will be conducted by the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT) under sponsorship by the Division of Acquired Immunodeficiency Syndrome (DAIDS), National Institute of Allergy and Infectious Diseases (NIAID) and The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). The DAIDS will submit and hold the IND for this study.

On July 16, 2010, ViiV requested a type B meeting with FDA and included the briefing document to discuss draft protocol P1093. In addition, ViiV submitted nonclinical information on August 5, 2010. FDA provided preliminary comments on September 2, 2010 and ViiV provided two slides for discussion via electronic mail in the morning of the teleconference. The meeting focused on ViiV's questions 2a, 2b, 2c, 2d, and 3b as well as FDA's comments 6b and 6c. Remaining items not discussed in the meeting will be addressed through written correspondence or further teleconference. ViiV mentioned there is a more recent version of P1093 protocol incorporating some of FDA's preliminary comments already. This revised protocol will be provided to the FDA.

**MEETING OBJECTIVES:**

To establish agreement with the FDA on the study design, study population and sample size for draft protocol P1093, a Phase II protocol in pediatric subjects with HIV-1 infection.

**DISCUSSION POINTS:**

ViiV's questions are in bold, FDA's preliminary comments are in italic, and the September 8, 2010 teleconference discussion is in regular font.

**2a. Does the Agency agree with the proposed target PK parameters [AUC(0- $\tau$ )] as the primary endpoint and C $\tau$  as the secondary PK endpoint) as well as the target PK exposure ranges (based on the available Ph II data in HIV-infected adults) for dose selection and adjustment?**

*FDA response: The proposed GSK1349572 target values for AUC<sub>(0- $\tau$ )</sub> (46  $\mu\text{g}\cdot\text{h}/\text{mL}$ ) and C $\tau$  (0.96  $\mu\text{g}/\text{mL}$ ) are acceptable. However, DAVP recommends the target range for the geometric mean to be 80% to 125% of the adult values as opposed to the 10<sup>th</sup> to 90<sup>th</sup> percentiles.*

*Secondly, the AUC of 14  $\mu\text{M}\cdot\text{hr}$  for dose adjusting GSK1349572 (equation in Section 6.24 of protocol) in the mini cohort is not supported by the available Phase 2 data in HIV-1 infected adults and it is unclear why the AUC over 12 hours is evaluated versus over 24 hours. The information appears to be a carryover from the raltegravir pediatric protocol.*

*In addition to comparing the mean and the range of exposure (e.g. AUC<sub>(0- $\tau$ )</sub>, C $\tau$ ) for the pediatric population versus adults in Stage 1, please also consider comparing the range of exposures in the two populations in Stage 2. You may use simulations (after updating the population PK model with pediatric data) to compare the 10<sup>th</sup> and 90<sup>th</sup> percentiles in adults and pediatrics. For example, you should evaluate whether <10% of pediatric exposures are below the 10<sup>th</sup> percentile for adult exposures to avoid low exposures in pediatrics. Finally, please submit all datasets, simulation codes, and analysis codes used in modeling and simulation.*

Meeting Discussion:

FDA and ViiV agreed to have different opinions on the proposed range of GSK1349572 exposure values around the target AUC for the pediatric population, a non-hold clinical issue. ViiV presented Slide 1 (see Attachment) displaying the changes in viral load on Day 11 compared to AUC values for 10 mg and 50 mg in adults. Slide 1 is an inhibitory E<sub>max</sub> model based on the GSK1349572 monotherapy data. ViiV also mentioned the 10 mg GSK1349572 dose showed a high level of efficacy (greater than 90% response at 24 weeks) in SPRING-1. ViiV maintained the 10<sup>th</sup> percentile is still three fold above the acceptable exposure even though the proposed 10<sup>th</sup> to 90<sup>th</sup> percentile seems broad. ViiV stated the proposed range of exposure should be more than sufficient to justify not dose adjusting subjects and accounts for variability in pediatric subjects as well as any potential drug drug interactions. FDA disagreed and emphasized a tighter target range is needed in Stage 1, especially if dose adjusting will not be implemented in Stage 2 because of potential drug drug interactions. FDA acknowledged the favorable data from the 10 mg dose in SPRING-1, but reminded the sponsor that the pediatric study is intended to match exposures in adults at the intended adult dose (50 mg). This is the only dose which will have efficacy and safety confirmed in randomized Phase 3 trials. HIV treatment programs historically have not gone back to the Phase 2 dose-ranging studies to identify the lowest feasible dose for pediatric patients; rather, it is routine to match adult exposures at the dose evaluated in the Phase 3 confirmatory trials. In addition, interpreting efficacy in pediatric subjects at the lower end of the target range is more difficult and could potentially impact efficacy in pediatric subjects with previous treatment experience who need a higher dose. ViiV assured FDA the pharmacokinetics of GSK1349572 will be evaluated two to three weeks after optimization of background to verify the exposure is not too low or too high.

FDA also confirmed the range of exposure comparison is for one pediatric population, not two populations as stated in the following sentence in FDA's preliminary comments (the populations that are to be compared are pediatrics versus adults—please see footnote 1 for further clarification)<sup>1</sup>: “In addition to comparing the mean and the range of exposure (e.g.  $AUC_{(0-\tau)}$ ,  $C_{\tau}$ ) for the pediatric population versus adults in Stage 1, please also consider comparing the range of exposures in the two populations in Stage 2.”

**2b. Does the Agency agree that the cohort size, PK sampling strategy and exclusion of use of certain antiretroviral agents (i.e., EFV, ATV/RTV, and TPV/RTV) as described for Stage 1 will be acceptable in determining chronic doses for Stage 1 and Stage 2 for each age cohort?**

*FDA response: DAVP agrees that the PK sampling scheme for Stage 1 is acceptable for determining the appropriate Stage 1 and Stage 2 GSK1349572 dosing regimens. However, please clarify whether there are protocol criteria (e.g. specific age groups or PK values) for defining which subjects are considered as having “extremes in PK values” and are therefore eligible for individual dosage adjustment.*

*Secondly, DAVP recommends that subjects receiving efavirenz or tipranavir/ritonavir after optimization of background therapy should have the GSK1349572 dosage regimen adjusted to provide GSK1349572 exposure equivalent to 50 mg once daily.*

*The written request specifies that the study be prospectively powered to target a 95% CI within 60% and 140% of the point estimate for the geometric mean estimates of clearance and volume of distribution in each age cohort.*

Meeting Discussion:

ViiV defined extreme PK values in the low end as less than 17 mcg\*hr/mL for  $AUC_{(0-24h)}$ . With regards to the upper limit value, this has not been clearly defined but will be based on exposure of atazanavir/ritonavir or data collected in VIKING 2 where 50 mg bid is being evaluated (assuming linearity in exposure). Hence, in lieu of no significant safety data, the upper limit value is currently defined as 92 ug/ml. ViiV mentioned the defined extreme parameters will be applied to Stage 1 only and not intended for Stage 2 since the latter stage involves random PK sampling with no dose adjustment. FDA is concerned there is no specified criteria in determining which subjects require dose adjustment when evaluating GSK1349572 pharmacokinetics after optimization of background treatment. ViiV stated this is currently being discussed.

ViiV again questioned the necessity for dose adjustment in subjects receiving efavirenz or tipranavir/ritonavir after optimization of background therapy given the wide range of efficacious exposure. FDA again emphasized a tighter PK range is needed in Stage 1 if ViiV decides to not dose adjust in Stage 2. ViiV mentioned dose adjusting medications are difficult for clinicians. IMPAACT agrees with ViiV to not dose adjust GSK1349572 as PK

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<sup>1</sup> In addition to comparing the mean and the range of exposure (e.g.  $AUC_{(0-\tau)}$ ,  $C_{\tau}$ ) for the pediatric population versus adults in Stage 1, please also consider comparing the range of exposures in the pediatric population versus adults in Stage 2.

check will be done in Stage 1 after optimization of background therapy. Again, FDA maintained the position that the protocol should either specify a dose adjustment with interacting drugs or provide a tighter PK range.

Regarding the Written Request specifying the study be powered to target a 95% CI within 60% and 140% of the point of estimate, FDA mentioned the goal is to design the study so that the PK parameters are obtained with an adequate degree of precision to allow for reliable dose recommendations and labeling. The mean and variance estimates of the PK parameters from adults can be used to guide the sample size and sampling scheme. ViiV expressed concern on the power for subjects who are < 2 years old as enrollment will be difficult. FDA responded that setting the power limit depends on ViiV and emphasized the values specified in the Written Request need to be targeted in the design of the study.

ViiV will take into account the discussion above and discuss further internally.

**2c. Does the Agency agree with the proposed initial dosing strategy (Appendix III of the protocol - Dosing Table A) for Cohort I?**

*FDA response: Justification for the proposed dosing strategy (Dosing Table A or B) has not been provided in the protocol. The population pharmacokinetic model previously derived in adults should be used to simulate the expected GSK1349572 exposure using the doses specified in Dosing Table A for Cohort I. In addition, before selecting doses for Stage 1 in each subsequent Cohort (II to V), pharmacokinetic data from the previous cohorts should be included in the pharmacokinetic model. The model should then be used to simulate expected GSK1349572 exposure in the next cohort at the proposed doses.*

Meeting Discussion:

ViiV stated the intensive PK data from each mini-cohort will be evaluated before dose selection for the subsequent cohort. If the PK exposures in the mini-cohort are acceptable, enrollment into Stage 1 of the next sequential age cohort will open using the same (per kg) dose. This approach allows ViiV to rapidly move the trial from one age group to the other with no delay. ViiV also contended incorporating the PK data into a pharmacokinetic model and simulating dosing in the next age cohort were not practical due to time and resource constraints. FDA disagreed, stating this approach has been used successfully in many previous pediatric trials. FDA suggested updating the pharmacokinetic model with intensive PK data from the mini-cohort should only take a few days and would be very useful to derive doses in subsequent cohorts. In any event, FDA reminded ViiV the Written Request states the selected dose(s) for the study must be agreed upon with the FDA prior to initiating the pediatric trial. FDA further requested ViiV shares PK data with FDA prior to dose selection.

ViiV will take into account the discussion above and discuss further internally.

**2d. Does the Agency agree that drug interaction data from the adult program can guide dosing strategies for the pediatric program?**

*FDA response: DAVP agrees that the drug-drug interaction data from adults can be used in determining the appropriate dosing regimens for pediatric subjects. However, we recommend that a nevirapine-GSK1349572 drug-drug interaction trial be conducted to determine whether a dosage adjustment for GSK1349572 is necessary in both adults and pediatric patients.*

*DAVP also recommends excluding the use of darunavir/ritonavir or etravirine (administered concurrently with darunavir/ritonavir) prior to optimization of background therapy because an approximately 40% decrease in GSK1349572 trough concentrations has been observed with coadministration with GSK1349572 with both medications. In addition, concurrent use of nevirapine or fosamprenavir/ritonavir should also be excluded for all stages of the trial pending the results of the fosamprenavir/ritonavir-GSK1349572 drug-drug interaction trial and GSK1349572-nevirapine drug-drug interaction data. The protocol should also exclude the use of any combination of two or more enzyme inducers (e.g. efavirenz, tipranavir/ritonavir) as part of the optimized background antiretroviral therapy with GSK1349572 coadministration.*

Meeting Discussion:

For the nevirapine-GSK1349572 drug-drug interaction trial, ViiV already conducted an efavirenz trial in healthy subjects and provided data comparing nevirapine and efavirenz induction potential. FDA does not object to ViiV's proposal to evaluate the nevirapine-GSK1349572 interaction in HIV-1 infected pediatric subjects at Stage 2, Week 4. FDA agreed it would not be feasible to do a drug-drug interaction trial with nevirapine in healthy subjects.

FDA's objective in proposing exclusion of darunavir/ritonavir prior to optimization of the background regimen is to have clean PK data as early as possible. ViiV proposes use of darunavir because the darunavir induction effects are moderate and there is a lack of available antiretroviral regimens (i.e., only lopinavir/ritonavir would be an acceptable PI regimen). FDA replied the use of darunavir/ritonavir is acceptable as long as ViiV keeps in mind the potential decreased GSK1349572 exposure.

**3b. Does the Agency agree with the definition of virologic failure and algorithm for resistance testing in the event of virologic failure?**

*FDA response: We agree with your failure definition of "A confirmed decrease from baseline plasma HIV-1 RNA of  $<1.0 \log_{10}$  and HIV-1 RNA  $>400$  copies/ml at **Week 24 or later.**" However, please incorporate pre-week 24 assessments to identify earlier instances of virologic failure/rebound. For the purpose of efficacy analysis, such subjects should be classified as virologic failures. Investigators should use their clinical judgments to decide whether study drug(s) should be continued in these subjects.*

*Please include in your resistance testing subjects who discontinue from the study early and have HIV-1 RNA >400 copies/mL at the time of discontinuation.*

Meeting Discussion:

ViiV agrees to incorporate pre-week 24 assessments to identify virologic failure/rebound in the most recent version of P1093 protocol.

*6b. Please propose an exclusion criteria for subjects with renal impairment, evident by confirmed abnormal baseline serum creatinine and/or creatinine clearance (CrCl).*

Meeting Discussion:

ViiV stated an exclusion criterion is already included in the protocol; i.e., subjects with  $\geq$  Grade 3 laboratory values are excluded from enrollment.

*6c. Please include toxicity and adverse events management plan for subjects who may experience Grade  $\geq 2$  elevation in serum creatinine or a decrease in CrCl by more than 10% when compared to baseline.*

Meeting Discussion:

ViiV does not agree with the proposed cut of 10% in CrCl decrease and stated a 10% decrease may be seen as a normal variation from baseline.

FDA's objective in this preliminary comment is to recommend that ViiV consider implementing a management plan similar to the adult protocol for pediatric subjects who may experience the above events during study treatment. ViiV does not have to follow the exact proposed criteria but needs to include an adequate renal toxicity management plan in the protocol.

ViiV agrees a toxicity management plan for subjects with renal adverse events (increase in creatinine or decrease in creatinine clearance) is needed. The monitoring and management plans have been incorporated in the newer version of the pediatric protocol and will be submitted to FDA. ViiV also clarified the Schwarz formula will be used for calculating creatinine clearance.

**DECISIONS (AGREEMENTS) REACHED:**

1. FDA and ViiV decided to have differing opinions on the proposed range of exposure values around the target AUC for the pediatric population.
2. The nevirapine-GSK1349572 drug-drug interaction will be evaluated at Stage 2, Week 4 in HIV-1 infected pediatric patients receiving nevirapine as part of their optimized background regimen.
3. Pre-week 24 assessments to identify virologic failure/rebound and a toxicity management plan for subjects with renal adverse events will both be included in the P1093 protocol.

**ACTION ITEMS:**

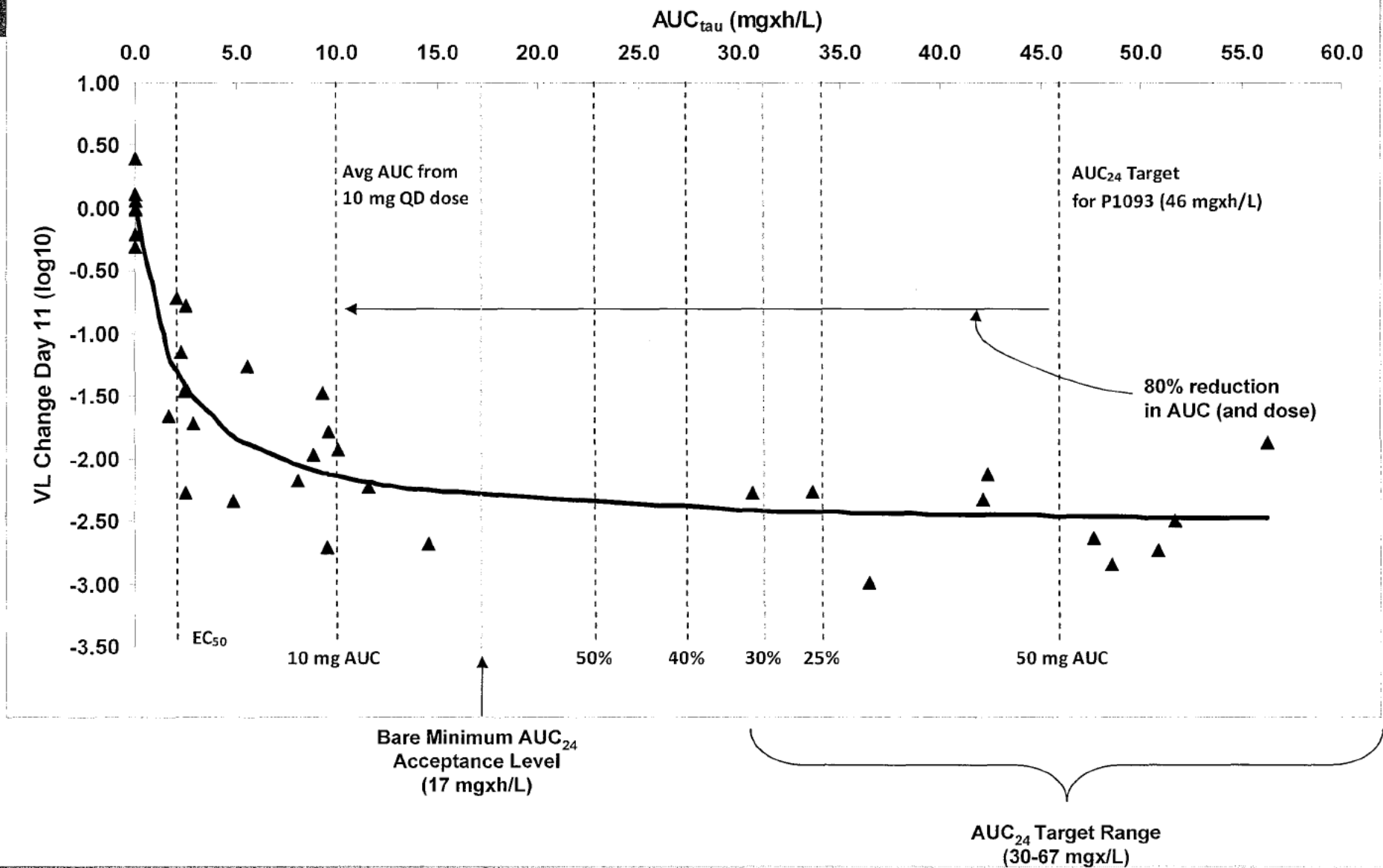
1. Remaining items not discussed in the meeting will be addressed through written correspondence or further teleconference.
2. ViiV will provide the most recent version of P1093 protocol to the FDA.

draft peds P1093 telecon  
page 8

**ATTACHMENTS/HANDOUTS:**

Attachment: ViiV's Slide Presentation

### AUC<sub>tau</sub> vs. Day 11 VL Change: Inhibitory Emax Model



# NVP and EFV induction comparison

|                                             | Nevirapine         |                     |                    | Efavirenz          |                 |                   |
|---------------------------------------------|--------------------|---------------------|--------------------|--------------------|-----------------|-------------------|
|                                             | AUC                | Cmax                | Cmin               | AUC                | Cmax            | Cmin              |
| ATV/RTV<br>400/100                          | ↓19%<br>↓35% - ↑2% | ↓2%<br>↓15% - ↑24%  | ↓59%<br>↓73-40%    | ↔                  | ↑17%<br>↑8-27%  | ↓42%<br>↓31-51%   |
| LPV/RTV 400/100                             | ↓27%<br>↓47-2%     | ↓19%<br>↓38% - ↑5%  | ↓51%<br>↓72-26%    | ↓19%<br>↓36% - ↑3% | ↔               | ↓39%<br>↓3-62%    |
| Maraviroc<br>NVP: 300 SD<br>EFV: 100 BID    | ↑1%<br>↓35% - ↑55% | ↑54%<br>↓6% - ↑151% | ↔                  | ↓45%<br>↓38-51%    | ↓51%<br>↓37-62% | ↓45%<br>↓28-57%   |
| Indinavir 800 q8h                           | ↓31%<br>↓39-22%    | ↓15%<br>↓24-4%      | ↓44%<br>↓53-33%    | ↓46%<br>↓37-54%    | ↓29%<br>↓11-43% | ↓44%<br>↓50-63%   |
| Nelfinavir 750 TID                          | ↔                  | ↔                   | ↓32%<br>↓50% - ↑5% | ↑20%<br>↑8-34%     | ↑21%<br>↑10-33% | ↔                 |
| Clarithro<br>500 BID                        | ↓31%<br>↓38-24%    | ↓23%<br>↓31-14%     | ↓56%<br>↓70-36%    | ↓39%<br>↓30-46%    | ↓26%<br>↓15-35% | ↓53%<br>↓42-63%   |
| Ethinyl Estradiol<br>0.035 mg               | ↓20%<br>↓33-3%     | ↔                   | ↔                  | ↔                  | ↔               | ↔                 |
| N:Norethindrone<br>EFV: Norelgestromin      | ↓19%<br>↓30-7%     | ↓16%<br>↓27-3%      | ND                 | ↓64%<br>↓62-67%    | ↓46%<br>↓39-52% | ↓82%<br>↓79-85%   |
| Rifabutin<br>N:150-300QD<br>EFV:300 QD      | ↑17%<br>↓2% - ↑40% | ↑28%<br>↑9-51%      | ↔                  | ↓38%<br>↓28-47%    | ↓32%<br>↓15-46% | ↓45%<br>↓31-56%   |
| Zidovudine<br>N:100-200 TID<br>EFV: 300 BID | ↓28%<br>↓40-4%     | ↓30%<br>↓51% - ↑14% | ND                 | ↔                  | ↔               | ↑225%<br>↑43-640% |



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

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/s/

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DEBRA B BIRNKRANT  
09/28/2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

IND 75,382

MEETING MINUTES

GlaxoSmithKline  
US Agent for ViiV Healthcare Company  
Attention: Sherry L. Watson  
Global Pre-Approval, CMC Regulatory Affairs  
P.O. Box 13398, Bldg 5.5420  
Five Moore Drive  
Research Triangle Park, NC 27709

Dear Ms. Watson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for GSK1349572, HIV Integrase Inhibitor.

We also refer to the teleconference between representatives of your firm and the FDA on Monday, July 26, 2010. The purpose of the meeting was to establish agreement regarding the chemistry, manufacturing and controls information used to support Phase 3, plans for data to be generated in support of the NDA and discussions on the dissolution method and preliminary specification for GSK1349572 Tablets.

A copy of the official minutes of the teleconference is attached for your information. Please notify us of any *significant* differences in understanding regarding the meeting outcomes.

If you have any questions, call Jeannie David, Regulatory Project Manager at (301) 796-4247.

Sincerely,

*{See appended electronic signature page}*

Scott N. Goldie, Ph.D.  
Regulatory Health Project Manager - Quality  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Assessment

Enclosure

## MEMORANDUM OF MEETING MINUTES

**Meeting Type:** Type B  
**Meeting Category:** End-of-Phase 2 (EOP2)  
Chemistry, Manufacturing and Controls (CMC)

**Meeting Date and Time:** Monday, July 26, 2010, 11:00 AM – 12:30 PM ET  
**Meeting Location:** Teleconference

**Application Number:** IND 75,382  
**Product Name:** GSK1349572  
**Indication:** Treatment of human immunodeficiency virus (HIV)-1 infection in combination with other antiretroviral agents  
**Sponsor/Applicant Name:** GlaxoSmithKline/Shinogi/ViiV Healthcare (ViiV)

**Meeting Chair:** Stephen P. Miller, Ph.D.  
**Meeting Recorder:** Scott N. Goldie, Ph.D.

### FDA ATTENDEES

Office of New Drug Quality Assessment / Division of New Drug Quality Assessment II

Scott N. Goldie, Regulatory Health Project Manager - Quality  
Houda Mahayni, Biopharmaceutics Reviewer  
Dorota M Matecka, Review Chemist  
Stephen P. Miller Chief, Branch V (*Acting*)  
Andrew B Yu, Review Chemist

Office of New Drugs / Division of Antiviral Products

Yodit Belew, Medical Officer  
Amalia Himaya, Regulatory Health Project Manager

Office of Clinical Pharmacology / Division of Clinical Pharmacology 4

Stanley Au, Clinical Pharmacologist

## SPONSOR ATTENDEES

### GlaxoSmithKline

Kenneth Campbell, Manager, Product Development  
Matthew Sharp, Ph.D, Team Manager, Synthetic Chemistry  
Frank DeMartin, Manager, Analytical Sciences  
Sherry Watson, Director, Global CMC Regulatory Affairs  
Alan Millar, Ph.D, Director, Synthetic Chemistry  
Catherine Barnes, Senior Scientist, Physical Properties  
John Hughes, Medicines Product Development Leader  
Richie Everett, Team Leader, Analytical Science  
Sherene Min, Director, Clinical Development

### Shionogi

Naoko Fujioka, Ph.D., CMC Leader  
Hideyuki Kitamura, Ph.D., Chemical Development  
Kumiko Miyamura, Analytical Development

### ViiV Healthcare

James M. Goodrich, Ph.D., M.D., Vice President, Global Medical Strategy

## 1.0 BACKGROUND

GlaxoSmithKline (GSK) requested a Type B End-of-Phase 2 (EOP2) Chemistry, Manufacturing, and Controls (CMC) meeting, letter dated June 1, 2010, to discuss to discuss the chemistry, manufacturing and controls for GSK1349572 for the treatment of human immunodeficiency virus (HIV)-I infection in combination with other antiretroviral agents. A parallel EOP2 meeting to discuss clinical topics between GSK and the Division of Anti-Viral Products is scheduled on July 13, 2010.

FDA's initial responses to GSK's questions in the CMC briefing package received June 28, 2010, are listed below with the meeting discussion of July 26, 2010.

## 2. DISCUSSION

### 2.1. DRUG SUBSTANCE

**Briefing Package Question 1:** GlaxoSmithKline propose to use the following (b) (4)

Does the Agency support our proposal? (b) (4)

**FDA Response to Briefing Package Question 1:** We agree (b) (4)

**Briefing Package Question 5:** Does the Agency accept the proposal to submit the NDA with 9 month stability data on three full scale drug product batches manufactured at the commercial site (using input drug substance batches at pilot scale using the proposed commercial route) with a 12 month update during review in support of a 24 month expiry date, with no impact on the action date?

**FDA Response to Briefing Package Question 5:** We recommend that the long-term stability testing cover a minimum of 12 months duration on at least three primary batches at the time of submission, in accordance with ICH Q1AR2. The impact of any proposed stability update on the action date will be a review issue. If it is not possible to collect 12 months of stability data by the time that your clinical studies are completed, we would be willing to re-evaluate your proposal.

**Discussion:** GSK acknowledged receipt of FDA's preliminary response communication. No further discussion occurred during the teleconference.

**Briefing Package Question 6:** GSK consider that the proposed stability protocols are appropriate to support the Phase 3 clinical trials and the NDA. Does the Agency agree?

**FDA Response to Briefing Package Question 6:** We agree that the stability protocols are appropriate to support the Phase 3 clinical trials. We recommend that you refer to ICH Q1A(R2) and ICH Q6A for your NDA submission.

Given that this product may ultimately have value to programs such as PEPFAR, you may wish to consider adding the long-term condition of 30°C/75%RH to the stability program. Along these lines, are you planning to develop a non-US packaging variant or tablet variant for use in PEPFAR recipient nations?

**Discussion:** GSK acknowledged receipt of FDA's preliminary response communication. GSK clarified that the long-term condition of 30°C/75%RH for global registration was included in the stability program. FDA recommended that these data be included in the NDA initial submission.

### **3. ISSUES REQUIRING FURTHER DISCUSSION**

There are no outstanding issues requiring further discussion.

### **4. ACTION ITEMS**

There are no other action items other than those included in the meeting discussion section.

### **5. ATTACHMENTS AND HANDOUTS**

There were no attachments or handouts for the meeting minutes.

**CONCURRENCE:**

*{See appended electronic signature page}*

Scott N. Goldie, Ph.D.  
Regulatory Health Project Manager - Quality  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Assessment

*{See appended electronic signature page}*

Stephen P. Miller, Ph.D.  
Chief, Branch V (*Acting*)  
Division of New Drug Quality Assessment II  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Assessment

| Application<br>Type/Number | Submission<br>Type/Number | Submitter Name          | Product Name                           |
|----------------------------|---------------------------|-------------------------|----------------------------------------|
| IND-75382                  | GI-1                      | GLAXOSMITHKLIN<br>E LLC | GSK1349572(HIV INTEGRASE<br>INHIBITOR) |

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

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/s/

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SCOTT N GOLDIE  
08/18/2010

STEPHEN P MILLER  
08/18/2010



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Silver Spring, MD 20993

IND 75,382

GlaxoSmithKline  
Attention: Martha Anne Moore, R.Ph.  
Senior Director, Global Regulatory Affairs  
P.O. Box 13398  
Five Moore Drive  
Research Triangle Park, NC 27709

Dear Ms. Moore:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for GSK1349572.

We also refer to the meeting between representatives of your firm and the FDA on July 13, 2010. The purpose of the meeting was to discuss and establish agreement with FDA on your plan to proceed into Phase 3 studies including your proposed doses, objectives, and designs of the protocols to support an NDA for accelerated approval and marketing application of GSK1349572 alone [REDACTED] (b) (4)

[REDACTED] for the treatment of HIV-1 infection.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Amalia Himaya, Regulatory Project Manager, at 301-796-3391 or the Division's main number at 301-796-1500.

Sincerely,

*{See appended electronic signature page}*

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

Enclosures - Meeting Minutes  
GlaxoSmithKline's Slide Presentation



**FOOD AND DRUG ADMINISTRATION**  
**CENTER FOR DRUG EVALUATION AND RESEARCH**

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**MEMORANDUM OF MEETING MINUTES**

**MEETING TYPE:** Type B  
**MEETING CATEGORY:** End of Phase 2

**MEETING DATE:** July 13, 2010  
**TIME:** 9:30AM-11:00AM EST  
**LOCATION:** White Oak, Building 22, Room 1313

**APPLICATION:** IND 75,382  
**DRUG NAME:** GSK1349572  
**INDICATION:** Treatment of HIV-1 infection  
**SPONSOR NAME:** GlaxoSmithKline (GSK)

**MEETING CHAIR:** Kimberly Struble, Pharm.D.  
**MEETING RECORDER:** Amalia Himaya

**FDA ATTENDEES:**

1. Jeffrey Murray, M.D., M.P.H., Deputy Director, Division of Antiviral Products (DAVP)
2. Kendall Marcus, M.D., Deputy Director for Safety, DAVP
3. David Roeder, Associate Director, Regulatory Affairs, Office of Antimicrobial Products (OAP)
4. Kimberly Struble, Pharm.D., Medical Team Leader, DAVP
5. Yodit Belew, M.D., Medical Officer, DAVP
6. Mark Seaton, Ph.D., Pharmacology/Toxicology Reviewer, DAVP
7. Julian O'Rear, Ph.D., Virology Team Leader, DAVP
8. Sung Rhee, Ph.D., Virology Reviewer, DAVP
9. Karen Winestock, Chief Project Management Staff, DAVP
10. Amalia Himaya, Regulatory Project Manager, DAVP
11. Kellie Reynolds, Pharm.D., Deputy Director, Division of Clinical Pharmacology 4 (DCP4)
12. Sarah Robertson, Pharm.D. Clinical Pharmacology Team Leader, DCP4
13. Stanley Au, Pharm.D., Clinical Pharmacology Reviewer, DCP4
14. Kevin Krudys, Ph.D., Pharmacometrics Reviewer, Pharmacometrics Staff
15. Guoxing (Greg) Soon, Ph.D., Biometric Team Leader, Division of Biometrics IV (DBIV)
16. Wen Zeng, Ph.D., Biometrics Reviewer, DBIV
17. Andrew Yu, Ph.D., Chemist, Division of New Drug Quality Assessment II (DNDQA II)
18. Antoine El-Hage, Ph.D., Pharmacologist, Division of Scientific Investigations (DSI)
19. Twanda Scales, Safety Regulatory Project Manager, Office of Surveillance and Epidemiology (OSE)

**SPONSOR ATTENDEES:**

*GSK*

1. Robert Cuffe, Ph.D., Statistics Infectious Diseases Medicines Development Center (ID MDC)
2. Rick Hailey, DVM, ACVP, Director, Regulatory and Discovery Pathology
3. Sherene Min, M.D., M.P.H., Physician Integrase Project Leader, ID MDC
4. Martha Anne A. Moore, R.Ph., Senior Director, Global Regulatory Affairs
5. W. Garrett Nichols, M.D., M.S., Project Leader, ID MDC
6. Stephen Piscitelli, Pharm.D., Director, Clinical Pharmacology, ID MDC
7. Ivy H. Song, Ph.D., Principal Clinical Pharmacokineticist, Clinical Pharmacology Modeling and Simulation
8. Mark Underwood, Ph.D., Lead Integrase Virologist, ID MDC

*Shionogi*

9. Tamio Fujiwara, Ph.D., HIV Integrase Inhibitor Project Leader, Pharmaceutical Development Division, Shionogi & Company, Ltd.
10. Susan A. Witham, Vice President, Regulatory Affairs and Quality Assurance, Shionogi USA, Inc.

*ViiV Healthcare*

11. James M. Goodrich, Ph.D., M.D., Vice President Global Medical Strategy
12. Neil Shortman, Vice President, Head of Regulatory

**BACKGROUND:**

GSK is developing GSK1349572, an HIV integrase inhibitor for the treatment of HIV-1 infection in adults and pediatric subjects in combination with other approved antiretroviral agents. GSK provided to the FDA currently available data from nonclinical pharmacology, pharmacokinetic, toxicology studies and completed clinical trials. Data from ongoing ING112276 (a Phase 2b dose-ranging or SPRING 1) and Phase 2 pilot (VIKING) trials were submitted. GSK is now planning Phase 3 clinical trials in adults. On May 12, 2010, GSK requested an End-of-Phase 2, type B meeting with FDA to discuss the current data and get concurrence on Phase 3 clinical development plans for GSK1349572. GSK submitted a briefing document on June 10, 2010 and FDA provided preliminary comments on July 9, 2010. GSK also provided the FDA with slides for the meeting via electronic mail on July 12, 2010. At the meeting, GSK decided to focus the meeting on clinical pharmacology, virology, clinical, regulatory, and statistical questions. GSK also plans to respond separately to the FDA protocol comments through written correspondence and/or teleconference request.

## MEETING OBJECTIVES:

To seek FDA's agreement on:

1. Proposed plans for additional assessments in SPRING 1 and Phase 3 trials to further investigate potential serum creatinine and proteinuria issues.
2. Phase 3 development plans including proposed doses, objectives, and designs of the protocols.
3. Proposed renal and hepatic impairment trials.
4. Proposed dosing for GSK1349572 in combination with tipranavir with ritonavir (TPV/r) and efavirenz (EFV).
5. Proposed non-inferiority trials.

## DISCUSSION POINTS:

The meeting started with GSK's presentation of the SPRING 1 24-week safety related data and proposed plans to address the creatinine clearance increases and proteinuria identified in the trial. GSK also provided a summary of the planned additional assessments in the Phase 3 trials including the rationale for the proposed dose of 50 mg once daily (qd) of GSK1349572 in the two Phase 3 therapy naïve trials. The discussion then proceeded on certain questions listed in the meeting package. GSK's slides referenced during the discussion are in Attachment 1.

The SPRING 1 data in treatment-naïve adult patients showed antiviral activity across all the three doses of 10 mg, 25 mg, and 50 mg with the majority of subjects achieving HIV-1 RNA to less than 50 copies/mL. GSK also presented two potential safety issues for SPRING 1: increase in serum creatinine and proteinuria.

First, the results of serum creatinine and creatinine clearance (CrCl) to date for this trial were discussed (see slide 5). No notable change beyond Grade 1 was observed for elevation in serum creatinine. GSK also emphasized that absolute number reported for the changes in creatinine values may appear large as the units used were micromole per liter ( $\mu\text{mol/L}$ ) instead of the conventional unit, milligram per deciliter (mg/dL). More importantly, GSK states that the increase in serum creatinine does not continue to rise indefinitely during the treatment period. By Week 16, there appears to be a decline in the overall increase from baseline. Based on the limited Week 32 information, by Week 32, serum creatinine appears to normalize back to baseline value. In addition, based on the graphical analysis (slide 6), a relationship between the change in creatinine from baseline versus  $\text{AUC}_{(0-\tau)}$  at Weeks 1, 16, 24 and 32 was not observed. GSK acknowledged this analysis was preliminary and would reassess the relationship at Week 48.

GSK hypothesized the rapid onset of small mean increases in serum creatinine without progression are likely due to blockade of tubular creatinine secretion via OCT2; hence, GSK is currently evaluating in vitro whether GSK1349572 inhibits the tubular secretion of creatinine. GSK presented the preliminary results (slide 8) of the in vitro OCT2 study. The preliminary results indicate that 25  $\mu\text{M}$  of GSK1349572 results in 91% inhibition of OCT2, with a similar percent inhibition when GSK1349572 was combined with either abacavir and lamivudine or tenofovir and emtricitabine. GSK did not investigate whether the glucuronide metabolite or any other metabolites can also be inhibitors of OCT2. The next steps in GSK's investigation are to titrate to

an IC<sub>50</sub> of GSK1349572 for OCT2 inhibition and test for additive effects of NRTIs with lower concentrations of GSK1349572.

Second, the proteinuria observed in the SPRING trial was discussed. There is a greater percentage of subjects in GSK1349572 with treatment-emergent shifts in proteinuria (via dipstick) compared with efavirenz (EFV) (see slide 9). GSK presented graphs (slides 10-13) showing no consistent pattern in the urine protein results of the 24 week data for the 3 doses of GSK1349572 (10 mg, 25 mg, and 50 mg qd) and with EFV control. But GSK acknowledges the difference between the GSK1349572 vs. EFV arm in that proteinuria was noted in a greater percentage of subjects in the GSK1349572 arm. The instrument used for reading the urine dipstick is Bayer U/A Multistix, an automated reader. The disadvantage of using such system for proteinuria analysis is that it uses a semi-quantitative method which, with any minor changes, can shift results one way or another bringing into question its reliability. In addition, some drugs and antiseptics may cause false positive results.

To address above concerns, GSK proposes to:

- analyse GSK1349572 parent compound interference with colorimetric assay for protein on dipstick U/A with results expected by late August 2010;
- conduct a Phase I trial in healthy subjects to assess the effect of GSK1349572 50 mg once daily on glomerular filtration rate (GFR, via iohexol clearance); to assess glomerular and tubular (distal and proximal) functions via serum Cystatin-C, 24-hour urine protein and albumin, beta2 microglobulin, and retinol binding protein. GSK plans to start the studies in 4<sup>th</sup> quarter of 2010.
- add urinalysis with dipstick, spot microalbumin/creatinine every 12 weeks in SPRING 1 and VIKING trials. Assessment will be made after 24 week and 48 week timepoints in VIKING and SPRING 1, respectively. Specifically, creatinine and electrolytes assessment will continue every 12 weeks in both studies post week 24 and post week 48 to look for any kidney damage. Additional guidance to the clinical investigators will also be provided for abnormal urine protein results.

FDA asked if any changes in electrolytes (including bicarbonate and phosphorus) have been noted and if GSK plans to assess those parameters in the additional studies. GSK stated it is difficult to conduct reliable testing on bicarbonate as the result is dependent on how soon a cap is placed on the specimen tube. However, to date, there does not appear to be a difference between the GSK1349572 and EFV arms. In addition, GSK plans to collect electrolytes in the Phase 3 trials as outlined in the protocol and proposes to have a grading system with cutoff on Grade 1 for phosphorus.

For the Phase 3 studies, GSK proposes the following additional assessments. Proposal details will be provided at a later time:

- Detailed renal disease history at baseline;
- Urinalysis with dipstick and spot morning (preferred) microalbumin/creatinine at baseline and Weeks 24, 48, 96 and withdrawal in Ph3 studies. Earlier timepoints will not be informative;

- Serum creatinine and electrolytes as outlined in the draft protocols (baseline and Weeks 4, 8, 12, 16, 24, 32, 40, 48, and then every 12 wks);
- Additional serum renal biomarkers (i.e., Cystatin-C) not proposed as confounded by HIV-1 RNA and CD4 cell count; and
- Guidance to investigators (including confirmatory testing and appropriate medical follow-up) for subjects with abnormal urine protein and creatinine/creatinine clearance results.

GSK concluded SPRING 1 (Ph2b dose-ranging trial) demonstrated acceptable safety and efficacy of 50 mg qd of GSK1349572 and plans to use this dose in the Phase 3 therapy naïve trials (ING113086 [SPRING 2] and ING114467). GSK believes the effect of GSK1349572 50 mg once daily on serum creatinine is likely transient and expects to see resolution as treatment continues beyond Week 32. Given these potential safety issues, FDA also reiterated the potential value of studying two doses in Phase 3. FDA does not oppose GSK's proposal in selecting solely the 50 mg dose for the Phase 3 trials but suggested GSK should wait for the Week 48 safety data to confirm the resolution of increases in serum creatinine. GSK mentioned screening of subjects in Phase 3 naïve trials will start late October and the SPRING 1 Week 48 data will be available by mid October. Hence, the data for SPRING 1 can be evaluated prior to dosing of subjects in the Phase 3 therapy naïve trials. In conclusion, FDA mentioned GSK could make the final determination in choosing the GSK1349572 dose based on risk-benefit assessment. In addition, GSK stated a plan to roll all patients over to the 50 mg dose at Week 48. FDA discouraged this plan and stated as long as subjects continue to have acceptable virologic response, the 3 dose arms should be continued as randomized beyond Week 48 (i.e. to Week 96). Long term data on the 3 doses can be helpful to address any unexpected exposure/response or exposure/safety issues.

The meeting proceeded to the discussion of the list of questions in the meeting package. GSK questions are in bold, FDA's preliminary comments are in italic, and the July 13, 2010, meeting discussions are highlighted in gray. Slides 41 and 42 were not discussed.

## 1.2 Clinical Pharmacology

- b. Based on the available pharmacokinetic (PK) and safety data collected in Phase 1 and Phase 2 studies, does the Agency agree that GSK1349572 can be administered without regard to food during Phase 3?**

*FDA's preliminary comments: We will provide further feedback on the appropriateness of administering the new 50 mg GSK1349572 tablets without regard to food when the results from Part 2 of the ING113674 trial have been submitted for review.*

Meeting Discussion: GSK agrees and anticipates preliminary data from Part 2 of ING113674 will be available within the next two weeks with the full study report completed in October 2010.

- c. The mass balance study (ING111853) demonstrated that renal excretion represents a minor pathway for elimination of GSK1349572; therefore the Company does not intend to conduct a study in subjects with renal impairment. Does the Agency agree with this plan?**

*FDA's preliminary comments: Please refer to the draft renal impairment guidance (Pharmacokinetics in Patients with Impaired Renal Function-Study Design, Data Analysis, and Impact on Dosing and Labeling) that was posted on March 17, 2010. The guidance recommends a reduced PK trial for medications that are primarily metabolized.*

**Meeting Discussion:** GSK plans to conduct a reduced design PK trial in subjects with severe renal impairment prior to the NDA submission. FDA had no comment.

**d. Does the Agency agree with our plan for additional clinical pharmacology studies during the Phase 3 program which will support initial registration of GSK1349572?**

*FDA's preliminary comments: The additional Clinical Pharmacology trials are acceptable; however, please provide additional information on the following items:*



**2. In reference to the hepatic impairment trial, please comment on the following issues:**

*a. We recommend a basic full study design (instead of a reduced study design) because a full study design would provide information regarding GSK1349572 pharmacokinetics in subjects with severe hepatic impairment.*

**Meeting Discussion:** Based on GSK's response below, FDA stated the plan was acceptable, but also encouraged GSK to start the trial as soon as possible because of potential difficulty in enrolling this population of HIV patients.

*GSK proposes to conduct a study in non-HIV infected subjects with moderate hepatic impairment in 4Q 2010. Since enrollment of severe hepatic impairment subjects is difficult, GSK proposes that this study be done as a post-approval trial. The study will likely evaluate HIV-infected subjects who will have a more favorable risk/benefit for receiving GSK1349572.*

*b. The guidance for hepatic impairment trials recommends a single dose trial if the drug and active metabolites exhibit linear and time independent pharmacokinetics. Because nonlinearity has been observed in GSK1349572 exposure over the range of 2 mg to 50 mg and 50 mg to 100 mg based on data from healthy and HIV-1 infected subjects, please provide further information as to why a single dose trial was selected versus a multiple dose trial.*

Meeting Discussion: FDA accepted GSK's response below and indicated that the main concern was the issue of nonlinearity in GSK1349752 exposure as commented in 2c below. GSK also mentioned the difficulty in determining the dose adjustment without additional data.

- *SPRING-1 demonstrates linear PK in AUC from 25 to 50mg (see next slide). The non-linearity between 10mg and 25mg (and 50mg) is likely due to differences in tablet strengths (10mg tablets vs 25 mg tablets for 25 and 50mg doses*
- *100mg as a single dose will not be studied in Phase 3 trials*
- *Based on ING111322 and ING111521, single dose PK predicts repeat dose PK*
- *These data demonstrate linear PK over the clinically relevant dose range and support a single dose trial design for the hepatic impairment study*

*c. Because nonlinearity in GSK1349572 exposure over the range of 2 mg to 50 mg and 50 mg to 100 mg has been reported, please comment on the method(s) that will be used to derive hepatic impairment dosage adjustment recommendations.*

Meeting Discussion: FDA had no comment on GSK's response below.

- *The need for dose adjustment in hepatically impaired subjects will depend on the magnitude of any increase observed.*
- *SPRING-1 demonstrates dose proportionality between 25mg and 50mg.*
- *A downward adjustment from 50mg to 25mg will be based on a linear relationship.*
- *Though we do not expect large increases in exposures, if seen, we will consider options for dosage recommendations requiring dosages lower than 25mg to achieve an exposure similar to 50mg.*

*3. Please specify the information and the analysis (including the relevant trials) used to conclude dose proportionality is observed for GSK1349572 tablets from 2 mg to 50 mg.*

Meeting Discussion: FDA had no comment on GSK's response below.

*Clarification: Dose proportionality exhibited linear PK from 2mg to 100mg with the suspension. For the tablet formulation, linear PK has been shown between 25mg and 50mg (ING112276). PK is nonlinear (less than dose proportional between 2mg and 100mg).*

*4. Please clarify whether the dose proportionality for the new GSK1349572 25 mg or 50 mg tablets is anticipated to be similar to the current formulation.*

Meeting Discussion: FDA had no comment on GSK's response below.

*Dose proportionality would be expected to be similar to the current formulation from 25 mg to 50 mg based on:*

- *The new formulation had only minor change in excipients [REDACTED] (b) (4)*
- *The new formulation demonstrated bioequivalence with the current formulation.*

5. Please clarify if there are any GSK1349572 metabolites that are considered active and should be further evaluated.

Meeting Discussion: FDA had no comment on GSK's response below.

*There are no significant active metabolites of GSK1349572 that require evaluation.*

- Plasma exposure is > 95% parent compound following administration of GSK1349572.*
- Primary metabolite is glucuronide (~19% of the dose) in the urine; substitution of the glucuronide at the conjugated position disrupts the metal binding and removes all antiviral activity.*
- The activity of the oxidative metabolites is unknown; however, they are not quantifiable in plasma and represent only 3% of the dose in urine.*

6. Please clarify if the following will be evaluated: a) the inhibitory effects of GSK1349572 on CYP 2C8, BCRP, and OCT2, and b) whether GSK1349572 is a substrate for BCRP.

Meeting Discussion: FDA had no comment on GSK's response below. GSK mentioned that the report evaluating the inhibitory potential of GSK1349572 will be forthcoming.

- o A full evaluation of the inhibition potential against CYP enzymes has been concluded and a draft report is currently under review. The study evaluated direct and metabolism dependent inhibition potential for CYPs 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4.*
- o Evaluation of BCRP is planned.*
- o Preliminary data on OCT2 inhibition was already presented earlier.*

**e. Does the Agency agree with our proposed dosing recommendations for GSK1349572 in combination with TPV/r and EFV?**

*FDA's preliminary comments: We do not agree with the proposal to coadminister GSK1349572 without a dose adjustment when combined with either tipranavir/ritonavir or efavirenz. We recommend that GSK consider a dose adjustment to provide exposures equivalent to either 50 mg once daily or 50 mg twice daily (depending on the final dosage regimens selected for the Phase 3 trials) when GSK1349572 is coadministered with either tipranavir/ritonavir or efavirenz. As you've indicated, GSK1349572 50 mg once daily in combination with either tipranavir/ritonavir or efavirenz would yield exposures similar to those achieved with the 10 mg once daily dose. The 10 mg once daily dose yields exposures about 3-4 times lower than those achieved with the 50 mg once daily dose. We have concerns about efficacy for these subjects. The ING112276 (SPRING-1) trial reported that the response, as measured by the proportion of subjects with a decrease in HIV-1 RNA to less than 50 copies/mL, for a once daily dosing regimen of either 10 mg, 25 mg or 50 mg was similar for all three dosage regimens. However, the subjects enrolled in the ING112276 trial did not have evidence of viral resistance to any antiretroviral medications and the efficacy results cannot be extrapolated to treatment experienced patients that may have one or more partially active antiretroviral medications. Alternatively, if you cannot provide dose adjustments for GSK1349572 with tipranavir/ritonavir or efavirenz then please exclude use of these medications in Phase 3 trials.*

Meeting discussion: GSK proposes no dose adjustment in ING111762 for co-administration of GSK1349572 50 mg once daily with TPV/r or EFV for the following reasons:

- *The 10mg arm in ING112276 has similar efficacy to the 25mg and 50mg arms demonstrating that the exposures at this dose have potent antiviral activity in treatment-naïve subjects.*
- *The 50 mg once daily dose is expected to achieve therapeutic concentrations in INI-naïve subjects with or without TPV/r and EFV. When GSK1349572 is administered with EFV or TPV/r, IQ values still exceed the PA-IC90 by greater than 4-fold.*
- *ING111762 provides the best opportunity to evaluate the impact of ARV drug interactions on the efficacy of GSK1349572 50 mg once daily in the INI-naïve, treatment experienced population.*
- *It would be difficult to dose adjust in a blinded, double dummy, randomized trial in patients taking EFV or TPV/r.*

In addition, GSK stated in the meeting package that 50 mg QD was selected to provide durable response and to compensate for any potential loss of efficacy from partially active antiretroviral medications.

FDA disagrees with GSK's proposal to not dose adjust GSK1349572 with TPV/r or EFV. Based on pharmacokinetic data submitted in the background package, GSK1349572 50 mg once daily in combination with either TPV/r or EFV would yield exposures of about 3-4 times lower than those achieved with 50 mg once daily, and that are similar to the exposure achieved with the 10 mg once daily dose. Although the 10 mg once daily has been shown to be effective in the Phase 2b trial, this is in the setting of 2 active medications in the background antiretroviral treatment regimen in treatment-naïve patients. There is no available data supporting the efficacy of GSK1349572 at exposures equivalent to 10 mg QD in the treatment experienced (INI-naïve) population, where the background regimen could have as little as one partially active drug.

FDA stated GSK's argument seems contradictory. On one hand, GSK does not want to continue the 10 mg QD arm in the Phase 2b trial beyond Week 48 nor does GSK want to consider evaluating the 10 mg QD dose (along with the 50 mg QD dose) in the phase 3 trials. On the other hand, in the more vulnerable population such as the treatment experienced population, GSK believes that an exposure equivalent to 10 mg QD is adequate and effective. FDA asked why GSK cannot dose-adjust during the Phase 3, randomized trial. GSK responded that dose adjusting during a randomized trial is difficult due to blinding issues, but is not impossible. GSK stated the main goal is to find a dose that is applicable to a broader population.

GSK believes the currently proposed phase 3 trial is the best opportunity to collect efficacy data when GSK1349572 50mg QD is co-administered with TPV/r or EFV in treatment experienced, INI-naïve population. However, FDA asked if GSK believes there will be enough patients enrolled into the trial who will be taking TPV/r or EFV to demonstrate efficacy. GSK is uncertain.

Furthermore, GSK stated that marketing considerations were among the reasons for selecting 50 mg once daily for all patient populations (excluding the raltegravir failure population).

GSK stated the efficacy of GSK1349572 at exposures equivalent to 10 mg QD supports not dose adjusting GSK1349572 and EFV is not a concern as not many subjects are expected to have EFV as part of their background regimen in treatment-experienced subjects. Although FDA prefers not to exclude subjects from the Phase 3 trial, FDA is concerned that not having the flexibility to dose adjust will deprive patients who may benefit from GSK1349572.

In the interest of time, this discussion will be addressed again at a later time.

**f. Does the Agency agree with the planned collection of PK samples in the Phase 3 program?**

*FDA's preliminary comments: Based on the estimated number of subjects that will have samples collected, approximately half of the subjects randomized to GSK1349572 in the Phase 3 trials (excluding the fixed dose combination trial) will have blood samples drawn for analysis of GSK1349572 plasma concentrations. While FDA recognizes the fact that not all trial sites have the ability to draw blood samples for PK analysis, we recommend that the Phase 3 trials allow all enrolled sites, where appropriate, to draw blood samples for PK analysis and maximize the number of subjects with PK samples. These data have been important in justifying drug interaction assessments and exploring exposure-response relationships to support effectiveness and dosing of GSK1349572.*

Meeting discussion: FDA had no comment on GSK's response below.

*PK data will be collected in as many subjects as possible, where appropriate, depending on the capabilities of the clinical site.*

**1.3. Virology**

**a. Does the Agency agree with the planned resistance testing across the Phase 3 studies?**

*FDA's preliminary comments: Yes. Please confirm that virus samples, baseline and on-treatment, from subjects who prematurely discontinue study therapy before Week 24 (for treatment-naïve subjects in Studies ING 113086 and 114467) or Week 16 (for treatment-experienced subjects in Study 111762) and have HIV-1 RNA  $\geq 400$  copies/mL at the time of discontinuation will be included in your resistance testing. Please also include screening pol genotype results (Studies ING 113086 and 114467) in your resistance analysis plan to identify any polymorphisms in HIV-1 IN affecting efficacy.*

Meeting discussion: GSK responded as follows.

- 1. Yes, baseline and on-treatment virus samples from subjects who prematurely discontinue before Week 24 (naïve subjects) or Week 16 (experienced subjects) with HIV-1 RNA  $\geq 400$  copies/mL will be included in our resistance testing.*
- 2. As screen samples may evolve we feel baseline samples should provide a better comparison. An association of IN polymorphisms with decreased response should reveal as a greater than expected number of such polymorphisms in subjects experiencing virologic failure. As such, both baseline and confirmed virologic failure samples for all subjects experiencing virologic failure will be subject to IN genotypic assay for the research analysis plan.*

GSK mentioned item 2 focuses on virologic failures. FDA requested that pre-treatment genotyping be conducted for all subjects as this serves as a good control in determining whether pre-existing polymorphic changes may be associated with treatment failure. GSK plans to use large databases of HIV-1 integrase sequences to identify polymorphisms and will evaluate these. This will be followed up further in the interest of time.

**b. Does the Agency agree with the virologic failure criteria proposed for patient management and resistance testing for each of the Phase 3 studies?**

*FDA's preliminary comments: Please include an additional virologic failure definition prior to reaching Week 24 for clinical management for subjects who have virologic non-response to GSK1349572 (e.g., <1 log<sub>10</sub> HIV-1 RNA copies/mL reduction from baseline at Week 4) in Studies ING113086 and 114467.*

Meeting discussion: GSK doesn't agree with this recommendation and believe imposing this definition for both studies may create bias in favor of GSK1349572. Detailed below are GSK's reasons.

- 1. Based on our SPRING-1 data we feel it will be extremely unlikely that we would not see a 1 log<sub>10</sub> decrease by week 4 for GSK1349572.*
- 2. There is an expected slower response rate for subjects receiving EFV, which can lead to preferentially withdrawal of Atripla subjects. This could unfairly bias the response in favor of Epzicom/GSK1349572 in ING114467.*
- 3. For ING113086, virologic failure criteria was the same as STARTMRK, since this is the pertinent study for the NI assessment.*
- 4. Purpose for including in Spring-1 was to assess if lower doses of GSK1349572 would perform as well as higher doses.*

FDA agreed.

#### **1.4. Clinical**

##### **1.4.1. General Questions Relative to GSK1349572** (b) (4)

**e. Does the Agency agree that the collective safety data supports broadening the eligible patient population for the Phase 3 studies to more accurately describe the safety profile of GSK1349572? We propose not including specific exclusion criteria for risk factors for cardiac and upper gastrointestinal complications. Does the Agency agree?**

*FDA's preliminary comments:*

Cardiac

*Please refer to your Study Assessments and Procedure Table. Under the foot note, you state that you plan to finalize a screening cardiovascular risk assessment. Please provide your proposed cardiovascular risk assessment plan. In addition, the purpose of the cardiovascular risk assessment is unclear. How do you intend to use the results of the cardiovascular risk assessment? Is this for investigators to decide between TDF/FTC or ABC/3TC use or is this intended as an exclusion criteria based on the assessment?*

*With regards to your exclusion criterion for QTc, TQT study report is currently under review by the FDA's QT IRT team. We defer response until completion of the review. If the QT IRT team reaches the same conclusion as you (i.e. GSK1349572 has no effect on QT), no QTc exclusion criteria are necessary for any of your protocols.*

GI

*Please consider excluding subjects with recent history of GI bleed. We are otherwise in agreement with your proposal.*

Meeting Discussion: FDA had no comments on GSK's response below.

- *Primary purpose of data is not to make determinations for nucleoside backbone choice.  
-Not intended to be used as an exclusion criterion;*
- *Primary purpose is to characterize CV risk profile at baseline for the entire population being studied, which is in line with large HIV cohort studies and baseline data collection (e.g., DAD);  
and*
- *Exclusion of recent history (3 months) of GI bleed will be added to the ph3 studies.*

**f. Does the Agency agree with the proposed safety monitoring across the Phase 3 program?**

**• Specifically, does the Agency agree that amylase and PT/PTT monitoring is not required in Phase 3?**

*FDA's preliminary comments: Based on the phase 2 data and preclinical data, PT/PTT data should be collected during phase 3. Please propose timelines for PT/PTT collections. As lipase will be collected, amylase monitoring is not required for your phase 3.*

Meeting Discussion: GSK will not include amylase monitoring based on FDA's preliminary comments. GSK also asked if there is any concern on the Phase 3 data because only small changes in PT/PTT and no changes in INR were observed in the Ph2b trials. In addition, preclinical changes in coagulation parameters were seen in subset of studies at highest dose evaluated and primarily observed in very sick animals. FDA responded this is the best opportunity to get controlled data in Phase 3 trials and suggested collecting the data to be consistent with the raltegravir trials. Given the nonclinical and clinical data to date, FDA did not feel strongly about routine monitoring of PT/PTT in the phase 3 trials and will leave the decision to GSK whether or not to include routine PT/PTT monitoring.

## **1.5. Protocol Specific Questions**

### **ING111762 (INI naive)**

**a. Does the Agency agree that the changes made to ING111762 since the conference call on May 18, 2010 (specifically, change in inclusion criteria to restrict the population to subjects with at least 2-class ARV resistance, inclusion of subjects with one partially active agent in the background regimen, and the inclusion of a key secondary analysis excluding subjects who are using DRV/r and whose virus shows no evidence of resistance to protease inhibitors),**

**could provide a more interpretable assessment of the non-inferiority of GSK1349572 to raltegravir?**

*FDA's preliminary comments: Your proposed secondary analysis may provide additional supportive assessment confirming non-inferiority of GSK to raltegravir. However, the non-inferiority of GSK1349572 to raltegravir needs to be demonstrated with the ITT population.*

Meeting Discussion: GSK presented a plan of changing the current protocol as it relates to use of DRV/r so that a more interpretable assessment of the non-inferiority of GSK1349572 to raltegravir can be demonstrated in the ITT population:

The current protocol excludes Protease Inhibitor (PI)-susceptible DRV/r recipients from analysis (AS population). An alternative option would be to exclude use of DRV/r in fully PI-susceptible patients (i.e. in patients without primary PI mutations); fully active PI/r stratification can be used as a simple surrogate for OBR activity. In addition, a triple ARV class resistance may be preferable over two ARV class resistance.

FDA does not agree with excluding DRV/r because DRV/r is commonly used in this population. GSK should solicit feedback from the HIV community on this plan. The original plan had allowed use of DRV/r without restrictions but proposed to cap enrollment of subjects with DRV/r as part of their OBR. GSK stated that based on a preliminary feasibility assessment, use of DRV/r is 0 to 20% in potential subjects from South Africa and Latin American because in some countries DRV is not approved. However, enrollment in these countries will remain a challenge as there is a lag in ART treatment history in the HIV-infected patients. The FDA agrees with the proposal to cap enrollment of subjects receiving DRV/r.

As previously stated, the NI margin is a review issue and depends on the baseline characteristics of the population enrolled. FDA recommended DRV/r use as a stratification factor. Also, it will be helpful to restrict the total number of subjects who will receive OBR PSS>1 and the total number of subjects with screening HIV-1 RNA viral load >400 and <1000 copies/mL. FDA recognizes GSK's efforts and agrees GSK should move forward with a trial in this patient population.

## **1.6. Statistical**

**b. The Company proposes different interpretations of the FDA's snapshot algorithm for each of the three non-inferiority studies to match the different consequences of a switch of the background regimen in each study. Does the FDA agree with this approach?**

*FDA's preliminary comments: No. Snapshot algorithm may not be changed or modified.*

Meeting Discussion: GSK provided the following response:

- will use snapshot algorithm
- MD=F name used for global trials as "snapshot" not yet internationally recognized
- Outstanding questions:
  - Can documentation of a decision to switch before or at Visit 1 exclude "failure"?

*-Transient changes in background therapy (e.g. rectified dispensing mistakes) as failure (ING113086, ING111762)?*

*-Visit schedule for ING111762, ING113086, ING111467 includes Weeks 32, 40.*

*Acceptable for Week 48 visit window to include Weeks 42-54?*

FDA agreed with the following proposal: Subjects who switched background regimen after Visit 1 due to toxicity will not be considered failures in the data as long as their intent to switch is documented and the viral load is <50 copies/mL at the time of switch. FDA clarified the time point of interest for the snapshot analysis was Week 48 and the corresponding window around the Week 48 visit was Weeks 42-54.

## 1.7. Regulatory

**a. Does the Agency agree that the planned clinical program [adult and adolescent (not described here) patients], with appropriate clinical pharmacology studies, is adequate to submit an initial New Drug Application (NDA) for accelerated approval of GSK1349572?**

*FDA's preliminary comments: An application with a 48 week data (e.g. your phase 3 trials in treatment-naïves) would be reviewed under standard approval.*

Meeting Discussion: FDA clarified an application with a 48 Week data would be reviewed under traditional approval with potential for priority review designation.

### 1.9.1. Clinical

#### ING114467

**a. Plasma samples will be collected during Phase 3 in ING113086, ING11762, and ING112754 for population PK analysis and to evaluate PK/PD relationships. The Company does not plan to collect samples for determination of PK in ING114467, the study to support a fixed dose combination of GSK1349572 with abacavir and lamivudine. Does the Agency agree with this proposal?**

*FDA's preliminary comments: We recommend you collect GSK1349572 PK blood samples during trial ING114467 because these data may be useful to further evaluate the relationship between GSK134957 exposure and renal function when administered in combination with abacavir and lamivudine. We anticipate approximately 30% may choose abacavir/lamivudine as background NRTI regimen in ING113086; therefore, you may have limited data with this combination for renal related safety analyses.*

*Also, for creatinine changes, you propose to change from FDC (Epizicom) to the individual agents (abacavir and lamivudine) and dose adjust accordingly for these agents but not for GSK1349572. As noted in section 1.4 we have concerns about the apparent dose related changes in renal function. An exposure/renal function analysis from the phase 2b trial will provide useful information on appropriate selection of 50 mg once daily only or 10 mg and 50 mg once daily for Phase 3 in treatment naïve subjects. These data may also be helpful to determine if a dose reduction for GSK1349572 is needed based on renal function changes or if discontinuation of the entire regimen is necessary.*

Meeting Discussion: GSK does not plan to collect GSK1349572 PK in ING114467 for the following reasons:

- *Enough PK data will be collected from ING112276 and ING113086 to evaluate the population PK and effect of patient characteristics on GSK1349572 PK*
- *Wide PK exposure range is needed in order to evaluate exposure-creatinine response relationship. ING114467 evaluates one dose, 50mg QD. Based on PK data from ING112276, PK variability is very small in the treatment-naïve population (CV% on AUC and Cmax is only ~40%). The best place to evaluate such relationship is in ING112276 where 3 dose levels of GSK1349572 from 10 to 50mg are being evaluated.*

FDA responded that this is an opportunity to obtain additional safety data to evaluate the relationship between GSK1349572 exposure when coadministered with abacavir and lamivudine and renal function and stated the preliminary comment to collect PK blood samples is only a recommendation.

### 1.9.2. Statistical

**b. Does the Agency consider that multiplicity adjustments (e.g. closed testing) are necessary for the secondary endpoints in ING114467?**

*FDA's preliminary comments: Only the endpoints that could be used in the label need to have consideration for multiplicity adjustments when necessary.*

Meeting Discussion: [REDACTED] (b) (4)

1. [REDACTED] (b) (4)
2. [REDACTED] (b) (4)
3. Change from baseline in CD4 cell count @ Wk 48.

FDA does not agree on items 1 and 2 and accepts item 3. Neither items 1 or 2 are information currently included in ARV drug labels. FDA clarified that even if time to suppression <50 copies/mL is shorter with GSK1349572, the clinical significance is unknown.

### 1.9.3. Regulatory

**d. In the event of the NDA submission for the single entity being based on the results of ING113086, ING114467 and ING112574, would the Agency rather see available data from ING111762 at the time of the initial submission or wait until all subjects have completed their Week 24 visit before seeing data from the study [REDACTED] (b) (4)?**

*FDA's preliminary comments: We prefer ING111762 be submitted [REDACTED] (b) (4).*

Meeting Discussion: [REDACTED] (b) (4) FDA prefers to wait until all subjects have completed their Week 24 visit before submitting the data. FDA doesn't want to break the blind nor compromise the integrity of an ongoing trial for < 24 weeks of data for an original NDA. If GSK decides to submit the available data from ING111762 at the time of the initial submission, then additional information requested by FDA on May 17, 2010 needs to be submitted to further evaluate if group sequential analysis would be acceptable.

## **DECISIONS (AGREEMENTS) REACHED:**

1. Additional assessments in SPRING 1 and Phase 3 trials will be conducted to further investigate potential increase in serum creatinine and proteinuria.
2. 50 mg once daily of GSK1349572 will be used in Phase 3 therapy naïve trials (SPRING 2 and ING114467) based on the efficacy and safety results of SPRING 1 dose-ranging trial. FDA recommended GSK evaluate the Week 48 data prior to initiation of the Phase 3 trial to confirm the appropriateness of only evaluating the 50 mg dose vs two doses in Phase 3 given the potential renal issues.
3. Conduct a reduced design PK trial in subjects with severe renal impairment prior to the NDA submission in accordance to FDA's draft renal impairment guidance.
4. Conduct a post-approval trial in HIV infected subjects with severe hepatic impairment; however, FDA recommended GSK starts the trial as soon as possible given the lengthy enrollment time for this population.
5. Single dose trial design for the hepatic impairment trial is acceptable.
6. Collect PK data in as many subjects as possible, where appropriate, depending on the capabilities of the clinical site in the Phase 3 program.
7. Additional virologic failure definition will not be included prior to reaching Week 24 for clinical management for subjects who have virologic non-response to GSK1349572 (e.g., <1 log<sub>10</sub> HIV-1 RNA copies/mL reduction from baseline at Week 4) in Studies ING113086 and ING114467.
8. Exclude patients with recent history (3 months) of GI bleed to the Phase 3 studies.
9. Amylase monitoring will not be included in Phase 3. PT/PTT monitoring is at GSK's discretion.
10. Snapshot algorithm for the three non-inferiority studies will be used. Subjects who switched background regimen after Visit 1 due to toxicity will not be considered failures in the data as long as their intent to switch is documented and the viral load is <50 copies/mL at the time of switch. Please see snapshot document for details.
11. GSK1349572 PK samples will not be collected in ING114467.
12. (b) (4) Week 24 trial results for all patients enrolled in ING111762 should be submitted.
13. For ING114467, the secondary endpoint of the change from baseline in CD4 cell count at Week 48 is acceptable for labeling.

## **ISSUES REQUIRING FURTHER DISCUSSION**

1. GSK's proposed plan to demonstrate non-inferiority of GSK139572 to raltegravir in the ITT population in the treatment experienced (INI-naïve population) remains a review issue.
2. Whether or not to dose adjust GSK1349572 with co-administration of TPV/r and EFV in ING111762.
3. Clarification if pre-treatment genotypic data in the resistance analysis plan will include all subjects or virologic failures only.

**ACTION ITEMS:**

1. GSK will provide preliminary data from Part 2 of the ING113674 within the next two weeks. The full study report of ING113674 is expected to be completed in October 2010.
2. GSK plans to evaluate whether GSK1349572 is a substrate for BCRP and the data for the inhibitory effects of GSK1349572 on CYPs 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A will be forthcoming.
3. If GSK decides to include ING111762 in the initial NDA submission, then additional information requested by FDA on May 17, 2010 needs to be submitted to further evaluate if group sequential analysis would be acceptable.
4. GSK plans to have additional communication, written or teleconference, with FDA to address FDA's preliminary comments to the briefing package questions and GSK protocols not discussed in the meeting.

**ATTACHMENTS/HANDOUTS:**

Attachment 1: GSK's Slide Presentation

Attachment 1

**GSK1349572 End of Phase 2 Meeting**  
**IND 75,382**

July 13, 2010



**SHIONOGI**



Shionogi - ViiV Healthcare, LLC

# **GSK1349572 (572) EOP2 Meeting Agenda**

**Introductions**

**Discussion of Safety Related Data from  
ING112276 (SPRING-1)**

**Discussion of Questions**

**Summary of Meeting Conclusions & Action Items**

**AOB**



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**ING112276 / SPRING-1**

**Week 24 Analysis – Top Line Summary  
Safety-Related Data**

**Spring-1**



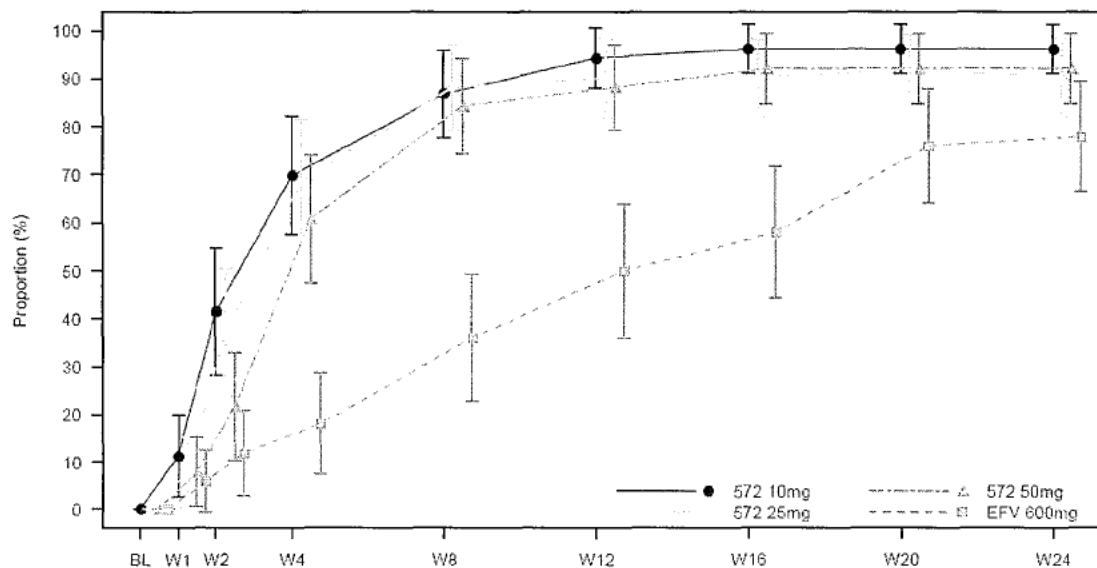
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# Primary: % <50 copies/mL (TLOVR)

|         | 572<br>10mg<br>(N=53) | 572<br>25mg<br>(N=51) | 572<br>50mg<br>(N=51) | 572<br>Subtotal<br>(N=155) | EFV<br>600mg<br>(N=50) |
|---------|-----------------------|-----------------------|-----------------------|----------------------------|------------------------|
| Week 1  | 6 / 53 (11%)          | 4 / 51 (8%)           | 4 / 51 (8%)           | 14 / 155 (9%)              | 3 / 50 (6%)            |
| Week 2  | 22 / 53 (42%)         | 19 / 51 (37%)         | 11 / 51 (22%)         | 52 / 155 (34%)             | 6 / 50 (12%)           |
| Week 4  | 37 / 53 (70%)         | 35 / 51 (69%)         | 31 / 51 (61%)         | 103 / 155 (66%)            | 9 / 50 (18%)           |
| Week 8  | 46 / 53 (87%)         | 45 / 51 (88%)         | 43 / 51 (84%)         | 134 / 155 (86%)            | 18 / 50 (36%)          |
| Week 12 | 50 / 53 (94%)         | 46 / 51 (90%)         | 45 / 51 (88%)         | 141 / 155 (91%)            | 25 / 50 (50%)          |
| Week 16 | 51 / 53 (96%)         | 46 / 51 (90%)         | 47 / 51 (92%)         | 144 / 155 (93%)            | 29 / 50 (58%)          |
| Week 20 | 51 / 53 (96%)         | 47 / 51 (92%)         | 47 / 51 (92%)         | 145 / 155 (94%)            | 38 / 50 (76%)          |
| Week 24 | 51 / 53 (96%)         | 46 / 51 (90%)         | 47 / 51 (92%)         | 144 / 155 (93%)            | 39 / 50 (78%)          |



# Lab – Creatinine, CRT Clearance

|                                                | 572<br>10mg<br>(N=53) | 572<br>25mg<br>(N=51) | 572<br>50mg<br>(N=51) | 572<br>Subtotal<br>(N=155) | EFV<br>600mg<br>(N=50) |
|------------------------------------------------|-----------------------|-----------------------|-----------------------|----------------------------|------------------------|
| <b>CRT Maximum Treatment Emergent Toxicity</b> |                       |                       |                       |                            |                        |
| Grade 1                                        | 0                     | 4 (8%)                | 0                     | 4 (3%)                     | 0                      |
| <b>Creatinine (µmol/L)</b>                     |                       |                       |                       |                            |                        |
| Baseline                                       | 82.0                  | 88.1                  | 82.2                  |                            | 79.5                   |
| Week 1 Change from Baseline (SD)               | 8.5 (8.04)            | 9.0 (8.85)            | 11.9 (6.79)           |                            | 1.1 (7.79)             |
| Week 16 Change from Baseline                   | 8.1 (8.83)            | 7.0 (9.77)            | 12.4 (9.39)           | 9.1 (10.65)*               | 0.8 (6.99)             |
| Week 24 Change from Baseline                   | 4.4 (9.15)            | 5.1 (11.91)           | 10.6 (7.75)           | 6.6<br>(10.08)**           | -2.0 (10.08)           |
| <b>Week 32 Change from Baseline</b>            | <b>2.8 (8.36)</b>     | <b>2.1 (11.85)</b>    | <b>6.0 (8.80)</b>     |                            | <b>-6.1 (8.31)</b>     |
| * data for ~44-50 subjects per arm             |                       |                       |                       |                            |                        |

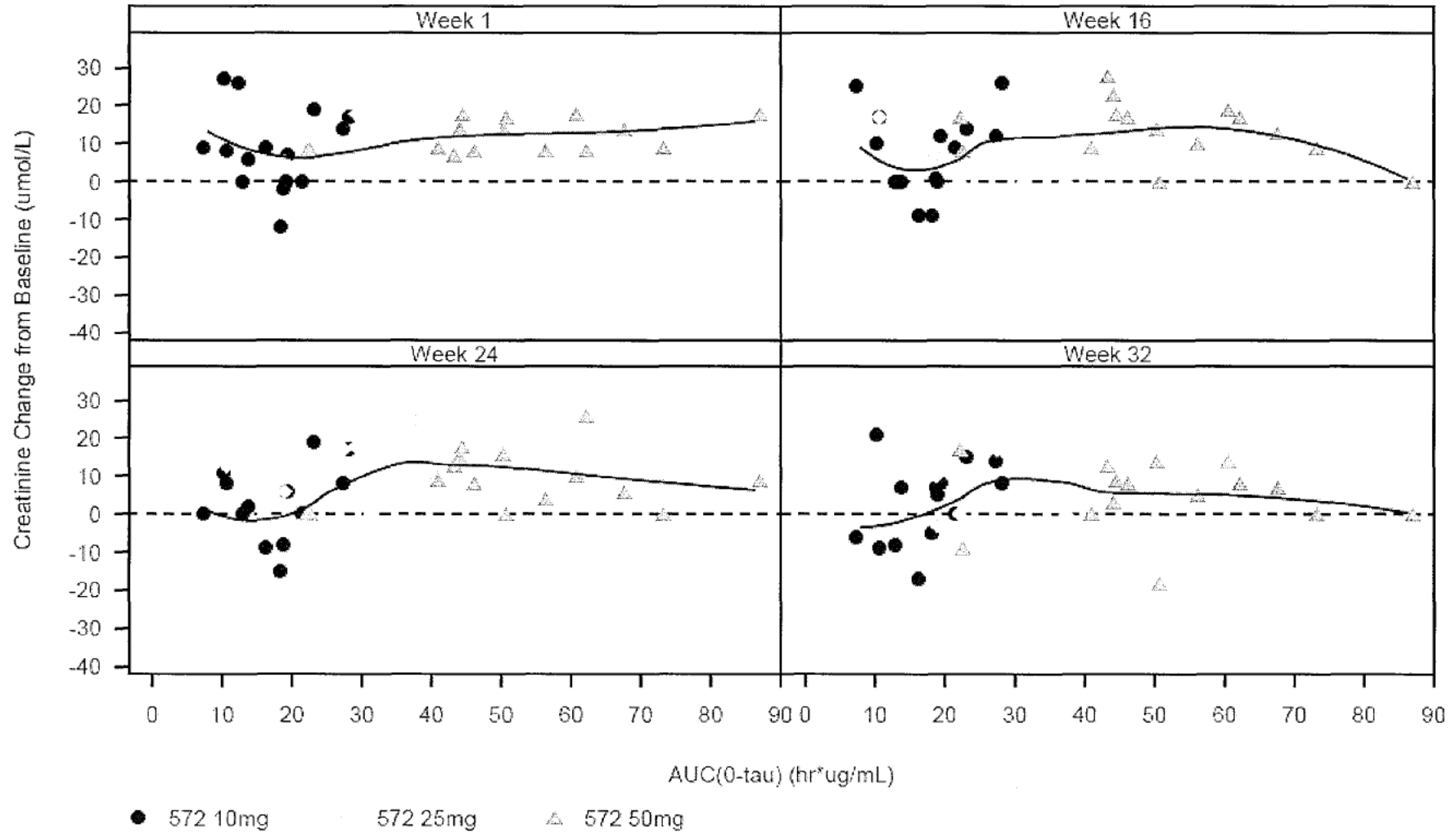
## Creatinine Clearance - Cockcroft-Gault (mL/min)

|                                   |              |              |              |  |             |
|-----------------------------------|--------------|--------------|--------------|--|-------------|
| Baseline                          | 116.0        | 115.8        | 118.6        |  | 118.5       |
| Week 24 Change from Baseline (SD) | -5.0 (13.55) | -4.5 (16.77) | -11.2 (9.42) |  | 4.7 (16.25) |

\* p<0.001 vs. EFV;      by NRTI:      TVD: p<0.001 vs. EFV      K VX: p=0.021 vs. EFV  
 \*\* p<0.001 vs. EFV;      TVD: p<0.001 vs. EFV      K VX: p=0.115 vs. EFV

# Exposure-response investigation (AUC)

Scatter Plot of Creatinine Change from Baseline vs. AUC(0-tau)



# **Creatinine increase: hypothesis**

- **Rapid onset of small mean increases in creatinine without progression are likely due to blockade of tubular creatinine secretion via OCT2 (similar to cimetidine or trimethoprim)**
  - Note: mean serum creatinine increases of ~10% observed in ph1/2a studies, resolved at f/u off drug (consistent with OCT2 inhibition)
- **Plan: Evaluate interference of GSK1349572 with OCT2 receptor**
  - Preliminary results available c/w hypothesis above



# Mechanism for effect of 572 on SCr: Potent OCT2 inhibition



| Condition                                                          | Cellular Accumulation (transporter) (pmol/min/cm <sup>2</sup> ) | Cellular Accumulation (control) (pmol/min/cm <sup>2</sup> ) | Net Transporter Mediated Cellular Accumulation (pmol/min/cm <sup>2</sup> ) | Inhibition (%) |
|--------------------------------------------------------------------|-----------------------------------------------------------------|-------------------------------------------------------------|----------------------------------------------------------------------------|----------------|
| vehicle (0.5% DMSO)                                                | 22.5 ± 3.45                                                     | 1.89 ± 0.249                                                | 20.7 ± 3.45                                                                | 0.00 ± 16.7    |
| 100 µM cimetidine                                                  | 11.1 ± 2.92                                                     | 1.84 ± 0.417                                                | 9.22 ± 2.92                                                                | 55.4 ± 27.6    |
| 200 µM cimetidine                                                  | 7.15 ± 1.37                                                     | 1.65 ± 0.196                                                | 5.51 ± 1.37                                                                | 79.3 ± 6.61    |
| 100 µM quinidine                                                   | 4.86 ± 0.935                                                    | 1.64 ± 0.210                                                | 3.22 ± 0.935                                                               | 84.4 ± 1.62    |
| 25 µM GSK1349572                                                   | 3.34 ± 0.749                                                    | 1.48 ± 0.192                                                | 1.87 ± 0.749                                                               | 91.0 ± 3.62    |
| 25 µM GSK1349572 + 10 µM abacavir + 10 µM lamivudine               | 2.79 ± 0.0426                                                   | 1.27 ± 0.0213                                               | 1.52 ± 0.0426                                                              | 92.6 ± 0.206   |
| 25 µM GSK1349572 + 1 µM tenofovir disoproxil + 10 µM emtricitabine | 3.11 ± 0.259                                                    | 1.67 ± 0.112                                                | 1.44 ± 0.259                                                               | 93.0 ± 1.25    |

## • Next steps

- Titrate to an IC50 for OCT2 inhibition, test for NRTI additivity with lower concentrations of 572

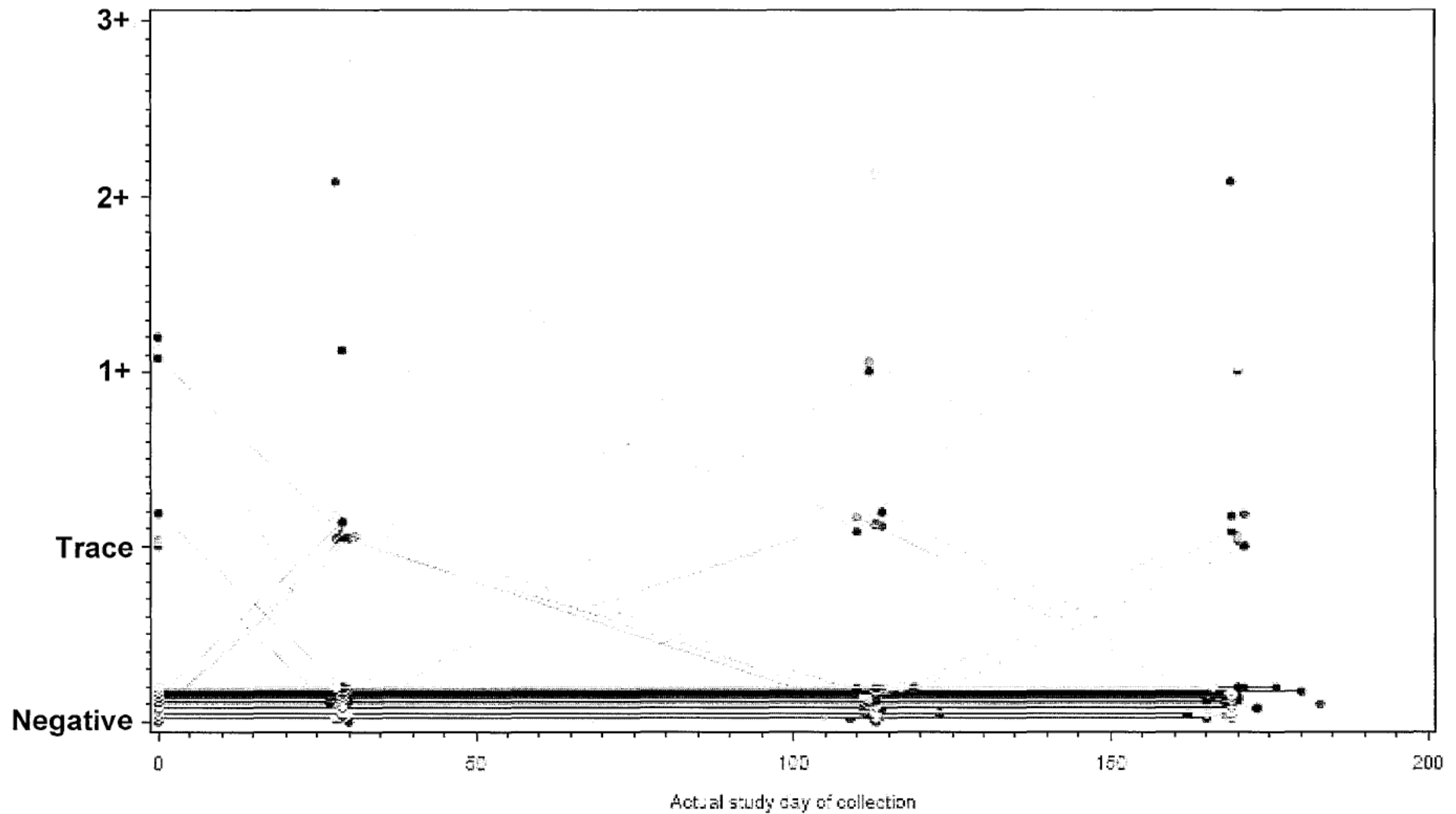


# SPRING-1 Urine protein results

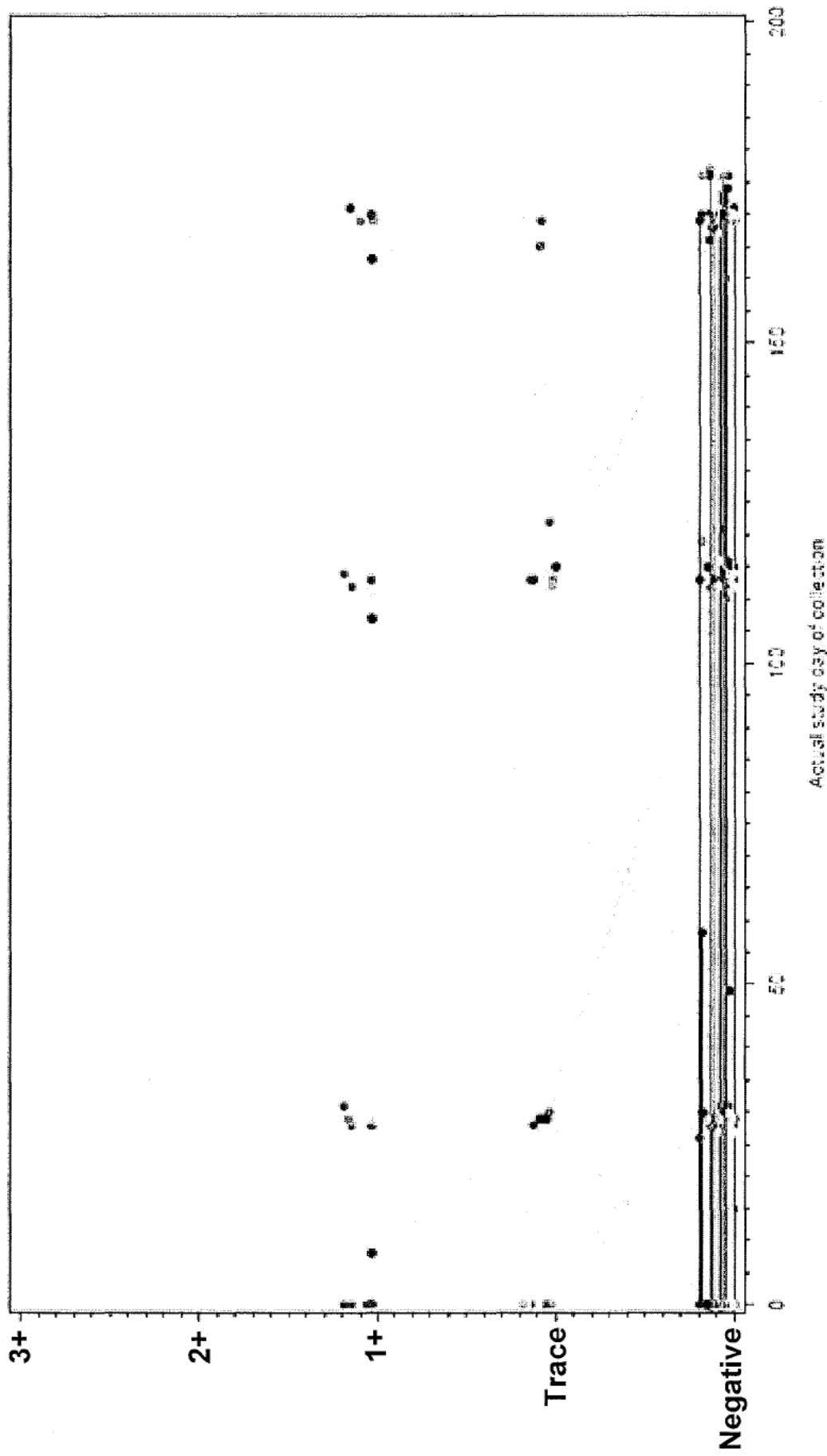
- In 572 arms – greater percentage of subjects (compared with EFV) with treatment-emergent shifts in urine protein dipstick results
  - ~35% in 572 arms vs. 6% in EFV (12% on 572 vs. 2% on EFV with  $\geq 1+$ )
  - Primarily neg to trace or trace to 1+
  - No time or dose trend apparent, intermittent
  - Confounders for some subjects with  $\geq 1+$  [WBCs, nitrites, LEs in UA, NSAID use, confounding medical conditions (e.g., HTN, Hep C, DM)]
- Bayer U/A Multistix performance characteristics
  - Urine protein via dipstick testing is semi-quantitative
    - Positive results based upon acid-base interactions
    - Some drugs and antiseptics cause false positive results
  - An automated reader (Bayer Clinitek Atlas) assesses the results
  - Minor changes could shift results in one or the other direction
- Urine protein by dipstick may be unreliable in HIV-infected subjects (Siedner et al., *J Acquir Immune Defic Syndr.* 2008 Feb 1;47(2):261-3)



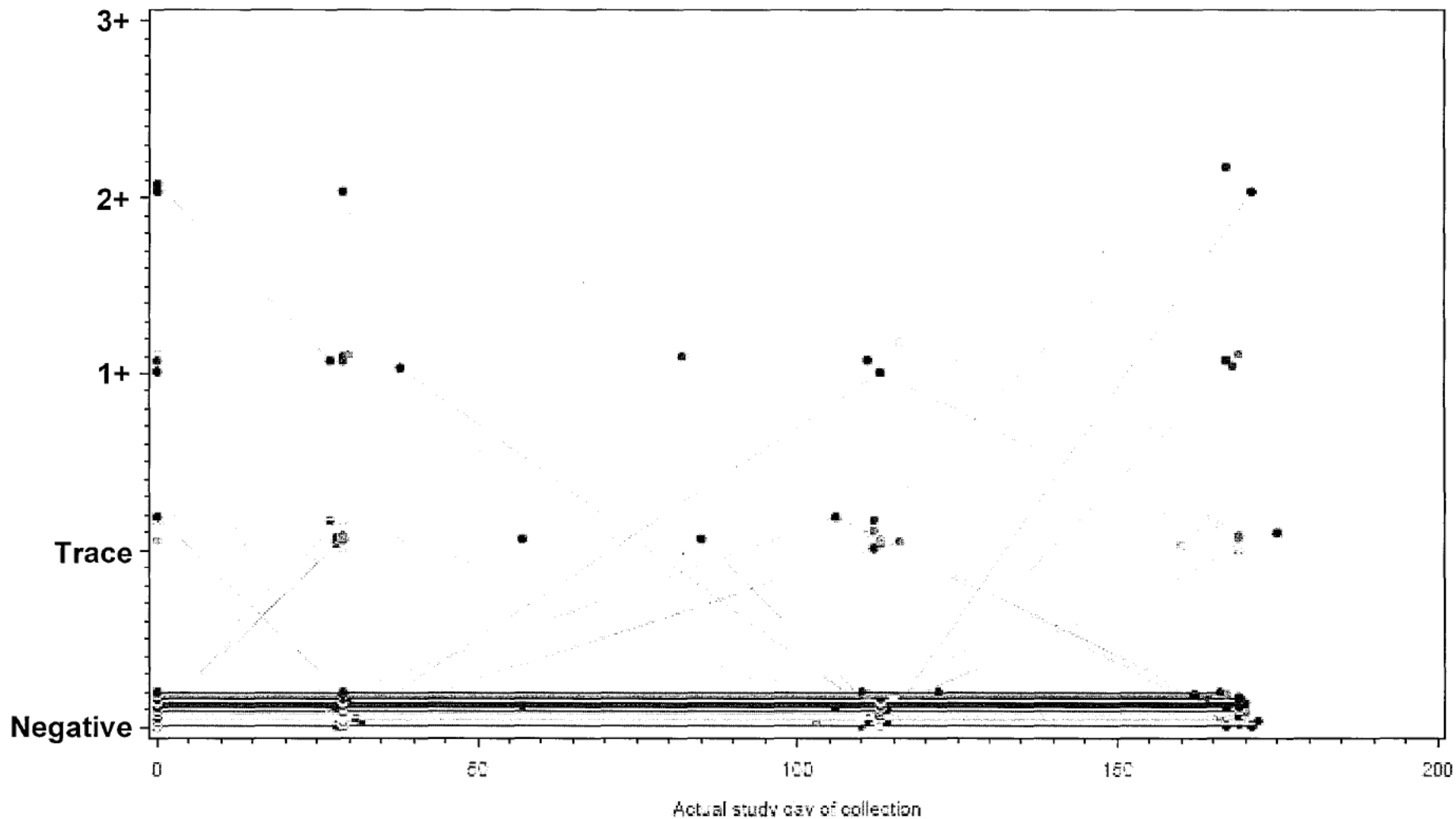
# Urine Protein (Dipstick): GSK1349572 10 mg once daily



# Urine Protein (Dipstick): GSK1349572 25 mg once daily



# Urine Protein (Dipstick): GSK1349572 50 mg once daily





# Proposed additional assessments (I)

- **Analysis of 572 parent compound interference with colormetric assay for protein on dipstick UA**
  - Being performed by Quest, results expected by end Aug 2010
- **Phase 1: Iohexol study in healthy subjects**
  - Study to assess the effect of GSK1349572 on glomerular filtration rate (GFR, via iohexol clearance), serum Cystatin-C and 24-hr urine protein and albumin in healthy subjects planned to start by 4Q2010
  - Will also look at proximal and distal tubular proteins (e.g.,  $\beta$ 2-microglobulin, retinol binding protein)
- **Phase 2b: SPRING-1 and VIKING**
  - Add urinalysis with dipstick, spot microalbumin/creatinine @ q12 wk assessment after 24 wk and 48 wk timepoints in Viking and Spring, respectively
  - Continue q12 wk creatinine and electrolytes in both studies post Wk 24 and 48
  - Additional guidance for abnormal urine protein results



# Proposed additional assessments (II): Phase 3 studies

- Detailed renal disease history at Baseline
- Urinalysis with dipstick and spot morning (preferred) microalbumin/creatinine at Baseline and Weeks 24, 48, 96 and withdrawal in Ph3 studies
- Serum creatinine and electrolytes as outlined in the draft protocols (Baseline and Weeks 4, 8, 12, 16, 24, 32, 40, 48, and then q12 wks)
- Additional serum renal biomarkers (i.e., Cystatin-C) not proposed as confounded by HIV-1 RNA and CD4 cell count
  - Mauss et al. Antiviral Therapy 2008; 13:1091-1095
- Guidance to investigators (including confirmatory testing and appropriate medical follow-up) for subjects with abnormal urine protein and creatinine/creatinine clearance results
- Further details will be communicated after the meeting



# Dose Selection for INI-naïve studies and Ph2b dose-ranging study

- **Efficacy supports selection of 572 50mg QD**
- **Safety supports selection of 572 50 mg QD**
  - **Creatinine elevation appears to be related to inhibition of creatinine secretion (rather than negative impact to GFR) based on pattern of change from baseline and preliminary OCT2 results**
    - **Further elucidation in in vitro and Phase 1 assessments**
  - **Significance of urine protein results is under evaluation and will be monitored appropriately in Ph3 as described**

# Questions for Review Team



**SHIONOGI**



Shionogi - ViiV Healthcare, LLC

# Questions to the Review Team – Clin Pharm

## 1.2 Clinical Pharmacology

b. Based on the available pharmacokinetic (PK) and safety data collected in Phase 1 and Phase 2 studies, does the Agency agree that GSK1349572 can be administered without regard to food during Phase 3?

- *Defer until results of Part B of ING113674 are available*
- *Preliminary data within next 2 weeks*
- *CSR in October 2010*



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# Questions to the Review Team – Clin Pharm

## Clinical Pharmacology continued

c. The mass balance study (ING111853) demonstrated that renal excretion represents a minor pathway for elimination of GSK1349572; therefore the Company does not intend to conduct a study in subjects with renal impairment. Does the Agency agree with this plan?

- *GSK plans to conduct a reduced design PK study in subjects with severe renal impairment prior to NDA submission*



# Questions to the Review Team – Clin Pharm

## Clinical Pharmacology continued

d. Does the Agency agree with our plan for additional clinical pharmacology studies during the Phase 3 program which will support initial registration of GSK1349572?

(b) (4)

# Questions to the Review Team – Clin Pharm

## Hepatic Impairment Trial

d. We recommend a basic full study design (instead of a reduced study design) because a full study design would provide information regarding GSK1349572 PK in subjects with severe hepatic impairment

*2. a. GSK proposes to conduct a study in non-HIV infected subjects with moderate hepatic impairment in 4Q 2010. Since enrollment of severe hepatic impairment subjects is difficult, GSK proposes that this study be done as a post-approval trial. The study will likely evaluate HIV-infected subjects who will have a more favorable risk/benefit for receiving 572.*

# Questions to the Review Team – Clin Pharm

## Hepatic Impairment Trial

- d) The guidance for hepatic impairment trials recommends a single dose trial if the drug and active metabolites exhibit linear and time independent PK. Because nonlinearity has been observed in GSK1349572 exposure over the range of 2mg to 50mg and 50mg to 100mg based on data from healthy and HIV-1 infected subjects, please provide further information as to why a single dose trial was selected vs a multiple dose trial.
- *SPRING-1 demonstrates linear PK in AUC from 25 to 50mg (see next slide). The non-linearity between 10mg and 25mg (and 50mg) is likely due to differences in tablet strengths (10mg tablets vs 25 mg tablets for 25 and 50mg doses*
  - *100mg as a single dose will be not be studied in Phase 3 trials*
  - *Based on ING111322 and ING111521, single dose PK predicts repeat dose PK*
  - *These data demonstrate linear PK over the clinically relevant dose range and support a single dose trial design for the hepatic impairment study*



# Summary of PK Parameter by Dose ING112276 SPRING-1

| Dose (mg) | Tablet  | Parameter | Cmax (µg/mL) | AUC(0-τ) (hr.µg/mL) | Cτ (µg/mL) | Cmin (ug/mL) |
|-----------|---------|-----------|--------------|---------------------|------------|--------------|
| 10        | 10mg    | N         | 15           | 15                  | 47         | 15           |
|           |         | GeoMean   | 1.10         | 16.0                | 0.30       | 0.33         |
|           |         | %CV       | 37           | 40                  | 71         | 64           |
| 25        | 25mg    | N         | 15           | 15                  | 44         | 15           |
|           |         | GeoMean   | 1.71         | 23.1                | 0.54       | 0.44         |
|           |         | %CV       | 43           | 48                  | 67         | 68           |
| 50        | 2x 25mg | N         | 15           | 15                  | 44         | 15           |
|           |         | GeoMean   | 3.40         | 48.1                | 1.20       | 0.94         |
|           |         | %CV       | 27           | 40                  | 62         | 74           |

Linear PK demonstrated between 25mg and 50mg



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## Questions to the Review Team – Clin Pharm

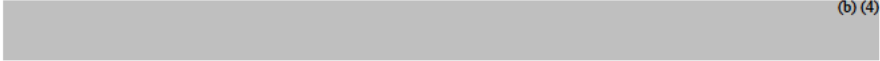
- Because nonlinearity in GSK1349572 exposure of the range of 2mg to 50mg and 50mg to 100mg has been reported, please comment on the method(s) that will be used to derive hepatic impairment dosage adjustment recommendations.
- *The need for dose adjustment in hepatically impaired subjects will depend on the magnitude of any increase observed.*
- *SPRING-1 demonstrates dose proportionality between 25mg and 50mg.*
- *A downward adjustment from 50mg to 25mg will be based on a linear relationship.*
- *Though we do not expect large increases in exposures, if seen, we will consider options for dosage recommendations requiring dosages lower than 25mg to achieve an exposure similar to 50mg*



## Questions to the Review Team – Clin Pharm

- Please specify the information and the analysis (including the relevant trials) used to conclude dose proportionality is observed for GSK1349572 tablets from 2mg to 50 mg.
- *Clarification: Dose proportionality exhibited linear PK from 2mg to 100mg with the suspension. For the tablet formulation, linear PK has been shown between 25mg and 50mg (ING112276). PK is nonlinear (less than dose proportional between 2mg and 100mg).*

## Questions to the Review Team – Clin Pharm

- Please clarify whether the dose proportionality for the new GSK1349572 25mg or 50mg tablets is anticipated to be similar to the current formulation
- *Dose proportionality would be expected to be similar to the current formulation from 25 mg to 50 mg based on:*
  - *The new formulation had only minor change in excipients*  
 (b) (4)
  - *The new formulation demonstrated bioequivalence with the current formulation*

# Questions to the Review Team – Clin Pharm

## Clinical Pharmacology continued

- Please clarify if there are any GSK1349572 metabolites that are considered active and should be further evaluated
- *There are no significant active metabolites of GSK1349572 that require evaluation*
  - *Plasma exposure is > 95% parent compound following administration of GSK1349572*
  - *Primary metabolite is glucuronide (~19% of the dose) in the urine; substitution of the glucuronide at the conjugated position disrupts the metal binding and removes all antiviral activity*
  - *The activity of the oxidative metabolites is unknown, however they are not quantifiable in plasma and represent only 3% of the dose in urine*



## Questions to the Review Team – Clin Pharm

- Please clarify if the following will be evaluated: a) the inhibitory effects of GSK1349572 on CYP 2C8, BCRP, and OCT2, and b) whether GSK1349572 is a substrate for BCRP
- *A full evaluation of the inhibition potential against CYP enzymes has been concluded and a draft report is currently under review. The study evaluated direct and metabolism dependent inhibition potential for CYPs 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4.*
- *Evaluation of BCRP is planned*
- *Preliminary data on OCT2 inhibition as shown in a previous slide.*

## Questions to the Review Team – Clin Pharm

- Does the Agency agree with our proposed dosing recommendations for GSK1349572 in combination with TPV/r and EFV?
- *The Agency suggested that the 10mg dose in ING112276 be continued past week 24; one benefit was to evaluate exposure-response in the event of drug interactions leading to reduced 572 exposures*
  - *The 10mg arm has similar efficacy to the 25mg and 50mg arms demonstrating that the exposures at this dose have potent antiviral activity in treatment-naïve subjects*
  - *We believe the 50 mg once daily dose achieves therapeutic concentrations in INI-naïve subjects with or without TPV/r and EFV*



# Questions to the Review Team – Clin Pharm

- When 572 is administered with EFV or TPV/r, IQ values still exceed the PA-IC90 by > 4-fold

| Study (Protocol )                    | 572 dose | AUC GLS mean ratio | 572 AUC0- $\tau$ ( $\mu\text{g}\cdot\text{h}/\text{ml}$ ) | $C_{\tau}$ GLS mean ratio | 572 $C_{\tau}$ ( $\mu\text{g}/\text{ml}$ ) | 572 IQ ( $C_{\tau}$ / PA-IC90) |
|--------------------------------------|----------|--------------------|-----------------------------------------------------------|---------------------------|--------------------------------------------|--------------------------------|
| Phase 2b treatment-naïve (ING112276) | 50mg     | NA                 | 48.1 (40) <sup>a</sup>                                    | NA                        | 1.20 (62) <sup>a</sup>                     | 19                             |
| Phase 2b treatment-naïve (ING112276) | 10 mg    | NA                 | 16.0 (40) <sup>a</sup>                                    | NA                        | 0.30 (71) <sup>a</sup>                     | 4.7                            |
| Etravirine (ING111603)               | 50 mg    | 0.294              | 14.1 <sup>b</sup>                                         | 0.121                     | 0.15 <sup>b</sup>                          | 2.3                            |
| Etravirine + LPV/RTV (ING112934)     | 50 mg    | 1.10               | 52.9 <sup>b</sup>                                         | 1.28                      | 1.54 <sup>b</sup>                          | 24                             |
| Etravirine + DRV/RTV (ING112934)     | 50 mg    | 0.75               | 36.1 <sup>b</sup>                                         | 0.63                      | 0.76 <sup>b</sup>                          | 12                             |
| Tipranavir/ritonavir (ING113096)     | 50 mg    | 0.41               | 19.7 <sup>b</sup>                                         | 0.24                      | 0.29 <sup>b</sup>                          | 4.5                            |
| Efavirenz (ING114005)                | 50 mg    | 0.43               | 20.7 <sup>b</sup>                                         | 0.25                      | 0.30 <sup>b</sup>                          | 4.7                            |

a = Observed data reported as Mean (CV%)  
 b = Estimated PK parameter based on mean ratio multiplied by 50mg value in ING112276

## Questions to the Review Team – Clin Pharm

- *ING111762 provides the best opportunity to evaluate the impact of ARV drug interactions on the efficacy of GSK1349572 50 mg once daily in the INI-naive, treatment experienced population*
- *It would be difficult to dose adjust in a blinded, double dummy, randomized trial in patients taking EFV or TPV/r*
- *Conclusion: We propose no dose adjustment in ING111762 for co-administration of GSK1349572 50 mg once daily with TPV/r or EFV*
  - *Dose adjustment for ING112574 will be addressed at a later time in that protocol*



# Questions to the Review Team – Clin Pharm

## Clinical Pharmacology continued

- Does the Agency agree with the planned collection of PK samples in the Phase 3 program?
- *PK data will be collected in as many subjects as possible, where appropriate, depending on the capabilities of the clinical site*

# Questions to the Review Team – Virology

**1.3.a. Does the Agency agree with the planned resistance testing across the Phase 3 studies?**

**GSK**

- 1. Yes, baseline and on-treatment virus samples from subjects who prematurely discontinue before Week 24 (naïve subjects) or Week 16 (experienced subjects) with HIV-1 RNA  $\geq 400$  copies/mL will be included in our resistance testing.**
- 2. As screen samples may evolve we feel baseline samples should provide a better comparison. An association of IN polymorphisms with decreased response should reveal as a greater than expected number of such polymorphisms in subjects experiencing virologic failure. As such, both baseline and confirmed virologic failure samples for all subjects experiencing virologic failure will be subject to IN genotypic assay for the research analysis plan.**



**SHIONOGI**

Shionogi - ViiV Healthcare, LLC



# Questions to the Review Team – Virology

**1.3.b. Does the Agency agree with the virologic failure criteria proposed for patient management and resistance testing for each of the Phase 3 studies?**

**FDA:**

- 1. Please include an additional virologic failure definition prior to reaching Week 24 for clinical management for subjects who have virologic non-response to GSK1349572 (e.g., <1 log<sub>10</sub> HIV-1 RNA copies/mL reduction from baseline at Week 4) in Studies ING113086 and 114467.***

**GSK: Thank you for the suggestion. However, for both studies we believe imposing this definition might bias the study in favor of GSK1349572.**

**Based on our SPRING-1 data we feel it will be extremely unlikely that we would not see a 1 log<sub>10</sub> decrease by week 4 for GSK1349572.**

**There is an expected slower response rate for subjects receiving EFV, which can lead to preferentially withdrawal of Atripla subjects. This could unfairly bias the response in favor of Epzicom/572 in ING114467.**

**For ING113086, virologic failure criteria was the same as STARTMRK, since this is the pertinent study for the NI assessment.**

**Purpose for including in Spring-1 was to assess if lower doses of 572 would perform as well as higher doses.**

**What is the rationale for including this additional virologic failure definition?**



**SHIONOGI**

**Shionogi - ViiV Healthcare, LLC**



# Questions to the Review Team - Clinical Relative to 572 and FDC

## Clinical continued

- Does the Agency agree that the collective safety data supports broadening the eligible patient population for the Phase 3 studies to more accurately describe the safety profile of GSK1349572? We propose not including specific exclusion criteria for risk factors for cardiac and upper gastrointestinal complications. Does the Agency agree?
  - See next slide

# Cardiovascular Risk Assessment and GI Exclusion

- **Primary purpose of data is not to make determinations for nucleoside backbone choice**
  - Not intended to be used as an exclusion criterion
- **Primary purpose is to characterize CV risk profile at baseline for the entire population being studied, which is in line with large HIV cohort studies and baseline data collection (e.g., DAD)**
- **Exclusion of recent history (3 months) of GI bleed will be added to the ph3 studies**



# Questions to the Review Team - Clinical Relative to 572 and FDC

- **Does the Agency agree with the proposed safety monitoring across the Phase 3 program?**
  - **Specifically, does the Agency agree that amylase and PT/PTT monitoring is not required in Phase 3?**
    - **See next slide**



# Coagulation Parameters – Results from Spring-1

**Table 11 Week 24 Mean Change from Baseline in Coagulation Parameters**

|                                                       | 572 10mg  | 572 25mg   | 572 50mg   | EFV         |
|-------------------------------------------------------|-----------|------------|------------|-------------|
| aPTT (sec)<br>Mean, Median<br>Change from<br>Baseline | 1.7, 0.0  | 3.5, 1.0   | 2.7, 1.0   | -0.5, 0.0   |
| PT (sec)<br>Mean, Median<br>Change from<br>Baseline   | 0.49, 0.0 | 0.08, 0.30 | 0.31, 0.20 | -0.15, 0.15 |
| INR<br>Mean, Median<br>Change from<br>Baseline        | 0.0, 0.0  | -0.04, 0.0 | 0.0, 0.0   | -0.05, 0.0  |

Preclinical changes in coagulation parameters were seen in subset of studies at highest dose evaluated, primarily observed in very sick animals

**Please clarify your concern so that we can have a better understanding of the clinical impact of these data.**



# Questions to the Review Team - Protocol Specific Questions

## ING111762

- Does the Agency agree that the changes made to ING111762 since the conference call on May 18, 2010 (*specifically, change in inclusion criteria to restrict the population to subjects with at least 2-class ARV resistance, inclusion of subjects with one partially active agent in the background regimen, and the inclusion of a key secondary analysis excluding subjects who are using DRV/r and whose virus shows no evidence of resistance to protease inhibitors*), could provide a more interpretable assessment of the non-inferiority of GSK1349572 to raltegravir?



# Demonstration of NI in ITT population

- **Current protocol:**
  - Exclude PI-susceptible DRV/r recipients from analysis (AS population)
- **Option:**
  - Exclude use of DRV/r in fully PI-susceptible patients<sup>1</sup>
- **Fully active PI/r stratification a simple surrogate for OBR activity**
  - Suggested DRV/r stratification acceptable
  - For option above, triple class resistance may be preferable

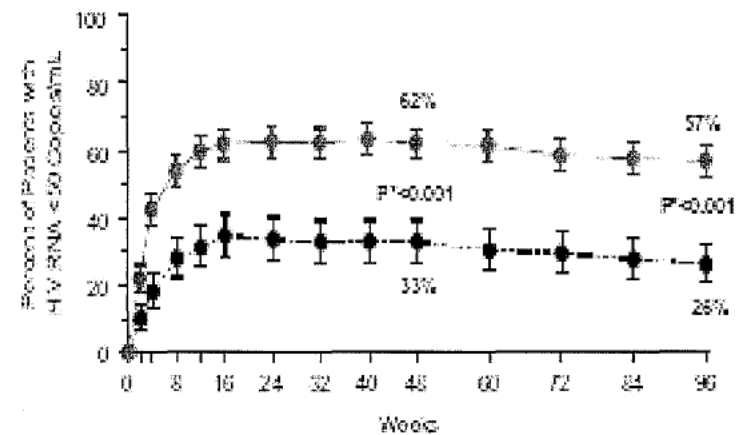
<sup>1</sup>: patients without primary PI mutations



# Pooled Benchmark Response Rates by PSS at Week 48 and Week 96

|     |     | Response Rate (%)    |                      |
|-----|-----|----------------------|----------------------|
|     |     | Week 48 <sup>1</sup> | Week 96 <sup>2</sup> |
| PSS | 0   | 33/65 (51)           | 30/63 (48)           |
|     | 1   | 83/137 (61)          | 85/131 (65)          |
|     | 2   | 99/139 (71)          | 93/134 (69)          |
|     | 1,2 | 182/276 (66)         | 178/265 (67)         |
|     | >=3 | 58/82 (71)           | 40/74 (54)           |

Percent of Patients (95% CI) Achieving HIV RNA < 50 Copies/mL (NC=F Approach)



Number of Contributing Patients

|                     |     |     |     |     |
|---------------------|-----|-----|-----|-----|
| ● Raltegravir + OBI | 462 | 461 | 459 | 460 |
| ● Placebo + OBI     | 237 | 237 | 237 | 237 |

1. Cooper et al NEJM 2008; 359:355-65
2. Steigbigel et al CID 2010; 50:605-612
3. Steigbigel et al (CROI, 2009)

# ING111762: Wk 48 v. Wk 96 Conduct

## Conclusions

- Richest dataset for comparison is contained in first 48 wks
- Increasing trial duration to 96 Wks does not substantively improve probability of showing significant reduction in failure rate relative to Raltegravir
- Safety evaluation
  - Subjects will remain on 572 until commercially available, so longer term safety data will be available for 572 subjects
  - Comparisons to RAL and EFV out to 96 wks in 2 naïve studies will provide a better assessment



# Questions to the Review Team - Statistical

- **The Company proposes different interpretations of the FDA's snapshot algorithm for each of the three non-inferiority studies to match the different consequences of a switch of the background regimen in each study. Does the FDA agree with this approach?**
  - See next slide.



# Snapshot Algorithm – GSK Response

- Intention is to use snapshot algorithm
- MD=F name used for global trials as “snapshot” not yet internationally recognised
- Outstanding questions:
  - Can documentation of a decision to switch before or at Visit 1 exclude “failure”?
  - Transient changes in background therapy (e.g. rectified dispensing mistakes) as failure (ING113086, ING111762)?
  - Visit schedule for ING111762, ING113086, ING111467 includes Weeks 32, 40. Acceptable for Week 48 visit window to include Weeks 42-54?



## Questions to the Review Team – Regulatory

- **Does the Agency agree that the planned clinical program with appropriate clinical pharmacology studies, is adequate to submit an initial New Drug Application (NDA) for accelerated approval of GSK1349572?**
- **GSK Response: Would the Review Team please clarify what you mean by “standard approval?”**
  - Traditional approval (48 week data) with potential for priority review



# Questions to the Review Team - GSK1349572

## FDC - Clinical

### Clinical - ING114467

- Plasma samples will be collected during Phase 3 in ING113086, ING11762, and ING112754 for population PK analysis and to evaluate PK/PD relationships. The Company does not plan to collect samples for determination of PK in ING114467 (GSK1349572 FDC protocol). Does the Agency agree with this proposal?

*GSK: we plan not to collect 572 PK in ING114467 for the following reasons:*

- *Enough PK data will be collected from ING112276 and ING113086 to evaluate the population PK and effect of patient characteristics on 572 PK*
- *Wide PK exposure range is needed in order to evaluate exposure-creatinine response relationship. ING114467 evaluates one dose, 50mg QD. Based on PK data from ING112276, PK variability is very small in the treatment-naïve population (CV% on AUC and C<sub>max</sub> is only ~40%). The best place to evaluate such relationship is in ING112276 where 3 dose levels of GSK1349572 from 10 to 50mg are being evaluated.*



# Questions to the Review Team - GSK1349572

## FDC - Statistical

### Statistical

- Does the Agency consider that multiplicity adjustments (e.g. closed testing) are necessary for the secondary endpoints in ING114467?

- GSK Response:  (b) (4)



 (b) (4)

– Change from baseline in CD4 cell count @ Wk 48



# Questions to the Review Team GSK1349572 FDC – Regulatory and Stats

- In the event that the GSK1349572 NDA is based on the results of ING113086, ING114467 and ING112574, would the Agency rather see available data from ING111762 at the time of the initial submission (e.g., group sequential analysis) or wait until all subjects have completed their Week 24 visit before seeing data from the study [REDACTED] <sup>(b) (4)</sup>?
- GSK: Regardless of the backup submission plan, in principle, would the Review Team accept a group sequential analysis of Week 24 data from ING111762 in the initial submission?



# Meeting Conclusions & Action Items

**Brief run through of action items**

**AOB**

| Application<br>Type/Number | Submission<br>Type/Number | Submitter Name      | Product Name                           |
|----------------------------|---------------------------|---------------------|----------------------------------------|
| IND-75382                  | GI-1                      | GLAXOSMITHKLIN<br>E | GSK1349572(HIV INTEGRASE<br>INHIBITOR) |

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JEFFREY S MURRAY  
08/06/2010