



16.1.9.3 BIOANALYTICAL REPORTS

Study ZRHM-REXA-08-US Sample Reconciliation Report



Study ZRHM-REXA-08-US
Sample Reconciliation Report

Study Title:

A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in apparently healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 86 days in an ambulatory setting

Sponsor:

Philip Morris Products S.A.
PMI Research & Development
Quai Jeanrenaud 5
2000 Neuchâtel, Switzerland

Authors:

Jasmine Ropers
Covance Project Manager

Amy Rainey
Senior Clinical Research Associate

Version:

Final

Date:

05 NOV 2015



Sample Reconciliation Report

Final 05 NOV 2015

ZRHM-REXA-08-US

APPROVALS

Covance:

Signature

Date

Jasmine Ropers / Project Manager
Printed Name/Title

Covance:

Signature

Date

Amy Rainey / Senior Clinical Research Associate
Printed Name/Title

Celerion:

Signature *

Date

Kirk Newland / Celerion Principal Investigator
Printed Name/Title

Technical Director, Tobacco Science

*As confirmation of activities performed at Celerion or via email with Celerion (steps 1, 3 and 4)

Sponsor:

Signature

Date

Dimitra Skiada / Manager Clinical Study
Printed Name/Title



Sample Reconciliation Report

Final 05 NOV 2015

ZRHM-REXA-08-US

APPROVALS

Covance:

Jasmine Ropers 14 Nov 2015
Signature Date
Jasmine Ropers / Project Manager
Printed Name/Title

Covance:

Signature Date
Amy Rainey / Senior Clinical Research Associate
Printed Name/Title

Celerion:

Kirk Newland 13-Nov-2015
Signature * Date
Kirk Newland / Celerion Principal Investigator Technical Director, Tobacco Science
Printed Name/Title

*As confirmation of activities performed at Celerion or via email with Celerion (steps 1, 3 and 4)

Sponsor:

Signature Date
Dimitra Skiada / Manager Clinical Study
Printed Name/Title



Sample Reconciliation Report

Final 05 NOV 2015

ZRHM-REXA-08-US

APPROVALS

Covance:

Signature _____ Date _____

Jasmine Ropers / Project Manager
Printed Name/Title

Covance:

Signature  Date 13 Nov 2015

Amy Rainey / Senior Clinical Research Associate
Printed Name/Title

Celerion:

Signature * _____ Date _____

Kirk Newland / Celerion Principal Investigator
Printed Name/Title

**As confirmation of activities performed at Celerion or via email with Celerion (steps 1, 3 and 4)*

Sponsor:

Signature _____ Date _____

Dimitra Skiada / Manager Clinical Study
Printed Name/Title



Sample Reconciliation Report

Final 05 NOV 2015

ZRHM-REXA-08-US

Contents

APPROVALS	2
1. Introduction	4
2. Rationale	4
3. Reconciliation Activities	4
4. Outcome of the Reconciliation	6
5. Conclusion	10
6. Additional Information	10



Sample Reconciliation Report

Final 05 NOV 2015

ZRHM-REXA-08-US

1. Introduction

This report summarizes the activities conducted and findings produced during the ZRHM-REXA-08-US Lab Reconciliation Project.

2. Rationale

In August 2014, the Celerion Laboratory in Lincoln, NE identified discrepancies between number of actual samples received vs. number of samples expected to be received and discrepancies between actual samples received vs the manifests provided for the samples shipped from Covance Dallas Clinical Site.

The activities that took place in order to reconcile and resolve the discrepancies and the outcome of the reconciliation activities are outlined in paragraphs 3 and 4 below.

3. Reconciliation Activities.

Step 1: Reconciliation between Covance Project Management and Celerion

Following the identification of the discrepancies from Celerion, Covance Project management team worked with Celerion and Covance Dallas clinical site to resolve discrepancies such as:

- Samples not collected but included in electronic shipping manifests as having been shipped
- Samples collected but had no notification of shipment to the lab
- Samples collected and did have notification of shipment on the electronic shipping manifest but not received by Celerion
- Resolution of other sample discrepancies identified by Celerion

Celerion reported the discrepancies between the manifests received and the samples actually received, as well as discrepancies in the number of expected versus received samples (e.g. more samples for a subject or time point than expected) to Covance Project Management who then worked with the clinical sites to reconcile the issues. Email and an Excel spreadsheet were used to track responses. This was the first reconciliation step to take place and discrepancies were resolved when possible.

Step 2: Reconciliation at Dallas Clinical Site by Covance CRAs

As step 1 was not sufficient to ensure full issue resolution, further investigation was deemed necessary. An Investigational Plan (attachment 9, appendix A) was put in place to detail further activities to be performed at Dallas Clinical site and Celerion Lab.

At Dallas Covance Clinical Site – Covance CRAs (Ann Hintz, Natasha Cropper, Amy Rainey, Fenitta 'Faye' Gardner and Patrick Obobo) traveled to the Covance Dallas Clinic and compared the data in output files from Celerion against source documents, according to Investigation Plan paragraph A.1 (Attachment 9 found in appendix A) Approximately 200 hours were spent comparing the output files from Celerion



Sample Reconciliation Report

Final 05 NOV 2015

ZRHM-REXA-08-US

against source documents at Dallas. The source documents used for the verification were processing logs and collection logs. Requisition forms are not a primary source as they are completed using collection logs. Shipping manifests were found to have errant information such as the wrong collection date listed for a sample and therefore were not used as a reliable source for the reconciliation. The outcome of the reconciliation process at Dallas Site is shown at the "Outcome of Reconciliation" paragraph below under attachments 5, 6, 7 and 8, where number of samples collected at site versus received at Celerion are noted and also samples with issues that require further investigation

Step 3. Reconciliation between Covance Data Management and Celerion

Following receipt of data transfers from Celerion to Covance Data Management (DM), Covance data management ran a reconciliation program that compared the data in the clinical database such as subject id, visit day and collection date, to what was reported in the Celerion files. Discrepancies were raised by Covance DM and addressed by Celerion when possible. Any discrepancies that could not be resolved were communicated to the CRAs for further manual sample check. The activities of this step are also outlined in the Investigational Plan.

Step 4a: At Celerion Lincoln

For samples that were identified and categorized through steps 1 to 3 as requiring further investigation a manual check of the sample label of the sample being present at Celerion Lab was performed. The Investigational Plan also describes the activities to be performed at this step in more details. Covance CRAs Amy Rainey and Ann Hintz traveled to the Celerion laboratory located in Lincoln, NE and were on-site March 3rd – 5th. During this time they reviewed sample labels for 94 urine and 43 plasma/blood samples identified during steps 1, 2, and 3.

In addition to reviewing these sample labels, they also reviewed sample labels for 337 randomly selected samples from both Daytona Beach and Dallas as described in section B of the investigational plan. Although no discrepancies had been noted for the Daytona Beach Site samples, Daytona Beach samples were also randomly selected to be verified as an additional check to ensure validity of samples across both sites participating in the study.

Step 4b: At Celerion Zurich

It was determined that 87 of the 337 randomly selected samples were located at Celerion's Zurich laboratory and it was agreed that the Bio-analytical Principal Investigator at Celerion Zurich laboratory would review the labels for these samples and provide required supportive documentation. The Investigational Plan (Attachment 9 found in appendix A) also describes the activities to be performed at this step.



Sample Reconciliation Report

Final 05 NOV 2015

ZRHM-REXA-08-US

4. Outcome of the Reconciliation

Outcome of Step 1:

A number of missing samples were identified in Covance Dallas clinical site and shipped to Celerion with final shipment from clinical site to Celerion on 01 October 2015. Discrepancies were resolved when possible via email and phone communication between Covance Project management, site and Celerion and excel worksheets were used to track resolution of issues.

Outcome of Steps 2, 3 and 4:

The comparison of the output files from Celerion with site source documents is provided in the attachments below. The attachments show: number of samples collected versus received at Celerion, samples expected to be collected and not collected from the sites when applicable, discrepancies that are categorized per issue Type according to the Investigational plan and resolution of the discrepancies.

At the time of the finalization of the Investigational Plan, it was believed that one reconciliation spreadsheet per analyte (18 in total for blood and urine) could be prepared to document the reconciliation process; however, as the investigation progressed, it became clear that a single reconciliation spreadsheet for the 24 hour urine samples would be more appropriate as samples were collected and processes for different analytes and hence the information regarding collection of samples was duplicating across the worksheets. Hence, instead 7 analytes were combined into 1 for urine samples (1 worksheet), 1 worksheet was done for CYP2A6 plasma samples, 1 for CYP1A2 and 1 for nicotine/cotinine samples. Therefore, attachment 5, 6, 7, and 8 comprise the findings of the reconciliation rather than the initially indicated 18 spreadsheets.

Blood Samples:

Attachment 5 – CYP2A6 samples

CYP2A6 Plasma Recon, found in Appendix A, is the spreadsheet used by Covance CRAs to identify potential issues with CYP2A6 Plasma Samples.

- 462 samples were collected at the site
- 462 samples were received at Celerion
- 4/462 samples were sent to Celerion by mistake as they were corresponding to Screen Failed subjects.
- 7 samples were not collected by error at the site
- 1/462 sample was required to be manually checked at Celerion Lab
- 1/462 sample was found to have an error on the processing log. This is listed as discrepancy type 6 in the CYP2A6 Recon spreadsheet. Type 6 is not defined in the Investigational Plan and describes an error at the processing log. The site will write a note to file to explain the error on the processing log. Note to file and applicable attachment is listed as Attachment 11.

The sample that was identified requiring further manual verification at Celerion lab, was checked during CRA visit at Celerion lab (Attachment 2 – Investigational Paperwork for Plasma Samples) and label match was confirmed (subject 2023, Day 91). All discrepancies regarding CYP2A6 samples were addressed.



Sample Reconciliation Report

Final 05 NOV 2015

ZRHM-REXA-08-US

Attachment 6 – CYP1A2 samples

CYP1A2 Plasma Recon, found in Appendix A, is the spreadsheet used by Covance CRAs to identify potential issues with CYP1A2 Plasma Samples.

- 466 samples were collected at the site
- 464 samples were received at Celerion
- 6 samples were not collected at the site but were not expected to be collected as subjects did not check in for the study visit.
- There is a discrepancy of 2 samples between samples collected and samples received: Day 0 for 2157 and Day 0 for 2257.
 - Source for subject 2257 indicates that two samples were collected; however, only 1 was received by Celerion. 1 sample for subject 2257 Day 0 is considered missing.
 - Subject 2157 was a screen failure. 2 samples were collected and 1 was shipped to Celerion. One sample was inadvertently shipped as it was not required to ship samples for screen failure subjects. The discrepancy for 2157 was closed as the sample was not expected to be received at Celerion.

No CYP1A2 samples were required to be checked at Celerion as there was not discrepancy with subject ID or visit day.

Attachment 7 – Nicotine Plasma samples

Nicotine Plasma Recon, found in Appendix A, is the spreadsheet used by Covance CRAs to identify potential issues with Nicotine Plasma Samples.

- 2699 samples were collected at site
- 2698 samples were received at Celerion
- There is a discrepancy of 1 sample. The source for the Day 0 sample for subject 2140 indicates 2 samples were collected; however, only 1 was received. This was classified as error on the processing log of the site.
- 16 samples were not collected at the site, 14 of which they were not expected to be collected as subject did not check in for the study visit. 2 samples were not collected as required per protocol according to the site source documents.
- 3 Type 6 discrepancies (processing log errors) were identified
- 13 type 5 discrepancies (incorrect data other than collection date reported in Celerion's file) were identified.
- 6 Type 4 discrepancies were identified

The CRAs and Celerion manually confirmed label match for the discrepant samples (Attachment 2 – Investigational Paperwork for Plasma Samples) when needed and verified the discrepancy. Corrections were done according to discrepancy type. All discrepancies regarding the Nicotine Plasma samples were addressed.

Urine Samples:**Attachment 8 – Urine samples**

Urine Recon Summary, found in Appendix A, is the spreadsheet used by Covance CRAs to identify potential issues with urine samples (Description of Sample Issue Tab). The spreadsheet contains data from 7 different analytes (NNN-NNAL, 3OHBP, SPMA-SBMA, MHBMA, Aromatic Amines, CEMA, HEMA), reported by Celerion.



Sample Reconciliation Report

Final 05 NOV 2015

ZRHM-REXA-08-US

The file shows when protocol required samples were not reported by Celerion, clarifies which samples were not collected and documents the need for protocol deviations in some cases.

- 238 Type 4 discrepancies (all analytes included)
- 30 Type 5 discrepancies (all analytes included)
- 8 Type 6 discrepancies (all analytes included)

The resolution per Type issue is provided in the Urine Recon Summary spreadsheet.

The samples that were reviewed by manual check at Celerion Labs are listed in Attachment 1 – Investigational Paperwork for Urine Samples

For subjects/time points where some available urine samples had been collected, but other aliquots were not collected or not received at Celerion as needed, it was decided to share available aliquots (when possible) in order to complete the analysis for some groups for which aliquots were not received. A list of the clinical samples that were shared between assays is included in the NTF provided by Celerion (attachment 10).

The CRAs and Celerion manually confirmed label match for the discrepant samples (Attachment 1) when needed and verified the discrepancy. Corrections were done according to discrepancy type. For the samples identified in the Urine Recon Summary worksheet as received at Celerion but not collected at site, further investigations were done by Covance CRAs and clinical site and it was confirmed that sufficient clinical documentation existed to support sample collection.

Manual checks of samples at Celerion Labs (Step 4a and 4b):

Any samples that were identified during the reconciliation process as requiring manual check of the sample label at Celerion Lab were included on the worksheet Investigational Paperwork for Plasma Samples (Attachment 2) for blood samples and on the Investigational Paperwork for Urine Samples (attachment 1) for urine samples. The results of the manual check are shown below:

List of plasma/blood samples noted as discrepancies requiring manual check identified during steps 1, 2, and 3 (n = 43, all Dallas)

- 39 samples physically verified as correctly labeled
- 3 samples confirmed as not received at Celerion (Day 2, COHb, subject 2298 / Day 60, COHb subjects 2285 and 2299)
- 1 sample confirmed to have been received frozen and therefore was not analyzed (Day 30, COHb, subject 2274)

The Blood sample Verification list showing label match between Covance CRA and Celerion, signed by both parties, is shown as attachment 2.

Please note that the initial list of samples provided to Celerion included samples that are not included on the final issues and actions tab for the plasma nicotine. The lists provided for physical sample reconciliation were prepared using the most conservative criteria so that we could be certain that all samples with potential issues were examined (i.e. number of samples checked was greater than the number of samples noted with issues on the previous worksheets including potential discrepancies from steps 1 to 3). During further review of the samples both prior to and during the reconciliation, it was noted



Sample Reconciliation Report

Final 05 NOV 2015

ZRHM-REXA-08-US

that some of those samples did not have notable issues/discrepancies or those issues/discrepancies were duplicated in another area. The issues/discrepancies outlined on the nicotine plasma spreadsheet represent the final results and findings of our reconciliation.

List of urine samples noted as discrepancies identified during steps 1, 2, and 3 (n = 94, all Dallas)

The investigational plan states that 88 samples will be checked at Celerion, however 94 samples were checked. Six additional samples were identified as having potential errors after the investigational plan had been finalized. From the 94 samples identified:

- 79 samples physically verified as correctly labeled
- 6 samples shipped to LabStat for Ames analysis and therefore were not present for verification. All urine was used during analysis and containers were discarded. (Day 0 samples for subjects 2046, 2048, 2053, 2058, 2076, 2077)
- 1 sample confirmed as not received at Celerion (Day -1, Nic-Eq, subject 2230)
- 7 samples were duplicated on the list in error
- 1 sample removed, included in error (2299, Day0 no analyte specified)

The Urine sample Verification list showing label match between Covance CRA and Celerion, signed by both parties, is shown as attachment 1.

As mentioned in Steps 4a and 4b In addition to reviewing the sample labels of samples identified from steps 1-3, sample labels for 337 randomly selected samples from both Daytona Beach and Dallas Clinical sites were manually checked as described in section B of the investigational plan. The results of this check are shown below:

List of randomly selected samples at Celerion Lincoln (n = 254)

- 1 sample selected for Ames, not present for verification.
- 250 samples physically verified as correctly labeled (125 Daytona, 125 Dallas)
- 2 duplicate sample identified on the list in error
- 1 sample confirmed as not received for Subject 2291 Day 0.

The list of randomly selected samples showing label match between Covance CRA and Celerion, signed by both parties, is shown as attachment 3 (254 Randomly Selected Samples Audited at Celerion Nebraska). The Day 30 COHb sample for subject 2274 was located late in the afternoon on 05 Mar 15 and thus was moved to a separate sheet of the attachment which is also included in attachment 3.

List of randomly selected samples located at Celerion Zurich (n = 87)

- o 87 samples physically verified as correctly labeled.

Attached is the file confirming verification of these samples by the Celerion Bioanalytical Principal Investigator (attachment 4 - 87 Randomly Selected Samples Audited at Celerion Zurich)

Attachments 1-4 (located in Appendix A) show confirmation from both Covance and Celerion, that all sample labels match. The investigational plan stated that an "X" would be used to indicate that the labels matched, however YES/NO was used by both Covance and Celerion instead.

None of the issues identified required any updates to sample labels at Celerion. In addition, samples labels and collection dates were verified and confirmed.



Sample Reconciliation Report

Final 05 NOV 2015

ZRHM-REXA-08-US

5. Conclusion

After the conclusion of the above listed reconciliation steps, all discrepancies were addressed, all the samples checked had a label match between Celerion and Covance and all samples received at the Celerion site had been confirmed by Covance CRAs as traceable based on site source documentation.

6. Additional Information

PMI QA and a third party auditor performed audits at Celerion Lab and the Dallas Clinical Site. Celerion Labs has drafted a NTF to provide further explanations and details linked to this reconciliation project. The NTF is attached (attachment 10)

Appendix A: Attachments.

Attachment 1 – Investigational Paperwork for Urine Samples



Investigation
Paperwork - Discrepa

Attachment 2 – Investigational Paperwork for Plasma Samples



REXA-08 Inv
Paperwork - Discrepa

Attachment 3 – 254 Randomly Selected Samples Audited at Celerion Nebraska



REXA-08 Inv
Paperwork Random s

Attachment 4 – 87 Randomly Selected Samples Audited at Celerion Zurich



AA99598 Sample
verification.pdf



Sample Reconciliation Report

Final 05 NOV 2015

ZRHM-REXA-08-US

Attachment 5 – CYP2A6 Plasma Recon



CYP2A6 Plasma
Recon.xlsx

Attachment 6 – CYP1A2 Plasma Recon



CYP1A2 Plasma
Recon.xlsx

Attachment 7 – Nicotine Plasma Recon



Nicotine Plasma
Recon.xlsx

Attachment 8 – Urine Recon Summary



Urine Recon
Summary_final.xlsx

Attachment 9 - Investigational Plan



REXA-08
Investigational Plan fr

Attachement 10 – Celerion NTF



AA99128 PMP NTF
27-Oct-2015.pdf

Attachment 11 – Processing Log error NTF an list of applicable samples



Processing errors eNote 1219008.pdf



REXA-08 NTFs
Needed for Procssing



Subject	Visit	Assay	Labels Match		Comment if Error Noted
			Cov	Cel	
2048	Day 2	3OHBaP	Y/N	Y/N	
2077	Day 2	3OHBaP	Y/N	Y/N	
2095	Day 2	3OHBaP	Y/N	Y/N	
2115	Day 91	3OHBaP	Y/N	Y/N	
2138	Day 60	3OHBaP	Y/N	Y/N	
2143	Day 60	3OHBaP	Y/N	Y/N	
2351	Day -1	3OHBaP	Y/N	Y/N	
2138	Day 4	Aromatic Amines	Y/N	Y/N	W198633-17 TA15
2143	Day 60	Aromatic Amines	Y/N	Y/N	W367724-16 TA15
2225	Day -1	Aromatic Amines	Y/N	Y/N	
2230	Day -1	Aromatic Amines	Y/N	Y/N	
2232	Day -1	Aromatic Amines	Y/N	Y/N	
2274	Day 30	Aromatic Amines	Y/N	Y/N	
2351	Day -1	Aromatic Amines	Y/N	Y/N	
2120	Day 1	CEMA-HPMA-HBMA	Y/N	Y/N	
2127	Day 0	CEMA-HPMA-HBMA	Y/N	Y/N	
2136	Day 0	CEMA-HPMA-HBMA	Y/N	Y/N	Continued to next spreadsheet KEN 05-Mar-2015
2138	Day 60	CEMA-HPMA-HBMA	Y/N	Y/N	W367734-14 TA15
2143	Day 60	CEMA-HPMA-HBMA	Y/N	Y/N	
2274	Day 30	CEMA-HPMA-HBMA	Y/N	Y/N	
2076	Day 3	Creatinine	Y/N	Y/N	
2089	Day 2	Creatinine	Y/N	Y/N	
2113	Day 3	Creatinine	Y/N	Y/N	
2138	Day 91	Creatinine	Y/N	Y/N	05115160002158 Day 91 on Cov label (Split 2)
2274	Day 30	Creatinine	Y/N	Y/N	
2138	Day 60	HEMA	Y/N	Y/N	
2143	Day 60	HEMA	Y/N	Y/N	
2274	Day 30	HEMA	Y/N	Y/N	
2176	Day 2	HEMA	Y/N	Y/N	
2197	Day 4	HEMA	Y/N	Y/N	
2200	Day 3	HEMA	Y/N	Y/N	
2251	Day 0	HEMA	Y/N	Y/N	
2073	Day 0	NNAL-NNN	Y/N	Y/N	
2089	Day 0	NNAL-NNN	Y/N	Y/N	
2115	Day 91	NNAL-NNN	Y/N	Y/N	05112460005552 Day 91 on Cov label Write over 2116 - But is 2115



Celerion

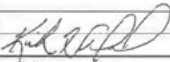
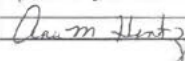
Document Prepared 03-Mar-2015

Subject	Visit	Assay	Labels Match		Comment if Error Noted
			Cov	Cel	
2140	Day 1	NNAL-NNN	Y / N	Y / N	
2303	Day -1	NNAL-NNN	Y / N	Y / N	
2351	Day -1	NNAL-NNN	Y / N	Y / N	
2085	Day 5	11-dTXB2	Y / N	Y / N	
2138	Day 60	11-dTXB2	Y / N	Y / N	Covance - 436773426 SV07 - Quid
2143	Day 60	11-dTXB2	Y / N	Y / N	Cov - 436773426 SV07 - Quid
2274	Day 30	11-dTXB2	Y / N	Y / N	
2138	Day 60	iPF2A	Y / N	Y / N	
2143	Day 60	iPF2A	Y / N	Y / N	
2274	Day 30	iPF2A	Y / N	Y / N	
2292	Day 0	Nic-Eq	Y / N	Y / N	
2046	Day 0	Ames	Y / N	Y / N	
2048	Day 0	Ames	Y / N	Y / N	
2053	Day 0	Ames	Y / N	Y / N	
2058	Day 0	Ames	Y / N	Y / N	
2076	Day 0	Ames	Y / N	Y / N	
2077	Day 0	Ames	Y / N	Y / N	
2299	Day 0		Y / N	Y / N	
2298	Day 90	3-OH8aP	Y / N	Y / N	Site changed D91 to D90 for split 1 - ans
Dup. 2115	Day 91	3-OH8aP	Y / N	Y / N	
2115	Day 91	Aromatic Amines	Y / N	Y / N	
2115	Day 91	CEMA-HPMA-HBMA	Y / N	Y / N	
2115	Day 91	HEMA	Y / N	Y / N	
Dup. 2351	Day -1	3-OH8aP	Y / N	Y / N	
Dup. 2351	Day -1	Aromatic Amines	Y / N	Y / N	
2351	Day -1	CEMA-HPMA-HBMA	Y / N	Y / N	
2351	Day -1	HEMA	Y / N	Y / N	
Dup. 2274	Day 30	3-OH8aP	Y / N	Y / N	
Dup. 2274	Day 30	Aromatic Amines	Y / N	Y / N	
Dup. 2274	Day 30	CEMA-HPMA-HBMA	Y / N	Y / N	
Dup. 2274	Day 30	HEMA	Y / N	Y / N	
2200	Day 4	3-OH8aP	Y / N	Y / N	
2200	Day 4	Aromatic Amines	Y / N	Y / N	
2200	Day 4	CEMA-HPMA-HBMA	Y / N	Y / N	
2200	Day 4	HEMA	Y / N	Y / N	



Celerion

Document Prepared 03-Mar-2015

Subject	Visit	Assay	Labels Match		Comment if Error Noted
			Cov	Cel	
2334	Day 91	CEMA-HPMA-HBMA	Y / N	Y / N	
2334	Day 91	NNAL-NNN	Y / N	Y / N	
2334	Day 91	HEMA	Y / N	Y / N	
2334	Day 91	Nic-Eq	Y / N	Y / N	
2334	Day 91	3-OHBP	Y / N	Y / N	
2334	Day 91	11-dTXB2	Y / N	Y / N	
2334	Day 91	iPF2A	Y / N	Y / N	
2334	Day 91	Creatinine	Y / N	Y / N	
2230	Day -1	CEMA-HPMA-HBMA	Y / N	Y / N	
2230	Day -1	NNAL-NNN	Y / N	Y / N	
2230	Day -1	HEMA	Y / N	Y / N	
2230	Day -1	Nic-Eq	Y / N	Y / N	Sample not received by Celerion KEN 3-Mar-2015
2230	Day -1	3-OHBP	Y / N	Y / N	
2230	Day -1	11-dTXB2	Y / N	Y / N	
2230	Day -1	iPF2A	Y / N	Y / N	
2230	Day -1	Creatinine	Y / N	Y / N	
2257	Day 91	CEMA-HPMA-HBMA	Y / N	Y / N	
2257	Day 91	NNAL-NNN	Y / N	Y / N	
2257	Day 91	HEMA	Y / N	Y / N	
2257	Day 91	Nic-Eq	Y / N	Y / N	
2257	Day 91	3-OHBP	Y / N	Y / N	
2257	Day 91	11-dTXB2	Y / N	Y / N	
2257	Day 91	iPF2A	Y / N	Y / N	
2257	Day 91	Creatinine	Y / N	Y / N	
Responsible Celerion Associate:			(Signature, Date, Printed Name)		 05-Mar-2015 Kirk Newland
Responsible Covance Associate:			(Signature, Date, Printed Name)		 05-MAR-2015 Ann M Hutz



Celerion

Document Prepared
03-Mar-2015

Subject	Visit	Assay	Labels Match		Comment of Error Noted
			Cov	Cel	
2023	Day 91	CYP2A6	Y / N	Y / N	
2298	Day 2	COHb	NA Y / N <i>split</i>	Y / N	No sample received KEN 04-Mar-2015 - per Source Sample Collected Not Rnd and
2053	Day 90	COHb	Y / N	Y / N	
2079	Day 30	COHb	Y / N	Y / N	
2048	Day 90	COHb	Y / N	Y / N	
2076	Day 90	COHb	Y / N	Y / N	
2274	Day 30	COHb	Y / N	Y / N	Continued to next spreadsheet KEN 05-Mar-2015
2274	Day 60	COHb	Y / N	Y / N	Continue Laback DI Caesari out of DGL & minimize
2285	Day 60	COHb	NA Y / N <i>split</i>	Y / N	No sample received KEN 04-Mar-2015 - per Source Sample Collected Not Rnd and
2299	Day 60	COHb	Y / N	Y / N	No sample received KEN 04-Mar-2015 - per Source Sample Collected Not Rnd and
2140	Day 0	Nicotine	Y / N	Y / N	
2100	Day 0	Nicotine	Y / N	Y / N	
2100	Day 90	Nicotine	Y / N	Y / N	
2110	Day 0	Nicotine	Y / N	Y / N	Split 2 - 0.004
2110	Day 90	Nicotine	Y / N	Y / N	
2116	Day 0	Nicotine	Y / N	Y / N	
2116	Day 90	Nicotine	Y / N	Y / N	
2251	Day 0	Nicotine	Y / N	Y / N	
2251	Day 90	Nicotine	Y / N	Y / N	
2257	Day 0	Nicotine	Y / N	Y / N	
2257	Day 90	Nicotine	Y / N	Y / N	
2316	Day 0	Nicotine	Y / N	Y / N	
2316	Day 90	Nicotine	Y / N	Y / N	
2334	Day 0	Nicotine	Y / N	Y / N	
2334	Day 90	Nicotine	Y / N	Y / N	
2336	Day 0	Nicotine	Y / N	Y / N	
2336	Day 90	Nicotine	Y / N	Y / N	
2340	Day 0	Nicotine	Y / N	Y / N	
2340	Day 90	Nicotine	Y / N	Y / N	
2351	Day 0	Nicotine	Y / N	Y / N	June 6 dated - 0.004
2351	Day 90	Nicotine	Y / N	Y / N	
2079	Day 0	Nicotine	Y / N	Y / N	



Celerion

Document Prepared
03-Mar-2015

Subject	Visit	Assay	Labels Match		Comment of Error Noted
			Cov	Cel	
2079	Day 90	Nicotine	Y/N	Y/N	D5 Label & D90 headlines - amk
2298	Day 0	Nicotine	Y/N	Y/N	
2298	Day 90	Nicotine	Y/N	Y/N	
2330	Day 0	Nicotine	Y/N	Y/N	
2330	Day 90	Nicotine	Y/N	Y/N	
2075	Day 5	Nicotine	Y/N	Y/N	T2, T3, Pw, T4, T5, T6, T7, T8 - amk
2095	Day 60	Nicotine	Y/N	Y/N	
2127	Day 6	Nicotine	Y/N	Y/N	240 T5 - amk
2138	Day 60	Nicotine	Y/N	Y/N	
2143	Day 60	Nicotine	Y/N	Y/N	
2232	Day 5	Nicotine	Y/N	Y/N	Pw, T1, T2, T3, T4, T5, T6, T7, T8 - amk

Responsible Celerion Associate: (Signature, Date, Printed Name)

05-Mar-2015 Kirk Newland

Responsible Covance Associate: (Signature, Date, Printed Name)

05-MAR-2015 Ann M Hinz



Celerion

Document Prepared

05-Mar-2015

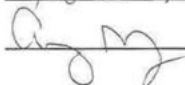
REXA08 Discrepant Blood/Plasma Sample Verifications

Subject	Visit	Assay	Labels Match		Comment if Error Noted
			Cov	Cel	
2274	Day 39	COHb	Y/N	Y/N	Sample received frozen; not analyzed KBN 05-Mar-2015

Responsible Celerion Associate: (Signature, Date, Printed Name)

 05-Mar-2015 Kirk Newland

Responsible Covance Associate: (Signature, Date, Printed Name)

 05-Mar-2015 Amy Rainey



Celerion

Document Prepared 03-Mar-2015

Subject	Visit	Assay	Labels Match		Comment if Error Noted
			Cov	Cel	
2029	DAY90	11-dTXB2	Y/N	Y/N	
2038	BASELINE	11-dTXB2	Y/N	Y/N	
2079	DAY0	11-dTXB2	Y/N	Y/N	
2155	DAY60	11-dTXB2	Y/N	Y/N	
2174	DAY30	11-dTXB2	Y/N	Y/N	
2174	BASELINE	11-dTXB2	Y/N	Y/N	
2176	BASELINE	11-dTXB2	Y/N	Y/N	
2351	DAY90	11-dTXB2	Y/N	Y/N	
1041	DAY3	3-OH8aP	Y/N	Y/N	
1060	DAY5	3-OH8aP	Y/N	Y/N	
1104	DAY5	3-OH8aP	Y/N	Y/N	
1105	DAY3	3-OH8aP	Y/N	Y/N	
1147	DAY0	3-OH8aP	Y/N	Y/N	
1210	DAY60	3-OH8aP	Y/N	Y/N	
1246	DAY90	3-OH8aP	Y/N	Y/N	
1281	DAY91	3-OH8aP	Y/N	Y/N	
1281	DAY5	3-OH8aP	Y/N	Y/N	
1297	BASELINE	3-OH8aP	Y/N	Y/N	
2023	DAY1	3-OH8aP	Y/N	Y/N	
2023	DAY91	3-OH8aP	Y/N	Y/N	
2045	DAY4	3-OH8aP	Y/N	Y/N	
2058	DAY60	3-OH8aP	Y/N	Y/N	
2100	DAY91	3-OH8aP	Y/N	Y/N	
2140	DAY5	3-OH8aP	Y/N	Y/N	
2140	DAY1	3-OH8aP	Y/N	Y/N	
2148	DAY1	3-OH8aP	Y/N	Y/N	
2274	DAY30	3-OH8aP	Y/N	Y/N	
2307	DAY30	3-OH8aP	Y/N	Y/N	
1010	DAY0	4-ABP	Y/N	Y/N	Continued to next spreadsheet. KEN 05-Mar-2015
1065	DAY4	4-ABP	Y/N	Y/N	
1097	DAY3	4-ABP	Y/N	Y/N	
1125	DAY0	4-ABP	Y/N	Y/N	
1144	BASELINE	4-ABP	Y/N	Y/N	
1181	DAY1	4-ABP	Y/N	Y/N	
1212	DAY0	4-ABP	Y/N	Y/N	



Celerion

Document Prepared 03-Mar-2015

Subject	Visit	Assay	Labels Match		Comment if Error Noted
			Cov	Cel	
1218	DAY1	4-ABP	Y/N	Y/N	
1234	DAY30	4-ABP	Y/N	Y/N	
1238	DAY3	4-ABP	Y/N	Y/N	
1251	DAY91	4-ABP	Y/N	Y/N	Continued to next spreadsheet KEN 05-Mar-2015
1253	DAY3	4-ABP	Y/N	Y/N	
2045	DAY1	4-ABP	Y/N	Y/N	Continued to next spreadsheet KEN 05-Mar-2015
2072	DAY0	4-ABP	Y/N	Y/N	
2100	DAY2	4-ABP	Y/N	Y/N	Continued to next spreadsheet KEN 05-Mar-2015
2100	DAY2	4-ABP	Y/N	Y/N	Continued to next spreadsheet Dup. Sample listing
2116	DAY91	4-ABP	Y/N	Y/N	
2225	DAY4	4-ABP	Y/N	Y/N	
2307	DAY60	4-ABP	Y/N	Y/N	
2330	DAY3	4-ABP	Y/N	Y/N	
1028	DAY90	Caffeine	Y/N	Y/N	
1069	DAY5	Caffeine	Y/N	Y/N	V225611-42 SV03 KEN 05-Mar-2015
1057	BASELINE	COHb	Y/N	Y/N	
1104	DAY30	COHb	Y/N	Y/N	
1104	DAY5	COHb	Y/N	Y/N	60 - UML
1106	DAY2	COHb	Y/N	Y/N	
1117	DAY91	COHb	Y/N	Y/N	
1117	BASELINE	COHb	Y/N	Y/N	
1124	DAY5	COHb	Y/N	Y/N	
1147	DAY2	COHb	Y/N	Y/N	
1230	BASELINE	COHb	Y/N	Y/N	
1246	DAY0	COHb	Y/N	Y/N	
1253	DAY6	COHb	Y/N	Y/N	
1281	DAY2	COHb	Y/N	Y/N	
1286	DAY91	COHb	Y/N	Y/N	
2023	DAY91	COHb	Y/N	Y/N	
2029	DAY3	COHb	Y/N	Y/N	
2045	DAY30	COHb	Y/N	Y/N	
2086	DAY5	COHb	Y/N	Y/N	
2169	DAY3	COHb	Y/N	Y/N	
2212	DAY2	COHb	Y/N	Y/N	
2344	DAY5	COHb	Y/N	Y/N	



Celerion

Document Prepared 03-Mar-2015

Subject	Visit	Assay	Labels Match		Comment if Error Noted
			Cov	Cel	
1028	DAY0	Cot	Y/N	Y/N	
1057	DAY0	Cot	Y/N	Y/N	
1177	DAY0	Cot	Y/N	Y/N	
1209	DAY91	Cot	Y/N	Y/N	
1210	DAY0	Cot	Y/N	Y/N	
1297	DAY6	Cot	Y/N	Y/N	
2076	DAY0	Cot	Y/N	Y/N	
2106	DAY0	Cot	Y/N	Y/N	
2307	DAY91	Cot	Y/N	Y/N	
1028	DAY90	Creatinine	Y/N	Y/N	
1093	DAY0	Creatinine	Y/N	Y/N	
1104	BASELINE	Creatinine	Y/N	Y/N	
1118	DAY91	Creatinine	Y/N	Y/N	
1170	DAY91	Creatinine	Y/N	Y/N	
1202	DAY1	Creatinine	Y/N	Y/N	
1221	DAY0	Creatinine	Y/N	Y/N	
2029	DAY90	Creatinine	Y/N	Y/N	
2029	DAY4	Creatinine	Y/N	Y/N	Cap not included with sample. Parafin used KEN 04-Mar-2015
2046	DAY91	Creatinine	Y/N	Y/N	
2077	DAY60	Creatinine	Y/N	Y/N	
2085	DAY3	Creatinine	Y/N	Y/N	
2095	DAY60	Creatinine	Y/N	Y/N	
2106	DAY0	Creatinine	Y/N	Y/N	
2110	DAY1	Creatinine	Y/N	Y/N	
2127	DAY2	Creatinine	Y/N	Y/N	
2188	BASELINE	Creatinine	Y/N	Y/N	
2196	DAY5	Creatinine	Y/N	Y/N	
2214	DAY91	Creatinine	Y/N	Y/N	
2232	DAY30	Creatinine	Y/N	Y/N	
1093	DAY1	HEMA	Y/N	Y/N	Continued to next spreadsheet KEN 05-Mar-2015
1101	DAY1	HEMA	Y/N	Y/N	
1106	DAY60	HEMA	Y/N	Y/N	Continued to next spreadsheet KEN 05-Mar-2015
1118	DAY60	HEMA	Y/N	Y/N	
1125	DAY60	HEMA	Y/N	Y/N	
1198	DAY30	HEMA	Y/N	Y/N	Continued to next spreadsheet KEN 05-Mar-2015



Celerion

Document Prepared 03-Mar-2015

Subject	Visit	Assay	Labels Match		Comment if Error Noted
			Cov	Cel	
1198	DAY91	HEMA	Y/N	Y/N	
1209	BASELINE	HEMA	Y/N	Y/N	Continued to next spreadsheet KEN 05-Mar-2015
1203	DAY4	HEMA	Y/N	Y/N	
1212	DAY91	HEMA	Y/N	Y/N	
1218	DAY4	HEMA	Y/N	Y/N	Continued to next spreadsheet KEN 05-Mar-2015
1219	DAY0	HEMA	Y/N	Y/N	
1230	DAY3	HEMA	Y/N	Y/N	
1280	DAY30	HEMA	Y/N	Y/N	
1297	DAY30	HEMA	Y/N	Y/N	
2038	DAY3	HEMA	Y/N	Y/N	
2089	DAY60	HEMA	Y/N	Y/N	
2162	DAY1	HEMA	Y/N	Y/N	
2188	DAY0	HEMA	Y/N	Y/N	
2225	DAY3	HEMA	Y/N	Y/N	
2232	DAY2	HEMA	Y/N	Y/N	
2298	DAY1	HEMA	Y/N	Y/N	
2303	DAY0	HEMA	Y/N	Y/N	
2310	BASELINE	HEMA	Y/N	Y/N	Continued to next spreadsheet KEN 05-Mar-2015
2336	DAY5	HEMA	Y/N	Y/N	
1038	DAY2	HPMA	Y/N	Y/N	
1092	BASELINE	HPMA	Y/N	Y/N	
1099	DAY4	HPMA	Y/N	Y/N	
1104	DAY2	HPMA	Y/N	Y/N	
1104	DAY60	HPMA	Y/N	Y/N	
1155	DAY1	HPMA	Y/N	Y/N	
1181	DAY3	HPMA	Y/N	Y/N	
1221	DAY90	HPMA	Y/N	Y/N	
1230	DAY1	HPMA	Y/N	Y/N	
1247	DAY30	HPMA	Y/N	Y/N	
2029	BASELINE	HPMA	Y/N	Y/N	
2073	BASELINE	HPMA	Y/N	Y/N	
2077	DAY3	HPMA	Y/N	Y/N	
2086	DAY4	HPMA	Y/N	Y/N	
2116	DAY0	HPMA	Y/N	Y/N	
2127	DAY4	HPMA	Y/N	Y/N	



Criterion

Document Prepared 05-Mar-2015

Subject	Visit	Assay	Labels Match		Comment if Error Noted
			Cov	Cel	
2138	DAY0	HPMA	Y/N	Y/N	
2143	DAY30	HPMA	Y/N	Y/N	
2165	BASELINE	HPMA	Y/N	Y/N	Continued to next spreadsheet KEN 05-Mar-2015
2196	DAY90	HPMA	Y/N	Y/N	
2334	DAY0	HPMA	Y/N	Y/N	
1041	DAY90	iPF2a-III	Y/N	Y/N	
1042	BASELINE	iPF2a-III	Y/N	Y/N	Continued to next spreadsheet KEN 05-Mar-2015
1098	BASELINE	iPF2a-III	Y/N	Y/N	
1143	DAY30	iPF2a-III	Y/N	Y/N	Continued to next spreadsheet KEN 05-Mar-2015
1221	DAY91	iPF2a-III	Y/N	Y/N	Subject PD crossed out Thru - assay
1247	DAY90	iPF2a-III	Y/N	Y/N	
2058	DAY5	iPF2a-III	Y/N	Y/N	Continued to next spreadsheet KEN 05-Mar-2015
2076	BASELINE	iPF2a-III	Y/N	Y/N	
2188	DAY5	iPF2a-III	Y/N	Y/N	
2194	DAY60	iPF2a-III	Y/N	Y/N	
1002	DAY2	Nic PI	Y/N	Y/N	
1009	DAY2	Nic PI	Y/N	Y/N	
1041	DAY4	Nic U	Y/N	Y/N	
1042	DAY5	Nic PI	Y/N	Y/N	
1069	DAY60	Nic PI	Y/N	Y/N	
1074	DAY90	Nic U	Y/N	Y/N	
1092	DAY30	Nic PI	Y/N	Y/N	
1092	DAY60	Nic PI	Y/N	Y/N	
1097	DAY6	Nic PI	Y/N	Y/N	
1101	DAY6	Nic	Y/N	Y/N	Continued to next spreadsheet KEN 05-Mar-2015
1101	DAY2	Nic PI	Y/N	Y/N	
1105	DAY4	Nic PI	Y/N	Y/N	
1110	DAY6	Nic PI	Y/N	Y/N	
1124	DAY5	Nic PI	Y/N	Y/N	TG KEN
1124	DAY5	Nic PI	Y/N	Y/N	TG KEN
1147	DAY5	Nic	Y/N	Y/N	Continued to next spreadsheet KEN 05-Mar-2015
1159	DAY2	Nic PI	Y/N	Y/N	
1168	DAY60	Nic PI	Y/N	Y/N	
1170	BASELINE	Nic U	Y/N	Y/N	
1218	DAY5	Nic PI	Y/N	Y/N	TG - KEN



Celerion

Document Prepared 03-Mar-2015

Subject	Visit	Assay	Labels Match		Comment if Error Noted
			Cov	Cel	
1221	DAY6	Nic PI	Y/N	Y/N	T9 KEN CA-Mar-2015
1238	DAY30	Nic PI	Y/N	Y/N	
1246	DAY91	Nic U	Y/N	Y/N	
1247	DAY1	Nic U	Y/N	Y/N	
1252	DAY60	Nic U	Y/N	Y/N	
1280	DAY3	Nic PI	Y/N	Y/N	
1283	DAY2	Nic PI	Y/N	Y/N	
2007	DAY5	Nic PI	Y/N	Y/N	T10-amp
2029	DAY3	Nic PI	Y/N	Y/N	
2045	DAY2	Nic PI	Y/N	Y/N	
2045	DAY90	Nic U	Y/N	Y/N	
2065	DAY4	Nic PI	Y/N	Y/N	
2071	DAY6	Nic PI	Y/N	Y/N	T1b - small
2075	DAY0	Nic PI	Y/N	Y/N	
2085	DAY5	Nic	Y/N	Y/N	Continued to next spreadsheet KEN 05-Mar-2015
2095	DAY5	Nic PI	Y/N	Y/N	T8 - amp
2095	DAY90	Nic U	Y/N	Y/N	
2100	DAY3	Nic U	Y/N	Y/N	
2100	DAY30	Nic PI	Y/N	Y/N	
2109	DAY90	Nic U	Y/N	Y/N	
2113	DAY5	Nic PI	Y/N	Y/N	T7-amp
2115	DAY90	Nic PI	Y/N	Y/N	
2127	DAY0	Nic U	Y/N	Y/N	
2138	DAY91	Nic U	Y/N	Y/N	
2146	DAY0	Nic PI	Y/N	Y/N	
2162	DAY4	Nic U	Y/N	Y/N	
2162	DAY1	Nic PI	Y/N	Y/N	
2164	DAY5	Nic PI	Y/N	Y/N	P10 - amp
2164	DAY5	Nic PI	Y/N	Y/N	T4 - amp
2165	DAY5	Nic	Y/N	Y/N	Continued to next spreadsheet KEN 05-Mar-2015
2169	DAY4	Nic PI	Y/N	Y/N	
2174	DAY5	Nic PI	Y/N	Y/N	T-3 - amp
2187	DAY91	Nic U	Y/N	Y/N	X086582-27 5V07 Clinic label damaged KEN
2197	DAY90	Nic U	Y/N	Y/N	Y165601-23 5V07 Subject confirmed KEN
2200	DAY1	Nic U	Y/N	Y/N	05-Mar-2015

PI indicates Plasma sample; U indicates a urine sample for NicEq - added by KEN 04-Mar-2015

Confirmed
21.87 KEN
04-Mar-2015



Subject	Visit	Assay	Labels Match		Comment if Error Noted
			Cov	Cel	
2209	DAY2	Nic U	Y/N	Y/N	
2212	DAY5	Nic	Y/N	Y/N	Continued to next spreadsheet KAV 05-Mar-2015
2260	DAY3	Nic U	Y/N	Y/N	
2285	DAY1	Nic U	Y/N	Y/N	
2307	DAY5	Nic PI	Y/N	Y/N	TG - amu
2307	DAY1	Nic U	Y/N	Y/N	
2344	DAY5	Nic PI	Y/N	Y/N	TI - amu
1001	DAY1	NNAL	Y/N	Y/N	
1038	DAY60	NNAL	Y/N	Y/N	
1052	DAY4	NNAL	Y/N	Y/N	
1074	DAY60	NNAL	Y/N	Y/N	
1087	DAY91	NNAL	Y/N	Y/N	
1105	DAY5	NNAL	Y/N	Y/N	
1110	DAY2	NNAL	Y/N	Y/N	
1124	DAY4	NNAL	Y/N	Y/N	
1125	DAY1	NNAL	Y/N	Y/N	
1155	BASELINE	NNAL	Y/N	Y/N	
1159	DAY4	NNAL	Y/N	Y/N	
1194	DAY3	NNAL	Y/N	Y/N	
1230	DAY4	NNAL	Y/N	Y/N	
1230	DAY3	NNAL	Y/N	Y/N	
1234	DAY5	NNAL	Y/N	Y/N	
1252	DAY0	NNAL	Y/N	Y/N	
1261	DAY4	NNAL	Y/N	Y/N	
1265	DAY0	NNAL	Y/N	Y/N	
1267	BASELINE	NNAL	Y/N	Y/N	
2007	DAY60	NNAL	Y/N	Y/N	
2065	DAY2	NNAL	Y/N	Y/N	
2072	DAY30	NNAL	Y/N	Y/N	
2087	DAY2	NNAL	Y/N	Y/N	
2113	DAY5	NNAL	Y/N	Y/N	
2115	DAY3	NNAL	Y/N	Y/N	
2138	DAY91	NNAL	Y/N	Y/N	Continued to next spreadsheet KAV 05-Mar-2015
2140	DAY2	NNAL	Y/N	Y/N	
2148	DAY90	NNAL	Y/N	Y/N	



Philip Morris Products S.A.

Clinical Study Report Appendix 16.1.9

Confidential

ZRHM-REXA-08-US

Version 1.0 / 25 May 2016

Page 28 of 77

Celerion

Document Prepared 03-Mar-2015

Subject	Visit	Assay	Labels Match		Comment if Error Noted
			Cov	Cel	
2169	BASELINE	NNAL	Y / N	Y / N	
2169	DAY4	NNAL	Y / N	Y / N	
2188	DAY90	NNAL	Y / N	Y / N	
2225	DAY2	NNAL	Y / N	Y / N	
2225	DAY2	NNAL	Y / N	Y / N	
2287	DAY0	NNAL	Y / N	Y / N	
2303	DAY4	NNAL	Y / N	Y / N	
2330	DAY1	NNAL	Y / N	Y / N	
Responsible Celerion Associate:			05-Mar-2015	Kirk Newland	
			(Signature, Date, Printed Name)		
Responsible Covance Associate:			05-MAR-2015	Anna M. Hantz	
			(Signature, Date, Printed Name)		



Celerion

Document Prepared
05-Mar-2015

REXA08 Random Sample Verifications

Subject	Visit	Assay	Labels Match		Comment if Error Noted
			Cov	Cel	
1010	DAY 0	4-ABP	Y / N	Y / N	
1251	DAY 91	4-ABP	Y / N	Y / N	
2045	DAY 1	4-ABP	Y / N	Y / N	
2100	DAY 2	4-ABP	Y / N	Y / N	
1093	DAY 1	HEMA	Y / N	Y / N	
1106	DAY 60	HEMA	Y / N	Y / N	
1198	DAY 30	HEMA	Y / N	Y / N	
1202	BASELINE	HEMA	Y / N	Y / N	
1218	DAY 4	HEMA	Y / N	Y / N	
2310	BASELINE	HEMA	Y / N	Y / N	
2169	BASELINE	HPMA	Y / N	Y / N	
1042	BASELINE	iPF2a-III	Y / N	Y / N	
1143	DAY 30	iPF2a-III	Y / N	Y / N	
2058	DAY 5	iPF2a-III	Y / N	Y / N	
1101	DAY 6	Nic - PI	Y / N	Y / N	T9 KEN 05-Mar-2015
1147	DAY 5	Nic - PI	Y / N	Y / N	T2 KEN 05-Mar-2015
2085	DAY 5	Nic - PI	Y / N	Y / N	T3 KEN 05-Mar-2015
2165	DAY 5	Nic - PI	Y / N	Y / N	See email for confirmation KEN 05-Mar-2015
2212	Day 5	Nic - PI	Y / N	Y / N	Pre KEN 05-Mar-2015
2138	DAY 91	NNAL	Y / N	Y / N	

Sample local
for review.
KEN 05-Mar-2015
T3

Responsible Celerion Associate:

(Signature, Date, Printed Name)

Kirk Newland 05-Mar-2015

Responsible Covance Associate:

(Signature, Date, Printed Name)

Amy Rainey 05-Mar-2015



Celerion

Subject	Visit	Assay	Labels Match	Comment if Error Noted
2138	Day 60	1-OHP	Y	
2143	Day 60	1-OHP	Y	
2274	Day 30	1-OHP	Y	
2176	Day 2	1-OHP	Y	
2115	Day 91	MHBMA	Y	
2138	Day 60	MHBMA	Y	
2143	Day 60	MHBMA	Y	
2274	Day 30	MHBMA	Y	
2351	Day -1	MHBMA	Y	
2046	Day 0	SPMA/SBMA	Y	
2053	Day 91	SPMA/SBMA	Y	
2053	Day 0	SPMA/SBMA	Y	
2073	Day 0	SPMA/SBMA	Y	
2076	Day 0	SPMA/SBMA	Y	
2077	Day 0	SPMA/SBMA	Y	
2115	Day 91	SPMA/SBMA	Y	
2138	Day 60	SPMA/SBMA	Y	
2143	Day 60	SPMA/SBMA	Y	
2232	Day -1	SPMA/SBMA	Y	
2274	Day 30	SPMA/SBMA	Y	
2351	Day -1	SPMA/SBMA	Y	

Dr. Markus Bachmann

10 MAR 2015

Responsible Celerion Associate:

(Signature, Date, Printed Name)



Celerion

Subject	Visit	Assay	Labels Match	Comment if Error Noted
1010	DAY5	1-OHP	Y	
1031	DAY1	1-OHP	Y	
1069	DAY91	1-OHP	Y	
1081	DAY90	1-OHP	Y	
1102	Day -1	1-OHP	Y	
1165	DAY2	1-OHP	Y	
1218	DAY1	1-OHP	Y	
1238	DAY5	1-OHP	Y	
1297	DAY5	1-OHP	Y	
1297	DAY4	1-OHP	Y	
2029	DAY2	1-OHP	Y	
2054	DAY2	1-OHP	Y	
2089	DAY90	1-OHP	Y	
2110	DAY5	1-OHP	Y	
2127	DAY1	1-OHP	Y	
2148	DAY0	1-OHP	Y	
2164	DAY1	1-OHP	Y	
2165	DAY0	1-OHP	Y	
2165	DAY91	1-OHP	Y	
2169	DAY3	1-OHP	Y	
2209	DAY2	1-OHP	Y	
2251	DAY60	1-OHP	Y	
1002	DAY30	MHBMA	Y	
1009	DAY0	MHBMA	Y	
1009	DAY5	MHBMA	Y	
1031	DAY1	MHBMA	Y	
1052	DAY1	MHBMA	Y	
1065	DAY90	MHBMA	Y	
1087	DAY0	MHBMA	Y	
1125	DAY60	MHBMA	Y	
1125	DAY91	MHBMA	Y	
1165	DAY91	MHBMA	Y	
1165	DAY30	MHBMA	Y	
1170	Day -1	MHBMA	Y	
1198	DAY30	MHBMA	Y	
1203	DAY2	MHBMA	Y	
1247	DAY91	MHBMA	Y	
2053	Day -1	MHBMA	Y	
2054	DAY4	MHBMA	Y	
2054	DAY60	MHBMA	Y	
2058	DAY4	MHBMA	Y	
2120	DAY30	MHBMA	Y	
2169	DAY1	MHBMA	Y	
2188	DAY5	MHBMA	Y	
2310	DAY60	MHBMA	Y	
2316	DAY60	MHBMA	Y	
1038	DAY4	SPMA/SBMA	Y	
1099	DAY90	SPMA/SBMA	Y	
1105	DAY2	SPMA/SBMA	Y	
1181	DAY0	SPMA/SBMA	Y	
1203	DAY2	SPMA/SBMA	Y	
1219	DAY3	SPMA/SBMA	Y	
1251	DAY60	SPMA/SBMA	Y	
1280	Day -1	SPMA/SBMA	Y	



Celerion

Subject	Visit	Assay	Labels Match	Comment if Error Noted
2029	DAY0	SPMA/SBMA	Y	
2048	DAY5	SPMA/SBMA	Y	
2089	Day -1	SPMA/SBMA	Y	
2113	DAY90	SPMA/SBMA	Y	
2138	DAY30	SPMA/SBMA	Y	
2162	DAY1	SPMA/SBMA	Y	
2188	DAY3	SPMA/SBMA	Y	
2197	DAY30	SPMA/SBMA	Y	
2232	DAY1	SPMA/SBMA	Y	
2298	DAY5	SPMA/SBMA	Y	
2351	DAY60	SPMA/SBMA	Y	
2351	DAY90	SPMA/SBMA	Y	

Dr. Markus Bachmann

10 MAR 2015

Responsible Celerion Associate:

(Signature, Date, Printed Name)



Sample Summary			
High level summary: Number of samples collected by the site and received by Celerion agree. One discrepancy was noted between site processing log and other site source. Seven samples not collected.			
Sample per Source Summary			
Non-Discrepant Samples	Subjects	Samples per Subject per Source	Total
All Samples collected	71	6	426
2146	1	4	4
2176	1	5	5
2196	1	5	5
2205	1	2	2
2295	1	4	4
2285	1	5	5
2292	1	2	2
2330	1	5	5
2344	1	4	4
*Missed sample detail (tab2)			
Sample # per source			462

Sample # Rcvd By Celerion	
CYP2A6	462

Number of Discrepant Samples

of Samples Not Collected*



Subject	Finding	Reconciliation	PD Reported	# of Samples Not Collected	# of Non-Required Samples Sent
2146	No Day 91 back up sample collected	Source and Celerion records agree	N/A	1	
2176	No Day 91 back up sample collected	Source and Celerion records agree	N/A	1	
2196	No Day 91 back up sample collected	Source and Celerion records agree	N/A	1	
2205	2 samples inadvertently sent for SF patient	Source and Celerion records agree		N/A	2
2295	No Day 91 back up sample collected	Source and Celerion records agree	N/A	1	
2285	No Day 5 back up sample collected	Source and Celerion records agree	N/A	1	
2292	2 samples inadvertently sent for SF patient	Source and Celerion records agree		N/A	2
2330	No Day 0 back up sample collected	Source and Celerion records agree	N/A	1	
2344	No Day 91 back up sample collected	Source and Celerion records agree	N/A	1	
Total				7	4



Subject	Day	Issue	Recommended Action	Finding
2023	91	CYP2A6 samples not documented on site processing log. Sample collection is documented on the primary subject source.	Since samples were received and confirmed by Celerion and the primary source indicates samples were collected, the processing log should be reconciled to the primary subject source.	Information on tube confirmed.



CYP1A2 Plasma Sample Summary

High level summary: All sample have been reconciled. 1 sample was collected per source but not received in Celerion.

4 samples were not collected (subject did not check in)

No coding or date issues were noted during the review of these samples

Sample per Source Summary

Non-Discrepant Samples	Subjects	Samples per Subject per Source	Total
All Groups	74	6	444
<u>2225</u>	1	4	4
<u>2146</u>	1	4	4
<u>2157</u>	1	2	2
<u>2257</u>	1	6	6
<u>2344</u>	1	4	4
<u>2292</u>	1	2	2
*Missed sample detail (tab2)		Sample # per source	466

Sample # Rcvd By Celerion

Caffeine Plasma	464
-----------------	-----

Total Number of Discrepant Samples 2

of Samples Not Collected* 4



Subject	Finding	Reconciliation	PD Reported	# of Samples Not Collected	# of Samples per Source	# of Samples per Celerion	Discrepant Samples
2225	Sample not collected as subject did not check in for Day 90 visit.	Source agrees with Celerion spreadsheet		2	0	0	0
2146	Sample not collected as subject did not check in for Day 90 visit.	Source agrees with Celerion spreadsheet		2	0	0	0
2157	Subject SF--1 Day 0 sample sent to Celerion	Source agrees with Celerion spreadsheet	N/A	N/A	2	1	1
2257	Day 0-Source indicates 2 samples, Celerion records indicate 1.	Review manifest to reconcile	N/A		2	1	1
2344	Sample not collected as subject withdrawn early-Day 90 sample not collected	Source agrees with Celerion spreadsheet	N/A	N/A	0	0	0
2292	Day -1 samples sent for SF subject	Source agrees with Celerion spreadsheet	N/A	N/A	2	2	0
Total # of Protocol Req Samples Not Collected				4	Total Discrepancies		2



Subject	Day	Issue	Recommended Action	Finding
No actions and issues for this analyte				



Nicotine Plasma Sample Summary

High level summary: The number of samples documented in site source matches the number received by Celerion with the exception of 1 sample.

There are 22 potential coding/data entry issues.

Sample per Source Summary

Non-Discrepant Samples	Subjects	Samples per Subject per Source	Total
THS Group-All Samples Collected	57	38	2166
2048*	1	36	36
2095*	1	36	36
2146*	1	34	34
2196*	1	37	37
2225*	1	34	34
2344*	1	36	36
2140*	1	38	38
Abs Group-All Samples Collected	14	20	280
2292*	1	2	2
*Missed sample detail (tab2)		Sample # per source	2699

Sample # Rcvd By Celerion

THS Group Spreadsheet	2416
Abs Group Spreadsheet	282
Total Rcvd by Celerion	2698

Total # of Discrepant Samples 1

of Samples Not Collected* 16



Subject	Finding	Reconciliation	PD Reported	# of Samples Not Collected	# of Discrepant Samples
2048	Per source subject did not check in for Day 60 visit.	Source agrees with Celerion spreadsheet	Yes	2	1
2095	Per source subject did not check in for Day 30 visit.	Source agrees with Celerion spreadsheet	Yes	2	
2140	Per source 2 Day 0 samples collected.	One sample received by Celerion		1	
2146	Per source subject did not check in for Day 60 or 90 visits.	Source agrees with Celerion spreadsheet	Yes	4	
2196	Per source only the primary sample was collected.	Source agrees with Celerion spreadsheet	Yes	1	
2225	Per source subject did not check in for Day 30 or 90 visits.	Source agrees with Celerion spreadsheet	Yes	4	
2344	Per source subject did not check in for Day 90 visit.	Source agrees with Celerion spreadsheet	Yes	2	
2292	2 Day 0 samples were collected prior to subject withdrawing consent	Source agrees with Celerion spreadsheet	N/A	0	
Total protocol required samples not collected				16	



Subject	Day	Issue	Recommended Action	Finding
2140	Day 0	Source shows 2 day 0 samples. Celerion records show 1	Review Day 0 samples to confirm which samples received.	1 Day 0 sample was received. Error appears to be on site processing log.
2100	Day0/Day 90	Source shows 2 day 90 and 2 day 0 samples. Celerion records show 3 Day 90 and 1 Day 0.	Error has already been corrected.	N/A
2110	Day0/Day 90	Source shows 2 day 90 and 2 day 0 samples. Celerion records show 3 Day 90 and 1 Day 0.	Error has already been corrected.	N/A
2116	Day0/Day 90	Source shows 2 day 90 and 2 day 0 samples. Celerion records show 3 Day 90 and 1 Day 0	Error has already been corrected.	N/A
2251	Day0/Day 90	Source shows 2 day 90 and 2 day 0 samples. Celerion records show 3 Day 90 and 1 Day 0	Error has already been corrected.	N/A
2257	Day0/Day 90	Source shows 2 day 90 and 2 day 0 samples. Celerion records show 3 Day 90 and 1 Day 1.	Error has already been corrected.	N/A
2316	Day0/Day 90	Source shows 2 day 90 and 2 day 0 samples. Celerion records show 3 Day 90 and 1 Day 0	Error has already been corrected.	N/A
2334	Day0/Day 90	Source shows 2 day 90 and 2 day 0 samples. Celerion records show 3 Day 90 and 1 Day 0	Error has already been corrected.	N/A
2336	Day0/Day 90	Source shows 2 day 90 and 2 day 0 samples. Celerion records show 3 Day 90 and 1 Day 0	Error has already been corrected.	N/A
2340	Day0/Day 90	Source shows 2 day 90 and 2 day 0 samples. Celerion records show 3 Day 90 and 1 Day 0	Error has already been corrected.	N/A



2351	Day0/Day 90	Source shows 2 day 90 and 2 day 0 samples. Celerion records show 3 Day 90 and 1 Day 0	Error has already been corrected.	N/A
2079	Day0/Day 90	Source shows 2 day 90 and 2 day 0 samples. Celerion records show 3 Day 90 and 1 Day 0	Error has already been corrected.	N/A
2298	Day0/Day 90	Source shows 2 day 90 and 2 day 0 samples. Celerion records show 3 Day 90 and 1 Day 0	Error has already been corrected.	N/A
2330	Day0/Day 90	Source shows 2 day 90 and 2 day 0 samples. Celerion records show 3 Day 90 and 1 Day 0	Error has already been corrected.	N/A
2075	Day 5	12 hour timepoint. Source error on processing log. Sample drawn per subject source. Celerion received sample.	Site should reconcile processing log with site source.	Confirmed
2095	Day 60	Date for Day 60 in Celerion file is 08 Apr 14. Per source date is 11 Apr 14.	Information on tube reviewed and confirmed. Date is not included on the tube.	Will be updated per RAVE date for the Day 60 visit.
2127	Day 6	Date for Day 6 in Celerion file is 05 Mar 14. Per source date is 04 Mar 14.	Source, EDC, and Celerion reviewed and date of sample collection was confirmed.	Error made during initial recon. Dates for this sample are correct.
2143	Day 60	Date of Day 60 in Celerion file is 28 Apr 14. Per source date is 30 Apr 14.	Information on tube reviewed and confirmed. Date is not included on the tube.	Will be updated per RAVE date for the Day 60 visit.
2162	Day 2	Date of Day 2 in Celerion file is 12 Mar 14. Per source date is 13 Mar 14	Error occurred only for one split. Source and split 2 agree.	Will be updated per RAVE date for the Day 60 visit.
2162	Day 30	Date of Day 30 in Celerion file is 10 May 14. Per source date is 10 Apr 14.	Error occurred only for one split. Source and split 2 agree.	Will be updated per RAVE date for the Day 60 visit.
2212	Day 60	Date of Day 5 in Celerion file is 18 May 14. Per source date is 10 May 14.	Error occurred only for one split. Source and split 2 agree.	Will be updated per RAVE date for the Day 60 visit.
2232	Day 5	8 hour timepoint-Source error on processing log. Sample drawn per subject source. Celerion received sample.	Information on tube reviewed and confirmed.	Site should reconcile processing log with site source.



Sample Summary
High level summary: The number of protocol required samples differs from the number of collected samples by 1204. The majority of missed samples resulted from insufficient urine to fill all back up tubes. Thirty-nine primary samples were not received by Celerion. This accounts for .2% of protocol required samples.

Sample per Source Summary			
	Subjects	# Expected per Protocol	Total Number Collected
Samples for Subject who Completed the Study	45	12150	12150
2005	1	270	267
2029	1	270	257
2045	1	270	257
2048	1	270	244
2053	1	270	257
2058	1	270	257
2089	1	270	257
2095	1	270	231
2079	1	270	265
2086	1	270	257
2087	1	270	244
2115	1	270	246
2140	1	270	257
2137	1	270	257
2146	1	270	192
2209	1	270	252
2162	1	270	262
2164	1	270	267
2196	1	270	249
2200	1	270	257
2212	1	270	240
2225	1	270	192
2230	1	270	249
2205	1	270	13
2257	1	270	264
2292	1	270	21
2299	1	270	257
2287	1	270	257
2298	1	270	257
2316	1	270	257
2330	1	270	231
2334	1	270	262
2336	1	270	231
2344	1	270	218
2351	1	270	265
Totals		21600	20396

Sample # Rcvd By Celerion	
All Urine Samples	20245

Number of protocol required samples not collected.	1204
Number of protocol required primary samples not collected per source but received by Celerion.	39

Samples with Issues Reviewed During On-Site Reconciliation at Celerion	94	NOTE: The number of samples with issues does not correlate to the number of discrepant samples as all types of issues did not require on-site review at Celerion.
--	----	---

Total received by Celerion	20245
Difference between received by Celerion and protocol required samples not collected.	20206
Number of samples collected but not received.	190



2005 Day	Source	Difference	Celerion	Difference
-1	26		26	
0	26		26	
1	22		22	
2	22		22	
3	22		22	
4	22		22	
5	26		26	
30	26		26	
60	26		26	
90	26		26	
91	23		23	
	267		267	

Bio-Risk	11-DTX-B2	14
	11-IPF2A	14
BIOEXP 1	1-OHP	22
	Nic	22
	Creatinine	22
BIOEXP 2	3OH-BAP	22
	Hema	22
	HPMA	22
	MHBMA	22
	NNAL	44
	SPMA	22
	4-ABP (Aromatic Amines)	22
0		270

2007			
-1	26		26
0	26		26
1	22		22
2	22		22
3	22		22
4	22		22
5	26		26
30	26		26
60	26		26
90	26	1	25
91	26		26
	270		269

2023			
-1	26		26
0	26		26
1	22	1	21
2	22		22
3	22		22
4	22		22
5	26		26
30	26		26
60	26		26
90	26		26
91	26		26
	270		269

2029			
-1	26		26
0	26		26
1	22		22
2	22		22
3	22		22
4	22		22
5	26		26
30	26		26
60	26		26
90	26		26
91	13	-1	14
	257		258

2038			
-1	26		26
0	26		26
1	22		22
2	22		22
3	22		22
4	22		22
5	26		26
30	26		26
60	26		26
90	26		26
91	26		26
	270		270

2045			
-1	13		13
0	26		26
1	22		22
2	22		22
3	22		22
4	22	1	21
5	26		26
30	26		26
60	26		26



	90	26	2	24
	91	26		25
		257		254
2046	-1	26		25
	0	26		25
	1	22		22
	2	22		22
	3	22		22
	4	22		22
	5	26		25
	30	26		25
	60	26	1	25
	90	26		25
	91	26		25
		270		269
2048	-1	26		25
	0	26		25
	1	22		22
	2	22		22
	3	22		22
	4	22		22
	5	26		25
	30	26		25
	60	0		0
	90	26		25
	91	26		25
		244		244
				0
2053	-1	26		25
	0	26		25
	1	22		22
	2	22		22
	3	22		22
	4	22		22
	5	26		25
	30	26		25
	60	26		25
	90	26		25
	91	13	-1	14
		257		258
				1
2058	-1	26		25
	0	26		25
	1	22		22
	2	22		22
	3	22		22
	4	22		22
	5	26		25
	30	26		25
	60	26		25
	90	26		25
	91	13		13
		257		257
				0
2076	-1	26		25
	0	26		25
	1	22		22
	2	22		22
	3	22		22
	4	22		22
	5	26		25
	30	26		25
	60	26		25
	90	26		25
	91	26		25
		270		270
				0
2077	-1	26		25
	0	26		25
	1	22		22
	2	22		22
	3	22		22
	4	22		22
	5	26		25



	30	26	25
	60	26	25
	90	26	25
	91	26	25
		1	25
	270		260
2054	-1	26	25
	0	26	25
	1	22	22
	2	22	22
	3	22	22
	4	22	22
	5	26	25
	30	26	25
	60	26	25
	90	26	25
	91	26	25
	270		270
			0
2065	-1	26	25
	0	26	25
	1	22	22
	2	22	22
	3	22	22
	4	22	22
	5	26	25
	30	26	25
	60	26	24
		2	24
	90	26	25
	91	26	25
	270		265
2071	-1	26	25
	0	26	25
	1	22	22
	2	22	22
	3	22	22
	4	22	22
	5	26	25
	30	26	25
	60	26	25
	90	26	25
	91	26	25
	270		270
			0
2072	-1	26	25
	0	26	25
	1	22	22
	2	22	22
	3	22	22
	4	22	22
	5	26	25
	30	26	25
	60	26	25
	90	26	25
	91	26	25
	270		270
			0
2073	-1	26	25
	0	26	25
	1	22	22
	2	22	22
	3	22	22
	4	22	22
	5	26	25
	30	26	25
	60	26	25
	90	26	25
	91	26	25
	270		270
			0
2075	-1	26	25
	0	26	25
	1	22	22
	2	22	22
	3	22	22



	4	22	22	
	5	26	26	
	30	26	26	
	60	26	26	
	90	26	26	
	91	26	26	
		270	270	0
2089	-1	26	26	
	0	26	26	
	1	22	22	
	2	22	22	
	3	22	22	
	4	22	22	
	5	26	26	
	30	26	26	
	60	26	26	
	90	26	26	
	91	13	13	
		257	257	0
2055	-1	26	26	
	0	26	26	
	1	22	22	
	2	22	22	
	3	22	22	
	4	22	22	
	5	26	26	
	30	0	0	
	60	26	26	
	90	26	26	
	91	13	13	
		231	231	0
2079	-1	21	-2	23
	0	26	26	
	1	22	22	
	2	22	22	
	3	22	22	
	4	22	22	
	5	26	1	25
	30	26	26	
	60	26	26	
	90	26	8	18
	91	26	26	
		258	258	
2085	-1	26	2	24
	0	26	26	
	1	22	22	
	2	22	22	
	3	22	22	
	4	22	22	
	5	26	26	
	30	26	1	25
	60	26	26	
	90	26	1	25
	91	26	26	
		270	266	
2086	-1	13	13	
	0	26	26	
	1	22	22	
	2	22	22	
	3	22	22	
	4	22	22	
	5	26	26	
	30	26	26	
	60	26	26	
	90	26	26	
	91	26	1	25
		257	256	
2087	-1	13	13	
	0	26	26	



	1	22	22
	2	22	22
	3	22	22
	4	22	21
	5	26	26
	30	26	26
	60	26	26
	90	26	26
	91	13	13
		244	249
2100	-1	26	26
	0	26	26
	1	22	21
	2	22	22
	3	22	22
	4	22	22
	5	26	25
	30	26	26
	60	26	26
	90	26	26
	91	26	26
		270	268
2106	-1	26	26
	0	26	26
	1	22	21
	2	22	22
	3	22	22
	4	22	22
	5	26	25
	30	26	26
	60	26	26
	90	26	26
	91	26	26
		270	268
2110	-1	26	26
	0	26	26
	1	22	22
	2	22	22
	3	22	22
	4	22	22
	5	26	26
	30	26	26
	60	26	26
	90	26	26
	91	26	26
		270	270
			0
2116	-1	26	26
	0	26	26
	1	22	22
	2	22	22
	3	22	22
	4	22	22
	5	26	26
	30	26	26
	60	26	26
	90	26	26
	91	26	26
		270	270
			0
2109	-1	26	26
	0	26	26
	1	22	22
	2	22	22
	3	22	22
	4	22	22
	5	26	26
	30	26	26
	60	26	26
	90	26	26
	91	26	26
		270	270
			0



2113	-1	26	26	
	0	26	26	
	1	22	22	
	2	22	22	
	3	22	22	
	4	22	22	
	5	26	26	
	30	26	26	
	60	26	26	
	90	26	26	
	91	26	26	
		270	270	0

2115	-1	26	7	19
	0	26	25	1
	1	22		22
	2	22		22
	3	22		22
	4	22		22
	5	26	2	24
	30	26		26
	60	26		26
	90	26		26
	91	2	-12	14
		246	224	12

2136	-1	26	26	
	0	26	22	4
	1	22		22
	2	22		22
	3	22		22
	4	22		22
	5	26		26
	30	26		26
	60	26		26
	90	26		26
	91	26	2	24
		270	246	2

2140	-1	26	2	24
	0	26	21	5
	1	22	1	23
	2	22		22
	3	22	1	23
	4	22		22
	5	26		26
	30	26		26
	60	26		26
	90	26		26
	91	13	-4	17
		257	236	4

2137	-1	26	26	
	0	26	24	2
	1	22		22
	2	22		22
	3	22		22
	4	22		22
	5	26		26
	30	26		26
	60	26		26
	90	26		26
	91	13		13
		257	233	4

2120	-1	26	26	
	0	26		26
	1	22		22
	2	22		22
	3	22		22
	4	22		22
	5	26		26
	30	26		26
	60	26		26
	90	26		26
	91	26		26



		270		270	0
2:27	-1	26		26	
	0	26		26	
	1	22		22	
	2	22		22	
	3	22		22	
	4	22		22	
	5	26		26	
	30	26		26	
	60	26		26	
	90	26		26	
	91	26		26	
		270		270	0
2:38	-1	26		26	
	0	26		26	
	1	22		22	
	2	22		22	
	3	22		22	
	4	22		22	
	5	26		26	
	30	26		26	
	60	26		26	
	90	26		26	
	91	26	1	25	
		270		769	
2:43	-1	26		26	
	0	26		26	
	1	22		22	
	2	22		22	
	3	22		22	
	4	22		22	
	5	26		26	
	30	26		26	
	60	26	1	25	
	90	26	1	25	
	91	26		26	
		270		768	3
2:46	-1	26		26	
	0	26		26	
	1	22		22	
	2	22	1	21	
	3	22		22	
	4	22		22	
	5	26		26	
	30	26		26	
	60	0		0	
	90	0		0	
	91	0		0	
		192		191	1
2:48	-1	26		26	
	0	26		26	
	1	22		22	
	2	22		22	
	3	22		22	
	4	22		22	
	5	26		26	
	30	26		26	
	60	26		26	
	90	26		26	
	91	26		26	
		270		270	0
2:55	-1	26		26	
	0	26		26	
	1	22		22	
	2	22		22	
	3	22		22	
	4	22		22	
	5	26		26	
	30	26	1	25	
	60	26		26	



	90	26	26
	91	26	25
		1	
	270		268
2165	-1	26	26
	0	26	26
	1	22	22
	2	22	22
	3	22	22
	4	22	22
	5	26	26
	30	26	26
	60	26	26
	90	26	26
	91	26	21
		5	
	270		265
2174	-1	26	26
	0	26	26
	1	22	22
	2	22	22
	3	22	22
	4	22	22
	5	26	26
	30	26	24
	60	26	26
	90	26	26
	91	26	26
		2	
	270		265
2176	-1	26	26
	0	26	26
	1	22	22
	2	22	22
	3	22	22
	4	22	22
	5	26	26
	30	26	26
	60	26	26
	90	26	26
	91	26	26
		1	
	270		269
2187	-1	26	26
	0	26	26
	1	22	22
	2	22	22
	3	22	22
	4	22	22
	5	26	26
	30	26	26
	60	26	26
	90	26	26
	91	26	26
	270		270
2197	-1	26	26
	0	26	26
	1	22	22
	2	22	22
	3	22	22
	4	22	22
	5	26	26
	30	26	26
	60	26	26
	90	26	26
	91	26	26
	270		270
2209	-1	13	13
	0	26	26
	1	22	22
	2	22	22
	3	22	22
	4	22	22
	5	26	26



	30	26	26
	60	26	26
	90	26	26
	91	21	5
		252	257
2162	-1	18	18
	0	26	26
	1	22	22
	2	22	22
	3	22	22
	4	22	22
	5	26	26
	30	26	26
	60	26	26
	90	26	26
	91	26	26
		262	262
			0
2164	-1	26	26
	0	26	26
	1	22	22
	2	22	22
	3	22	22
	4	22	22
	5	26	26
	30	26	26
	60	26	26
	90	26	24
	91	23	4
		267	261
			0
2169	-1	26	26
	0	26	26
	1	22	22
	2	22	22
	3	22	22
	4	22	22
	5	26	26
	30	26	26
	60	26	26
	90	26	26
	91	26	26
		270	270
			0
2194	-1	26	26
	0	26	26
	1	22	22
	2	22	22
	3	22	22
	4	22	22
	5	26	26
	30	26	26
	60	26	26
	90	26	26
	91	26	26
		270	270
			0
2196	-1	18	18
	0	26	26
	1	22	22
	2	22	22
	3	22	22
	4	22	22
	5	26	26
	30	26	26
	60	26	26
	90	26	24
	91	13	1
		243	246
2200	-1	13	13
	0	26	26
	1	22	22
	2	22	22
	3	22	22



	4	22	22	
	5	26	26	
	30	26	26	
	60	26	4	22
	90	26	2	24
	91	26		26
		257	251	
2212	-1	18	-3	21
	0	26		26
	1	22		22
	2	22		22
	3	22		22
	4	22		22
	5	26		26
	30	26		26
	60	26		26
	90	26		26
	91	4	-7	11
		240	250	
2188	-1	26		26
	0	26		26
	1	22		22
	2	22		22
	3	22		22
	4	22		22
	5	26		26
	30	26		26
	60	26		26
	90	26		26
	91	26		26
		270	270	0
2214	-1	26		26
	0	26		26
	1	22		22
	2	22		22
	3	22		22
	4	22		22
	5	26		26
	30	26		26
	60	26		26
	90	26		26
	91	26		26
		270	270	0
2225	-1	26		26
	0	26		26
	1	22		22
	2	22		22
	3	22		22
	4	22		22
	5	26		26
	30	0		0
	60	26		26
	90	0		0
	91	0		0
		192	192	0
2232	-1	26		26
	0	26		26
	1	22		22
	2	22		22
	3	22		22
	4	22		22
	5	26		26
	30	26		26
	60	26		26
	90	26		26

Note: Source states "subject did not provide enough sample". It does not specify how many.

Note: Source states "not enough urine to complete back up aliquots". It does not specify how many.



	91	26	26		
		270	270		0
2230	-1	18	18		
	0	26	26		
	1	22	22		
	2	22	22		
	3	22	22		
	4	22	22		
	5	26	26		
	30	26	26		
	60	26	26		
	90	26	26		
	91	13	-2	15	
		249	251	2	
2205	-1	13	11	2	
	0	0	0	0	
	1	0	0	0	
	2	0	0	0	
	3	0	0	0	
	4	0	0	0	
	5	0	0	0	
	30	0	0	0	
	60	0	0	0	
	90	0	0	0	
	91	0	0	0	
		13	2	13	
2251	-1	26	26		
	0	26	26		
	1	22	22		
	2	22	22		
	3	22	22		
	4	22	22		
	5	26	26		
	30	26	26		
	60	26	26		
	90	26	26		
	91	26	26		
		270	270		0
2257	-1	26	26		
	0	26	26		
	1	22	22		
	2	22	22		
	3	22	22		
	4	22	22		
	5	26	26		
	30	26	26		
	60	26	26		
	90	26	26		
	91	20	20		
		264	264		0
2260	-1	26	26		
	0	26	26		
	1	22	22		
	2	22	22		
	3	22	22		
	4	22	22		
	5	26	26		
	30	26	26		
	60	26	26		
	90	26	26		
	91	26	26		
		270	270		0
2262	-1	26	26		
	0	26	26		
	1	22	22		
	2	22	22		
	3	22	22		
	4	22	22		
	5	26	26		
	30	26	26		



	60	26	26		
	90	26	26		
	91	26	26		
		270	270	0	
2285	-1	26	1	25	
	0	26		26	
	1	22		22	
	2	22		22	
	3	22		22	
	4	22		22	
	5	26		26	
	30	26		26	
	60	26		26	
	90	26		26	
	91	26		26	
		270	269		
2292	-1	21		21	
	0	0		0	
	1	0		0	
	2	0		0	
	3	0		0	
	4	0		0	
	5	0		0	
	30	0		0	
	60	0		0	
	90	0		0	
	91	0		0	
		21	21		0
2299	-1	13		13	
	0	26		26	
	1	22		22	
	2	22		22	
	3	22		22	
	4	22		22	
	5	26		26	
	30	26		26	
	60	26		26	
	90	26		26	
	91	26		26	
		257	257		0
2287	-1	26	1	25	
	0	26		26	
	1	22		22	
	2	22		22	
	3	22		22	
	4	22		22	
	5	26		26	
	30	26		26	
	60	26		26	
	90	26		26	
	91	13		13	
		257	256		
2303	-1	26		26	
	0	26		26	
	1	22	1	21	
	2	22		22	
	3	22		22	
	4	22		22	
	5	26		26	
	30	26		26	
	60	26		26	
	90	26		26	
	91	26	1	25	
		270	268		
2307	-1	26		26	
	0	26		26	
	1	22		22	
	2	22		22	
	3	22		22	
	4	22		22	



	5	26	26	
	30	26	26	
	60	26	26	
	90	26	26	
	91	26	26	
		270	270	0
2310	-1	26	26	
	0	26	26	
	1	22	22	
	2	22	22	
	3	22	22	
	4	22	22	
	5	26	26	
	30	26	26	
	60	26	26	
	90	26	26	
	91	26	26	
		270	270	0
2298	-1	26	26	
	0	26	26	
	1	22	22	
	2	22	1	21
	3	22	1	21
	4	22	1	21
	5	26	1	25
	30	26	26	
	60	26	26	
	90	13	13	
	91	26	26	
		257	253	
2316	-1	26	26	
	0	26	26	
	1	22	22	
	2	22	22	
	3	22	22	
	4	22	22	
	5	26	26	
	30	26	26	
	60	26	26	
	90	13	13	
	91	26	26	
		257	257	0
2330	-1	13	13	
	0	26	26	
	1	22	22	
	2	22	22	
	3	22	22	
	4	22	22	
	5	26	26	
	30	26	26	
	60	26	26	
	90	13	2	15
	91	13	13	
		233	233	2
2334	-1	26	26	
	0	26	26	
	1	22	22	
	2	22	1	21
	3	22	22	
	4	22	22	
	5	26	26	
	30	26	26	
	60	26	26	
	90	26	26	
	91	18	18	
		267	261	
2336	-1	13	13	
	0	26	26	
	1	22	22	
	2	22	22	



	3	22	22
	4	22	22
	5	26	25
	30	26	25
	60	26	25
	90	13	13
	91	13	13
		231	231
2340	-1	26	25
	0	26	25
	1	22	22
	2	22	22
	3	22	22
	4	22	22
	5	26	25
	30	26	25
	60	26	25
	90	26	25
	91	26	25
		270	267
2274	-1	26	25
	0	26	25
	1	22	22
	2	22	22
	3	22	22
	4	22	22
	5	26	25
	30	26	25
	60	26	25
	90	26	25
	91	26	25
		270	269
2344	-1	26	25
	0	26	25
	1	22	22
	2	22	22
	3	22	22
	4	22	22
	5	26	25
	30	26	25
	60	26	25
	90	0	0
	91	0	0
		218	218
2351	-1	21	21
	0	26	25
	1	22	22
	2	22	22
	3	22	22
	4	22	22
	5	26	25
	30	26	24
	60	26	25
	90	26	25
	91	26	25
		265	261

*Note on source states "not all backups" but does not list how many.

20396

20245

Number of samples collected per source, but not received by Celerion.

Number of samples received by Celerion, but not collected per source.



	Number Discrepant	Sample missing from Celerion file
Sample Discrepancy		
1 day 90 sample not received by Celerion. Per source all		
2007 samples were collected.		1 IPF2A
1 day 1 sample not received by Celerion. Per source all		
2023 samples were collected.		1 1-OHP
Per source no back up, but one back up was received by		
2029 Celerion [4-ABP]	-1	
1 day 4 sample not received by Celerion. Per source all		
2045 samples were collected.		1 NNN/NNAL
1 day 90 sample not received by Celerion. Per source all		
samples were collected.		1 Creatinine
1 day 90 sample not received by Celerion. Per source all		
samples were collected.		1 MHBMA
1 day 60 sample not received by Celerion. Per source all		
2046 samples were collected.		1 4-ABP
Per source no back up, but one back up was received by		
2053 Celerion [11-DTX-B2]	-1	
1 Day 91 sample not received by Celerion. Per source all		
2077 samples were collected.		1 Nic-Eq
2 day 60 samples not received by Celerion. Per source		
2065 all samples were collected.		2 23OH BAP
2 samples not received by Celerion. Per site source		
note, only 5 back up samples were collected for Day -1.		
Celerion received 7 back up samples [1 Nic; 1 OHP; 1		
2079 HEMA; 1 NNN; 1 HPMA; 1 SPMA; 1 MHBMA.	-2	
1 Day 5 sample not received by Celerion. Per source all		
2079 samples were collected.		1 11-DTX-B2
		1 IPF2a; 1 Nic;
		2 Creatinine; 2
		OHP; 2 11 DTX-
8 Day 90 samples not received by Celerion. Per source		
2079 all samples were collected.		8 B2
2 day -1 samples not received by Celerion. Per source		
2085 all samples were collected.		1 Creatinine; 1
		2 IPF2A
1 day 5 sample not received by Celerion. Per source all		
2085 samples were collected.		1 OHP
1 day 90 sample not received by Celerion. Per source all		
2085 samples were collected.		1 MHBMA
1 Day 91 sample not received by Celerion. Per source all		
2086 samples were collected.		1 Nic-Eq
1 Day 4 sample not received by Celerion. Per source all		
2087 samples were collected.		1 HEMA
1 Day 1 sample not received by Celerion. Per source all		
2100 samples were collected.		1 OHP
1 Day 5 sample not received by Celerion. Per source all		
2100 samples were collected.		1 SPMA
1 Day 1 sample not received by Celerion. Per source all		
2106 samples were collected.		1 OHP
1 day 5 sample not received by Celerion. Per source all		
2106 samples were collected.		1 SPMA
1 Day 1 sample not received by Celerion. Per source all		
2116 samples were collected.		1 OHP
		1 4ABP; 1
		OHBAp; 1
		HEMA; 1
		NNN; 1
		HPMA; 1
		SPMA; 1
7 Day -1 samples not received by Celerion. Per source		
2115 all samples were collected.		7 MHBMA
		All except 1
		HPMA
25 Day 0 samples not received by Celerion. Per source		
2115 all samples were collected.		25 sample.



2 Day 5 samples were not received by Celerion. Per source all samples were collected.	2 1 Nic; 1 NNN
Per source only primary OHP and Nic were processed. Celerion received 14 samples. [1 11DTXB2; 1 4ABP; 1OHBaP; 1 Creatinine; 1 HEMA; 2 HPMA; 1 iPF2a; 1 MHBMA; 1 Nic; 2 NNN; 2 SPMA]	-12 Creatinine; Nic; NNN; 22 OHP 1 11 DTXB2; 1 2 OHP 2 2 OHBaP 1 4ABP; 1 HEMA; 1 HPMA; 1 SPMA; 1 21 MHBMA 1 NNN/NNAL 1 NNN/NNAL -4 All missing except 1 Creatinine 24 and 1 OHP 1 Creatinine 1 SPMA 1 iPF2A 1 Creatinine 1 4-ABP 1 Nic-Eq 1 Creatinine; 1 iPF2a; 1 11 dtxb2; 1 Nic; 1 5 OHP 1 NNN; 1 4- 2 ABP 1 NNN/NNAL
22 Day 0 samples were not received by Celerion. Per source all Day 0 samples were collected.	
2 day 91 samples were not received by Celerion. Per source, all samples were collected.	
2 day -1 samples not received by Celerion. Per source all samples were collected.	
21 day 0 samples not received by Celerion. Per source all samples were collected.	
1 Day 1 sample not received by Celerion. Per source all samples were collected.	
1 Day 3 sample not received by Celerion. Per source all samples were collected.	
Per source no back up, but four back ups were received.	
2140 [Creatinine; iPF2a; 11 dtxb2; HEMA]	
24 day 0 samples not received by Celerion. Per source all samples were collected.	
1 Day 91 sample not received by Celerion. Per source all samples were collected.	
1 Day 60 sample not received by Celerion. Per source all samples were collected.	
1 Day 90 sample not received by Celerion. Per source all samples were collected.	
1 Day 2 sample not received by Celerion. Per source all samples were collected.	
1 Day 30 sample not received by Celerion. Per source all samples were collected.	
1 Day 91 sample not received by Celerion. Per source all samples were collected.	
5 Day 91 samples not received by Celerion. Per source all samples were collected.	
2 day 30 samples not received by Celerion. Per source all samples were collected.	
1 day 90 sample not received by Celerion. Per source all samples were collected.	
Per source only 21 samples were collected. All samples received by Celerion. [1 Nic; 1 OHP; 1 11DTX; 1 iPF2a; 1 Creatinine]	
2 day 90 samples not received by Celerion. Per source all samples were collected.	
4 day 4 samples not received by Celerion. Per source 23 samples were collected and 19 were received.	
2 day 90 samples not received by Celerion. Per source all samples were collected.	
1 day 90 sample not received by Celerion. Per source all samples were collected.	
4 day 60 samples not received by Celerion. Per source all samples were collected.	
	Missing result expected. The 11 DTXB2 maybe be a missing result. Missing result expected. Missing result expected.



2 day 90 samples not received by Celerion. Per source		
2200 all samples were collected.	2 2 30HBaP	Missing result expected.
2 day 60 samples not received by Celerion. Per source		
2212 all samples were collected.	2 2 30HBaP	Missing result expected.
Per source 4 day 91 samples were collected. 5 samples		
received by Celerion. [Source says 1 Nic; 1 OHP; 1		
11DTX; 1 IPF2a. Celerion received 1 4ABP; 1 HEMA; 2		
2212 NNN; 1 MHBMA]	-1	Missing result expected for NNN.
2 Samples for dropped subject sent. 13 collected per		
2205 source. Recorded to track discrepancy in number.	13	
Per source no back up samples were collected. Celerion		
2230 received 5 back up samples [1 4ABP; 1 HEMA]	-2	
1 day -1 sample not received by Celerion. Per source all		
2285 samples received.	1 1 IPF2A	
1 Day 4 sample not received by Celerion. Per source all		
2287 samples were collected.	1 1 HEMA	
1 Day 1 sample not received by Celerion. Per source all		
2303 samples were collected.	1 1 OHP	
1 Day 91 sample not received by Celerion. Per source all		
2303 samples were collected.	1 1 Nic	
1 Day 2 sample not received by Celerion. Per source all		
2298 samples were collected.	1 NNN/NNAL	
1 Day 3 sample not received by Celerion. Per source all		
2298 samples were collected.	1 NNN/NNAL	
1 Day 4 sample not received by Celerion. Per source all		
2298 samples were collected.	1 NNN/NNAL	
1 Day 5 sample not received by Celerion. Per source all		
2998 samples were collected.	1 NNN/NNAL	
Per source no back up samples were collected. Celerion		
2330 received 2 back up samples [1 30HBaP; 1 NNN]	-2	
1 Day 1 sample not received by Celerion. Per source all		
2334 samples were collected.	1 NNN/NNAL	
1 Day 0 sample not received by Celerion. Per source all		
2340 samples were collected.	1 ABP	
1 Day 5 sample not received by Celerion. Per source all		
2340 samples were collected.	1 IPF2A	
1 Day 91 sample not received by Celerion. Per source all		
2340 samples were collected.	1 SPMA	
1 Day -1 sample not received by Celerion. Per source all		
2274 samples were collected.	1 IPF2A	
2 Day 30 sample not received by Celerion. Per source all		
2351 samples were collected.	2 2 NNN/NNAL	



Subject	Day	Issue	Recommended Action	Finding
2048	Day 2	The Day 2 split 1 sample appears to be mis-coded as a day 3 sample. Date of day 2 visit is 01 Feb 14.	Check tube to confirm if the split 1 sample dated 01 Feb 14 is a Day 2 sample.	Celerion file updated and no issue noted



Subject	Reason # of Samples Expected Varies
<u>2146</u>	Subject withdrew consent. No Day 60, 90, or 91 samples collected.
<u>2205</u>	Subject dropped during Day 1. Should have only Day -1 and 0.
<u>2225</u>	Subject dropped during Day 6. No day 30, 60, 90, or 91.
<u>2292</u>	Only Day -1 and 0 samples collected. Subject withdrew consent.
<u>2344</u>	PI withdrew subject before Day 90 and 91

PHILIP MORRIS
PRODUCTS S.A.

PMI RESEARCH & DEVELOPMENT

**ZRHM-REXA-08-US Investigational Plan for Sample
Reconciliation by Covance CRAs at Celerion's Lincoln, NE site****Final Version 1.0
2Mar2015**

The purpose of this document is to describe the plan to reconcile bioanalytical sample data between the Covance clinical sites and Celerion's bioanalytical laboratory in Lincoln, NE. The steps will be performed by Covance Clinical Research Associates (CRAs) with assistance from Celerion and Covance Data Management. The data will be reconciled in regards to the collection at the Covance clinical sites, receipt at Celerion and reporting by Celerion.

Two main activities will take place. A manual sample reconciliation and a random sample audit.

A. Manual sample reconciliation.

1. Covance CRAs will compare Celerion's files against collection logs and processing logs (source) at the Covance Dallas Clinical Research Site. Spreadsheets will be created for each analyte to report number of samples expected to be collected for each subject vs. number of samples actually collected for each subject, broken down by time point. Discrepancies will be noted in the files. The different types of discrepancies noted are broken down in step two.
2. Following the CRA's manual reconciliation at Covance Dallas Clinical Research Site, the CRAs will send to Celerion and PMI a list of samples identified as being discrepant (data reported in Celerion's file that does not match source at Covance Dallas Clinical Research Site).

Discrepancies will be broken down into 5 types:

- Type 1 - Sample was protocol required, but not collected.
- Type 2 - Sample was reported by Celerion, but no supporting source exists at clinical site.
- Type 3 - Sample was collected by Covance, but not received by Celerion.
- Type 4 - Incorrect Collection Date reported in Celerion's file.
- Type 5 - Incorrect data other than collection date reported in Celerion's file.

ZRHM-REXA-08-US
Investigational Plan
Final V 1.0
2Mar2015



PHILIP MORRIS
PRODUCTS S.A.

PMI RESEARCH & DEVELOPMENT

For issue type 1 – Protocol required samples that were not collected will be compared against protocol deviations (PD) to see if there is documentation/an explanation for why it was not collected, processed or sent. If no PD exists, one will be created. These samples do not need to be reviewed manually.

For issue type 2 - Samples reported by Celerion without confirmation of collection at clinical site, will require further investigation and will be noted in the list of samples to be pulled for manual review. Covance will compare the Covance label against the Celerion label and if they are in agreement the results will not be reported because there is no source at the clinical site to support the data. If the Celerion label does not match the Covance label, Celerion's database will be updated to reflect what is on the Covance label. Any time the Celerion database is updated, output will be produced so the Covance CRA can verify the change was made successfully.

For issue type 3 - Samples collected and processed by Covance, but not reported by Celerion will be documented as lost. PDs will be cross-checked to determine if there is an explanation for why a sample was not sent. Samples will be listed in a NTF to document they were lost.

For issue type 4 - Incorrect Collection Date reported in Celerion's file. - The Visit Day and Subject ID on the Covance labels will be compared against the Celerion labels and if they match, no further action is needed. If the Visit and Subject ID do not match, the discrepancy will be investigated and if deemed necessary, Celerion's database will be updated to reflect what is on the Covance label. Results will be provided so Covance can verify the change was made correctly.

For issue type 5 - Incorrect collection dates in Celerion's files will not be corrected. The samples will be pulled and the Covance and Celerion labels will be compared to ensure they are coded correctly. If the labels do not match, Celerion's database will be updated and Covance will verify. The dates will not be corrected in Celerion's file because the data from Celerion is merged into the clinical database (RAVE), based on the Subject ID and Visit Day. The collection dates in the Celerion file will not be used. Instead, the collection dates in RAVE (all have been source document verified by Covance CRAs) will be used. Covance will provide the spreadsheet that documents the correct collection date to Celerion for their records.

3. Following receipt of data transfers from Celerion to Covance Data Management (DM), discrepancies were raised by Covance DM and addressed by Celerion. The CRAs will

PHILIP MORRIS
PRODUCTS S.A.**PMI RESEARCH & DEVELOPMENT**

review the list of discrepancies against the list of discrepant samples identified during the manual check of Celerion's QA reviewed electronic data files against site source data. Any issues that have not already been identified will be added to the list to be manually checked at Celerion (Covance label will be compared against Celerion's label and updates made to Celerion's database if necessary).

4. In cases where type 2 and type 4 discrepancies are located at Celerion Zurich, the verification of samples will be performed by Celerion Zurich personnel as agreed with the Bionalytical Principal Investigator. Celerion will check the Covance label against the Celerion label.

B. Random sample audit

1. PMI will generate and send to Covance and Celerion a random list of samples that will additionally be checked at Celerion.
2. Randomly selected samples list will include samples from all clinical sites to ensure QC of the full set of samples associated with ZRHM-REXA-08-US study.
3. The CRAs in collaboration with Celerion will perform the reconciliation (compare Covance label against Celerion label) of randomly selected samples to ensure sample traceability from collection on site up to EDC. If the Subject ID and Visit Day on the labels match, it is evident that the data was loaded into EDC correctly, as Celerion data is loaded/merged based on the Subject ID and Visit Day. If discrepancies are noted between the two labels, PMI will be notified and further actions will be discussed.
4. A spreadsheet will be created to list the samples to be randomly checked. Covance will mark an X in one column and Celerion will mark an X in another column, next to each sample that has been verified as correct. If issues are found, they will be documented in the spreadsheet in line with the discrepant sample.

In all cases, discrepancies will be noted, investigated, provided to and discussed between Covance, Celerion and PMI and necessary actions decided and documented. A meeting will be scheduled at the end of each day the Covance CRAs are on-site to discuss progress and findings. The meeting will be attended by the Covance CRAs, Covance PM and Celerion. The Covance PM will then update PMI via email or meeting held the next morning, depending on types of issues found. If unexpected issues are found, they will be discussed with PMI.

ZRHM-REXA-08-US
Investigational Plan
Final V 1.0
2Mar2015

PHILIP MORRIS
PRODUCTS S.A.**PMI RESEARCH & DEVELOPMENT**

Celerion has already reviewed the current data listings within the Watson database, noted any errors and corrections made from the data uploads and sent this list to Covance and PMI.

Upon completion of the reconciliation process a report will be generated, including

- This investigation plan as an amendment
- Any additional steps taken not outlined in this plan
- 18 Spreadsheets listing each discrepancy and the action for each discrepancy.
- Summary of issues found and the corrective actions taken

The visit is planned for March 3rd to 5th 2015. The reconciliation team will consist of two Covance CRAs, a Sample Management Associate and the Bioanalytical Principal Investigator from Celerion to support the CRAs as needed.

The Covance CRAs will not be allowed to perform any changes to the label of the samples. Any changes, in case necessary, are to be performed by qualified Celerion staff and to be documented as per Celerion's Quality Management System (QMS).

The resolution of discrepancies identified by the CRA's will be discussed together with Celerion and PMI prior to implementation and documented as required by the QMS of Covance or Celerion respectively.

Date

Signature

Dimitra Skiada
Manager Clinical Study
PMI R&D PASS

Date

Signature

ZRHM-REXA-08-US
Investigational Plan
Final V 1.0
2Mar2015



PHILIP MORRIS
PRODUCTS S.A.

PMI RESEARCH & DEVELOPMENT

Kirk Newland
Technical Director Tobacco Science
Celerion

Date

Signature

Jasmine Ropers
Project Manager
Covance Early Clinical Development



PHILIP MORRIS
PRODUCTS S.A.

PMI RESEARCH & DEVELOPMENT

02-Mar-2015

Kirk Newland
Technical Director Tobacco Science
Celerion

Date

Signature

Jasmine Ropers
Project Manager
Covance Early Clinical Development



PHILIP MORRIS
PRODUCTS S.A.

PMI RESEARCH & DEVELOPMENT

Celerion has already reviewed the current data listings within the Watson database, noted any errors and corrections made from the data uploads and sent this list to Covance and PMI.

Upon completion of the reconciliation process a report will be generated, including

- This investigation plan as an amendment
- Any additional steps taken not outlined in this plan
- 18 Spreadsheets listing each discrepancy and the action for each discrepancy.
- Summary of issues found and the corrective actions taken

The visit is planned for March 3rd to 5th 2015. The reconciliation team will consist of two Covance CRAs, a Sample Management Associate and the Bioanalytical Principal Investigator from Celerion to support the CRAs as needed.

The Covance CRAs will not be allowed to perform any changes to the label of the samples. Any changes, in case necessary, are to be performed by qualified Celerion staff and to be documented as per Celerion's Quality Management System (QMS).

The resolution of discrepancies identified by the CRA's will be discussed together with Celerion and PMI prior to implementation and documented as required by the QMS of Covance or Celerion respectively.

Date

Signature

02 MARCH 2015

Dimitra Skiada
Manager Clinical Study
PMI R&D PASS

Date

Signature

ZRHM-REXA-08-US
Investigational Plan
Final V 1.0
2Mar2015



PHILIP MORRIS
PRODUCTS S.A.

PMI RESEARCH & DEVELOPMENT

02-Mar-2015

Kirk Newland
Technical Director Tobacco Science
Celerion

Date

Signature

2 Mar 2015

Jasmine Ropers
Project Manager
Covance Early Clinical Development



NOTE TO FILE ID:	NTF-AA99128-AA99598-Sample Traceability Investigation
------------------	---

GENERAL DESCRIPTION OF ISSUE:	Statement on sample traceability for study ZRHM-REXA-08-US
-------------------------------	--

Initial Sample Receipt and Check-In

During the execution of study ZRHM-REXA-08-US (AA99128/AA99598) multiple issues related to the receipt and traceability of the clinical samples. For this study Covance Central Laboratory did not receive or review the samples prior to shipment to the bioanalytical laboratories. Two clinical sites were employed for the clinical study (Daytona Beach, FL and Dallas, TX). A total of 67 shipments of clinical samples were received between 29-Jan-2014 and 01-Oct-2014.

The clinical sample shipments were to be preceded by an electronic shipping list. Once the samples were received they were counted by the Celerion sample management team, verified against the electronic shipping list, and relabeled with a Celerion Watson LIMS barcoded label. The Watson LIMS label was affixed in a manner to ensure the original clinical label was not obscured. Discrepancies between the primary records, the electronic sample shipping list and the clinical sample label, were recorded and reported to Covance project management. Discrepancies were identified as the shipments were received and not only at the end of the clinical study. When possible the paper records were used to further elucidate any discrepancies between the electronic shipping lists and the clinical sample labels. Typically discrepancies were resolved through communication between the Covance project management team and the site personnel.

A review of the records confirms that shipments from the Daytona site remained consistent in terms of the electronic shipping lists, sample labeling and shipment paperwork. The paper records received from the Dallas site did change over time. Copies of the paper requisition forms from the Dallas site were not included in later shipments. Additionally the paper shipping list was poorly produced. As these were not to be used to establish initial sample traceability (the electronic shipping list verified against the clinical sample label were), no issue was raised by the bioanalytical site at the time of the receipt of the clinical samples.

Missing Samples Identified by Celerion

Towards the end of the clinical phase of the study Celerion notified the sponsor and Covance that a significant number of samples remained unreceived. This notification was provided in July and August of 2014. In August this issue was noted in the meeting minutes for the ERS-09 study. After the scheduled date of the expected final shipment Celerion notified the sponsor and the Covance team that approximately 5,700 samples (mostly back-up samples from the Dallas site) had not been received.

Initial Sample Reconciliation Process

Using the Watson LIMS database a non-QC reviewed spreadsheet was provided to Covance to assist in the identification of the missing samples. The spreadsheet was produced manually by the Bioanalytical Principal Investigator as a quick reference of the samples that had been received for the study. The expected samples were identified based on the protocol design. For the purpose of generating a quick



reference for the missing samples, active subjects were identified by the receipt of some other samples for the subject.

The spreadsheet of missing samples was provided to the sponsor and the global project management for Covance (initial spreadsheet sent 23-Sep-2014). It was confirmed that samples were missing. Additional resources were put into the search for additional clinical samples, mostly from the Dallas clinical site.

Receipt of Missing Clinical Samples

From the end of August through October 1st multiple shipments of samples were received and reconciled at Celerion. During this period of time of rapid shipment and check-in of samples additional discrepancies were identified by Celerion. The Project Management team from Covance worked directly with the sites to provide updates and discrepancy resolution. The spreadsheet generated by Celerion to identify possible missing samples was used by the Covance project management team as a tool to help identify possible discrepancies and missing samples.

As agreed with the sponsor, for subjects/time points where some available urine samples had been collected, samples would be shared as volume allowed to complete analysis for some groups for which aliquots were not received. A list of the clinical samples that were shared between assays is included within this document. The sharing of samples was limited by the condition of storage and the location of the analysis.

Sponsor QA Audit of Study

On the 6th and 7th of November, 2014, 2 auditors from PMIP and a third party auditor from CVO-Europe performed an audit of study ZRHM-REXA-08-US (AA99128/AA99598). A review of the paper shipping records, and sample traceability issues occurred. Scanned copies of a few examples of the shipping records from each site were provided to the PMIP auditors. The audit report concluded that Celerion has quality processes for the establishment of sample traceability.

Final Data Reconciliation

After reconciliation between the Celerion and Covance PM team was completed, two outputs were provided by Celerion. The first output was the complete set of bioanalytical results sent via the Covance secure FTP site to the data management team after completion of the analysis. The second was a list of all clinical samples that had been received for the study which was provided to the Covance PM team and the sponsor via email (19-Jan-2015).

The bioanalytical QA reviewed data was reconciled by the Covance data management team by comparison to the clinical data set. Multiple corrections were identified that were primarily related to two issues. The first issue was the inadvertent inclusion of some back-up samples that had not been assayed within the final data set. For this study only 1 result for each collection should have been included within the data output.

The second issue was an error in the uploaded Visit codes which were traced back to errors in the electronic Sample Manifests that were received with the samples. It was additionally noted that a significant number of collection dates were also erroneous again due to problems with the electronic Sample Manifests. Celerion was able to correct the inclusion of a small number of non-assayed back-up



samples within the data sets and the incorrect Visit codes based on the nominal collection days which had been confirmed against the clinical sample tubes. Celerion did not perform any correction to the dates of collection. Corrections related to the dates of collection were performed by the Covance data team by merging the bioanalytical data with the finalized clinical data set.

Final Samples Received Reconciliation

Using the list of samples received provided by Celerion, the Covance team worked to reconcile this list with the clinical records according to the investigational plan. The following were key issues noted:

- Type 1: Sample was protocol required, but not collected
- Type 2: Sample was reported by Celerion, but no supporting source exists at clinical site.
- Type 3: Sample was collected by Covance, but not received by Celerion Inc.
- Type 4: Incorrect Collection Date reported in Celerion's file
- Type 5: Incorrect data other than collection date reported in Celerion's file

The sponsor requested to have clinical monitors from Covance travel to Celerion-Lincoln to perform a physical review of a select number of samples to resolve the outstanding issues. Initially it was hoped that the clinical sample labels could be used to confirm the collection time points with a hand written collection date. It was however confirmed by Celerion that the clinical sample labels did not include the collection dates.

The scope of the investigation was therefore limited to a verification of the existence of samples noted as not collected (Type 2) and matching of the clinical and bioanalytical labels (Type 4). In addition the sponsor selected random samples to have the labels verified.

The Covance monitors were present at Celerion-Lincoln for the physical verifications. The verifications at the Celerion-Zurich site were performed and documented by the responsible local bioanalytical principal investigator. At both sites 100% of the samples reviewed confirmed the identities provided by Celerion. There were no instances of labeling discrepancies. Samples noted to have been received, without clinical source documentation, were confirmed as present.

Confirmation of Sufficient Clinical Documentation to Support Sample Traceability

After the conclusion of the above listed investigations Covance confirmed that they have sufficient clinical documentation to support the sample traceability for all of the samples listed as present at the Celerion site.



PREPARED BY:

01-Nov-2015

Kirk Newland
Technical Director, Tobacco Services

Signature of the Celerion user personnel who initiated the documentation.

APPROVED BY:

05-Nov-2015

Markus Bachmann, PhD
Bioanalytical Principal Investigator

Signature of the Celerion personnel indicates approval of the Note to File described in this document.

APPROVED BY:

04-Nov-2015

Raymond Farmer, PhD
Vice President, Global Bioanalytical Services

Signature of the Celerion Management personnel indicates approval of the Note to File described in this document.

QUALITY ASSURANCE UNIT:

05-Nov-2015

Sarah Pickersgill
Director, Quality Assurance

Signature of Celerion Quality Assurance indicates this document complies with applicable rules and regulations.

SPONSOR/APPROVED BY:

05 NOV 2015

Dimitra Skiada
Manager Clinical Study
Philip Morris International

Signature of the sponsor representative indicates approval of the Note to File described in this document.



Study Number	Assay	Matrix	Protocol		Received		Assayed	Analysis not required		Samples in poor condition for analysis	
			For Analysis	Back-up	For Analysis	Back-up		For analysis	Back-up	For analysis	Back-up
AA99128-01 and 2	Nicotine	Plasma	2680	2680	2593	2593	2555	133	133	0	0
AA99128-03	CEMA	Urine	1760	1760	1655	1634	1633	72	72	2	0
AA99128-04	NNAL*	Urine	1760	1760	1583	1543	1611	72	72	0	0
AA99128-04	NNN*	Urine	1760	1760	1656	1615	1611	72	72	1	0
AA99128-05	HEMA	Urine	1760	1760	1657	1615	1633	72	71	0	0
AA99128-06 and 13	Nic Eq	Urine	1760	1760	1645	1611	1630	71	71	1	3
AA99128-07	3-OH BaP	Urine	1760	1760	1654	1613	1598	72	72	1	0
AA99128-08	Caffeine	Plasma	480	480	453	453	447	18	18	0	0
AA99128-09	Aromatic amines	Urine	1760	1760	1657	1616	1633	72	72	0	0
AA99128-10	CYP2A6	Plasma	480	480	453	455	448	20	20	0	0
AA99128-11	11-dTXB2	Urine	1120	1120	1031	997	1010	36	36	0	0
AA99128-12	iPF2a-III	Urine	1120	1120	1030	997	1025	37	36	0	0
AA99128-14	Creatinine	Urine	1760	1760	1654	1612	1606	72	72	0	0
AA99128-15	Ames	Urine	480	0	448	0	430	18	0	0	0
AA99128-16	COHb	Blood	2560	0	2393	1017	2149	49	49	201	23
AA99598-01	SPMA	Urine	1760	1760	1656	1615	1585	72	72	1	0
AA99598-02	MHBMA	Urine	1760	1760	1658	1615	1586	72	72	2	0
AA99598-03	1-OHP	Urine	1760	1760	1651	1610	1580	72	72	1	1

*This assay was originally split into 2. We therefore planned to receive 4 aliquots, 2 for NNAL and 2 for NNN. The assay of NNN and NNAL was completed with the same sample therefore the number of NNAL results are equivalent to the number of NNN results.

**COVANCE.****eNotes**

Version: 2.17.0

Printed by Gabriela Jacome on 10 Jul 2015, 09:50 PM (GMT -5)

Tracking Id: 1219008
Study Number: 8278-008
Descriptive Title: Processing Log Errors
Status: Approved
Approval by William Lewis on 9 Jul 2015 06:32AM(GMT -5)

Workflow

Author: Gabriela Jacome
Recipients:
Interim Approver:
Approver: William Lewis
Post Approval:

Summary Information

Area of Impact: n/a
Category: Memo To File (Clarification)
Subcategory: Procedural
Effective Date: n/a
Site: Dallas, TX
Department / CC: Clinical Pharmacology / 3530

Communication**Gabriela Jacome**

08 Jul 2015, 08:16 PM (GMT -5)

The following note to file is to clarify the discrepancies in documentation between the subject source and processing logs for blood and urine samples obtained during study conduct.

When a urine or blood sample is obtained, the time of collection is documented on the subject source. Then the sample is delivered to the laboratory to be processed according to the manual instructions and documented on the processing logs. The samples listed on the attached spreadsheet deviated from this process. The samples were obtained (as it was verified with the source documents) and processed; however, the processing logs were not completed for these samples. Celerion (the receiving laboratory) confirmed that the samples were processed and received in good conditions.

Attachments

REXA-08 NTF Processing Log Errors.xlsx (10KB);



Subject	Day	Issue	Recommended Action	Finding	Outcome	Discrepancy for EYB	Need NTF
2022	Day 1	CYP2A6 samples not documented on site processing log. Sample collection is documented on the primary subject source.	Since samples were received and confirmed by Celerion and the primary source indicates samples were collected, the processing log should be reconciled to the primary subject source.	Information on tube confirmed.	No changes necessary.	CYP2A6	Need NTF
2140	Day 0	Source shows 2 day 0 samples. Celerion records show 1 12 hour timepoint. Source error on processing log. Sample drawn per subject source. Celerion received sample.	Review Day 0 samples to confirm which samples received.	1 Day 0 sample was received. Error appears to be on site processing log.	Celerion only reports the one sample to Covance. No action necessary.	Nicotine Plasma	Need NTF
2075	Day 5	8 hour timepoint. Source error on processing log. Sample drawn per subject source. Celerion received sample.	Site should reconcile processing log with site source.	Confirmed.	No action required.	Nicotine Plasma	Need NTF
2232	Day 5	Information on tube reviewed and confirmed.	Site should reconcile processing log with site source.	Information on tube reviewed and confirmed.	No action required. Processing logs will not be updated. Collection log supports the collection of the date.	Nicotine Plasma	Need NTF
2115	Day 91	No sample was collected per source. Per Celerion records, 1 sample received.	Review tubes to confirm if samples received. Review primary subject source to confirm if sample collected. If samples are collected primary source should be reconciled with processing log.	Day 91 sample confirmed as present. Processing logs appear discrepant.	3CHBAP	6 - Processing Log Error	Need NTF
2115	Day 91	All BIO EXP I samples	Confirm how many samples were received.	All samples collected except for 3CHBAP and MHBMA.	N/A	All BIO EXP II	PD created
2115	Day 91	Per source no Day 91. Day 91 samples are recorded as received by Celerion.	Review tubes to confirm if samples received. Review primary subject source to confirm if sample collected. If samples are collected primary source should be reconciled with processing log.	Day 91 sample confirmed as present. Processing logs appear discrepant.	Sample was collected and was shipped on 12AUG2014. Processing log was filled out incorrectly. Per documentation, only 88.7 ml of urine was collected enough for ANI tubes only. No change necessary.	NNAL/NNH	Need NTF
2140	Day 3	Split 4 sample not coded.	Investigate if samples were received, confirm if Day -1 and confirm why not coded.	Day 91 sample confirmed as present. Processing logs appear discrepant.	For D-1 or D1 - per processing log, all samples were collected. For D0 - per processing log, all primary were collected. Unable to confirm if back ups were collected. By reviewing the log, the volume collected during the interval (253 ml) was not enough to collect all back up tubes. No change necessary.	NNAL/NNH	Need NTF
2237	Day 91	Per source no back up samples were collected. Celerion records report back up sample received.	Review tubes to confirm if samples received. Review primary subject source to confirm if sample collected. If samples are collected primary source should be reconciled with processing log.	Processing logs appear discrepant.	The processing log incorrectly states that 7 out of the 13 back-up samples were collected. No changes necessary.	All 24 hr urine	Need NTF
2351	Day -1	Per source only 1 Day -1 sample was collected. Celerion records show receipt of 2 samples.	Review tubes to confirm if samples received. Review primary subject source to confirm if sample collected. If samples are collected primary source should be reconciled with processing log.	Error in source Celerion received receipt of 2 samples received.	Sample was collected and was shipped on 07AUG2014 and 18AUG2014. The processing source was not filled out correctly. No change necessary.	3CHBAP	Need NTF
2351	Day -3	Per source only 1 sample was collected. Celerion records indicate 2 samples received.	Review tubes to confirm if samples received. Review primary subject source to confirm if sample collected. If samples are collected primary source should be reconciled with processing log.	Site Processing log appears discrepant.	Sample was collected and was shipped on 11AUG2014 and 26AUG2014. The processing source was not filled out correctly. No change necessary.	Acetaminophen	Need NTF
2351	Day -1	Per source no back up samples were collected. Celerion records report back up sample received.	Review tubes to confirm if samples received. Review primary subject source to confirm if sample collected. If samples are collected primary source should be reconciled with processing log.	Site source is discrepant.	Sample was collected and was shipped on 12AUG2014 and 26AUG2014. Log was filled out incorrectly. No changes necessary.	NNAL/NNH	Need NTF