

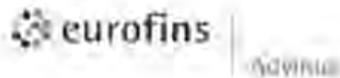
## **APPENDIX K: CLINICAL PATHOLOGY**

### **PRODUCT IDENTIFICATION**

*L. reuteri* 3630 & *L. reuteri* 3632

Submitted By:

Eurofins Advinus Ltd  
21 & 22, Phase II, Peenya Industrial Area  
Bengaluru, 560 058, India



DRAFT CLINICAL PATHOLOGY PHASE REPORT (23 August 2021)

**STUDY TITLE**

*Limosilactobacillus reuteri*: 28-DAY REPEAT-DOSE ORAL GAVAGE TOXICITY  
STUDY IN RATS

PSL STUDY NUMBER: 55164

EUROFINS ADVINUS STUDY PHASE NUMBER: G23206

PRINCIPAL INVESTIGATOR: K. C. JAYACHANDRA, M.V.Sc., DABT

**PATHOLOGY PHASE REPORT COMPLETED ON**  
Will be included in Final Report

**SPONSOR**

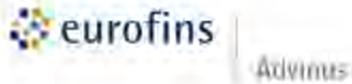
ELANCO ANIMAL HEALTH INCORPORATED  
2500 INNOVATION WAY  
GREENFIELD, INDIANA, 46140

**TEST FACILITY**

PRODUCT SAFETY LABS  
2394 US HIGHWAY Y 130  
DAYTON, NEW JERSEY 08810, USA

**TEST SITE**

EUROFINS ADVINUS LIMITED  
#21 & 22, PEENYA INDUSTRIAL AREA - PHASE II  
BENGALURU- 560 058, INDIA



**GLP COMPLIANCE STATEMENT AND DECLARATION**

**PSL Study No.** : 55164  
**Eurofins Advinus Study Phase No.** : G23206  
**Eurofins Advinus Study Phase Code** : Clin\_PATH  
**Principal Investigator** : Dr. K. C. Jayachandra  
**Location** : Department of Safety Assessment, Pathology section, Eurofins Advinus Limited, Bengaluru, India

I hereby confirm that the Phase of Clinical Pathology data interpretation of the above mentioned study was performed and documented in compliance with U.S. FDA GLP: 21 CFR Part 58, 1987 which is compatible with OECD Principles of Good Laboratory Practice (as revised in 1997) published in ENV/MC/CHEM (98)17, OECD, Paris, 1998. A copy of audited clinical pathology data was provided by PSL for the preparation of clinical pathology data interpretation phase report.

It is assured that the reported results faithfully represent the data provided by PSL during the experimental work. No circumstances have been left unreported which may have affected the quality or integrity of the data or which might have a potential bearing on the validity and reproducibility of this study phase.

\_\_\_\_\_  
K. C. Jayachandra, M.V.Sc., DABT  
Principal Investigator, Pathology Section,  
Dept. of Safety Assessment  
Eurofins Advinus Limited, Bengaluru

\_\_\_\_\_  
Date



**QUALITY ASSURANCE STATEMENT**

The clinical pathology data interpretation phase (Eurofins Advinus Study phase No. G23206) of PSL Study No. 55164 entitled “*Limosilactobacillus reuteri*: 28-Day repeat-dose oral gavage toxicity study in rats” was inspected in accordance with U.S. FDA GLP: 21 CFR Part 58, 1987 which is compatible with OECD Principles of Good Laboratory Practice (as revised in 1997) published in ENV/MC/CHEM (98)17, OECD, Paris, 1998.

The clinical pathology data interpretation phase report was reviewed and findings reported to Principal Investigator, Study Director, Lead QAU, Test Site Management and Test Facility Management on the dates shown below:

Inspection / Audit		Reporting to Principal Investigator and Test Site Management	Reporting to Study Director, Lead QAU and Test Facility Management
Date	Phase	Date	Date
14 July 2021	<b>Initiation Phase</b> Review of study plan	14 July 2021	15 July 2021
22 July 2021	<b>Reporting Phase</b> Draft clinical pathology evaluation phase report review	22 July 2021	23 July 2021

Report review was performed according to the Standard Operating Procedures of the test site’s Quality Assurance Unit. The report of the clinical pathology data interpretation phase of the study was inspected against the approved study plan and pertinent data provided by the study director, and it accurately reflects that data.

\_\_\_\_\_  
D. V. Krishnamurthy, M.Sc., RQAP-GLP  
Quality Assurance Unit-GLP  
Eurofins Advinus Limited,  
Bengaluru

\_\_\_\_\_  
Date



## LIST OF ABBREVIATIONS AND SYMBOLS

### General

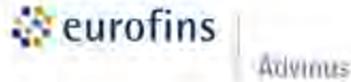
.	-	No Data
-	-	No Data
dl	-	decilitre
fL	-	femtolitre
g	-	gram
N	-	Number Of Values Used In Calculation
ng	-	nanogram
SD	-	Standard Deviation
Sligh...	-	Slightly Cloudy
mg	-	milligram
mmol/L	-	millimole/litre
µL	-	microlite
picogram	-	picogram
WNL	-	Within Normal Limits
QNS	-	Quantity Not Sufficient
%Diff	-	Per cent Difference

### Hematology

ABAS	-	absolute basophil
AEOS	-	absolute eosinophil
ALUC	-	absolute large unstained cell
ALYM	-	absolute lymphocyte
AMON	-	absolute monocyte
ANEU	-	absolute neutrophil (all forms)
HCT	-	hematocrit
HGB	-	hemoglobin
MCH	-	mean corpuscular (cell) hemoglobin
MCHC	-	mean corpuscular (cell) hemoglobin concentration
MCV	-	mean corpuscular (cell) volume
PLT	-	platelet count
RBC	-	red blood cell count
RDW	-	red cell distribution width
WBC	-	white blood cell count

### Coagulation

APTT	-	activated partial thromboplastin time
PT	-	prothrombin time



LIST OF ABBREVIATIONS AND SYMBOLS contd.

Clinical Chemistry

ALB	-	Albumin
ALKP	-	alkaline phosphatase
ALT	-	alanine aminotransferase
AST	-	aspartate aminotransferase
BUN	-	Blood urea nitrogen
CALC	-	calcium
CHOL	-	cholesterol
CL	-	chloride
CREAT	-	Creatinine
ELISA	-	enzyme-linked immunosorbent assay
GLOB	-	globulin
GGT	-	gamma glutamyl transferase
GLU	-	glucose
HDL	-	high density lipoprotein cholesterol
K	-	potassium
LDL	-	low density lipoprotein cholesterol
NA	-	sodium
IPHS	-	inorganic phosphorous
SDH	-	sorbitol dehydrogenase
T3	-	triiodothyronine
T4	-	thyroxine
BILI	-	total bilirubin
TP	-	total protein
TRIG	-	triglycerides
TSH	-	thyroid stimulating hormone
U/L	-	units/litre

Urinalysis

DK	-	dark
EU	-	ehrlieh units
LT	-	light
NT	-	Not tested
pH	-	negative log of the hydrogen ion
SG	-	Specific Gravity
TR	-	Trace
URO	-	urobilinogen
WNL	-	within normal limits



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**TEST SITE STUDY PERSONNEL**

TEST SITE:	Eurofins Advinus Limited # 21 & 22, Peenya Industrial Area, Phase II, Bengaluru 560058 India
Principal Investigator:	K. C. Jayachandra, M.V.Sc., DABT Pathologist Department of Safety Assessment
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Test site management:	Rajiv Malik
Test site QA:	D V Krishnamurthy, M.Sc., RQAP-GLP Quality Assurance Unit-GLP
Report compilation:	M. Tejaswini, B.Sc. Electronic Data Processing (EDP) Department of Safety Assessment



1. STUDY PHASE DETAILS

Study Title : *Limosilactobacillus reuteri*: 28-Day repeat-dose oral gavage toxicity study in rats

Study Phase : Clinical Pathology evaluation

Test Facility Study Number : 55164

Test Site Study Phase No. : G23206

Test Facility : Product Safety Labs (PSL)  
2394 US Highway 130  
Dayton, New Jersey 08810

Test Site : Eurofins Advinus Limited  
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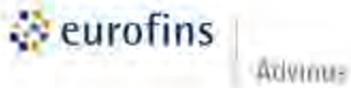


Lead QAU : Edward Hyman, BA, MBA, RQAP-GLP,CQA  
Director, Quality Assurance  
Product Safety Labs  
Email: [EdwardHyman@Productsafetylabs.com](mailto:EdwardHyman@Productsafetylabs.com)

Study Phase Schedule

Study Phase Initiation Date : 9 July 2021  
Final Clinical pathology Phase : Will be included in final report  
Report (Study Phase Completion Date)

DRAFT PHASE REPORT



**2. OBJECTIVE**

The objective of this study was to evaluate the potential toxicity of *Limosilactobacillus reuteri* (*L. reuteri*) ATCC PTA-126787 (*L. reuteri* 3630) and ATCC PTA-126788 (*L. reuteri* 3632) in male and female rats likely to arise from repeated exposure via oral gavage over a test period of 28 days. A no-observed-adverse-effect-level (NOAEL) was also sought for each sex. This clinical pathology phase report includes interpretation of hematology, coagulation, clinical chemistry and urinalysis data and the conclusions drawn from respective data.

**3. STUDY DESIGN**

Experimental procedures applicable to clinical pathology are summarized in the tables below. More details can be found in the main toxicology report.

The selected male and female rats were assigned to control and various treated groups as shown below:

Group	Number of Rats Males/ Females	Test article (mg/kg bw/day)	Targeted Dose Level (CFU/kg bw/day)	Calculated <sup>b</sup> Dose (CFU/kg bw/day)	Dose Volume mL/kg bw/day	Test Article Concentration (mg/mL <sup>a</sup> )
1	10/10	0 Vehicle only	0	0	5	0
2	10/10	L. reuteri 3630 (126.5) + L. reuteri 3632 (75.8)	1.668E+10 + 1.668E+10	3.1E+09 + 7.5E+09		L. reuteri 3630 (25.3) + L. reuteri 3632 (15.2)
3	10/10	L. reuteri 3630 (253.3) + L. reuteri 3632 (151.6)	3.337E+10 + 3.337E+10	4.5E+09 + 1.4E+10		L. reuteri 3630 (50.7) + L. reuteri 3632 (30.3)
4	10/10	L. reuteri 3630 (760) + L. reuteri 3632 (455)	1.001E+11 + 1.001E+11	1.6E+10 + 5.7E+10		L. reuteri 3630 (152) + L. reuteri 3632 (91)

<sup>a</sup> LR3630 = 132 000 000 000 CFU/g (1.32E+11) and LR3632 = 220 000 000 000 CFU/g (2.2E+11), as determined by Product Safety Labs prior to study initiation.

<sup>b</sup> Calculated using the geometric mean



#### 4. METHODS

##### 4.1 CLINICAL PATHOLOGY INVESTIGATIONS

###### 4.1.1 SAMPLE COLLECTION

Clinical pathology analyses were conducted on samples collected on the fifth week (Day 30/31) of the study for hematology, coagulation clinical chemistry, and urinalysis. Blood samples were not collected from one Group 2 male (3829) which was sacrificed humanely on Day 19. The coagulation clinical chemistry, and urinalysis samples were analyzed at PSL (Test facility) and hematology samples were analyzed at Corteva agrisciences (Test site for hematology sample analysis). The electronic copies of the results were shared by PSL with Eurofins Advinus (Test site) for interpretation of the data.

###### 4.1.2 HEMATOLOGY AND COAGULATION

Complete blood counts, including reticulocytes, were determined on an ADVIA 120 Hematology System. Coagulation times were determined on a Siemens Sysmex CA620 automated coagulation system.

The following hematological and coagulation parameters were determined by PSL and the electronic copies of results were shared with the test site for inclusion in the clinical pathology phase report:

red blood cells count	hemoglobin concentration
hematocrit	mean corpuscular volume
mean corpuscular hemoglobin	red cell distribution width
reticulocyte count	platelet count
white blood cells and differential leukocyte counts of neutrophils, lymphocytes, monocytes, eosinophils, basophils, large unstained cells.	
mean corpuscular hemoglobin concentration was calculated	
prothrombin time	
activated partial thromboplastin time	



#### 4.1.3 CLINICAL CHEMISTRY

The following parameters were determined on a COBAS C311 automated clinical chemistry analyzer at PSL and the electronic copies of results were shared with test site for inclusion in the pathology phase report:

Serum aspartate aminotransferase	Serum alanine aminotransferase
Sorbitol dehydrogenase	Alkaline phosphatase
Gamma-glutamyl transferase	Total bilirubin
Urea nitrogen	Total cholesterol
Blood creatinine	Fasting glucose
Triglycerides	Albumin
Total serum protein	Calcium
Globulin	Sodium
Inorganic phosphorus	Chloride
Potassium	
L- and D-Lactic acid*	

\*(additional serum sample was sent to the Sponsor for evaluation)

#### 4.1.4 URINALYSIS

The following parameters were determined at PSL and the electronic copies of results were shared with test site for inclusion in the pathology phase report:

Bilirubin	Ketones	Specific gravity
Blood	Microscopic urine sediments	Volume
Color	pH	Urobilinogen
Clarity	Protein (total)	
Glucose	Quality	



## 5. RESULTS AND DISCUSSION

### 5.1 CLINICAL PATHOLOGY

#### 5.1.1 HEMATOLOGY

Refer Tables [1](#) and [2](#), Appendices [1](#) and [2](#)

There were no test article-related changes in hematology parameters at all dose levels tested.

Decreased haemoglobin in Group 3 males, and reduced haematocrit in Group 3 males and females were considered toxicologically insignificant as there was no dose progression, the magnitude of the change was minimal, and the values were within ranges of historical controls. Further, there were no corresponding changes in MCH, MCHC, or red blood cell count. The increased neutrophil count in Group 3 males also was considered toxicologically insignificant as there was no dose progression and/or magnitude of the change was minimal.

All other changes in hematology parameters were considered unrelated to test article, because they occurred sporadically, or were considered due to biological variance among rats as magnitude of variation was minimal.

#### 5.1.2 COAGULATION

Refer Tables [3](#) and [4](#), Appendices [3](#) and [4](#)

There were no test article-related changes in coagulation parameters at all dose levels tested.

#### 5.1.3 CLINICAL CHEMISTRY

Refer Tables [5](#) and [6](#), Appendices [5](#) and [6](#)

There were no test article-related changes in clinical chemistry parameters at all dose levels tested.

Increased creatinine in Group 4 females was considered toxicologically insignificant as it was not associated with any renal lesions, values were within ranges of historical controls, and there were no effects of the test material on urinalysis.



#### 5.1.4 URINALYSIS

Refer Tables 7 and 8, Appendices 7 and 8

There were no test article-related changes in urinalysis parameters at all dose levels tested.

#### 6. SUMMARY

Administration of test articles *Limosilactobacillus reuteri* (*L. reuteri*) ATCC PTA-126787 (*L. reuteri* 3630) and ATCC PTA-126788 (*L. reuteri* 3632) in male and female rats by the oral gavage route over a test period of 28 days did not induce any changes in hematology, coagulation, clinical chemistry and urinalysis parameters.

#### 7. ARCHIVES

Eurofins Advinus will archive documents of the study such as electronic copy of the study plan, draft clinical pathology phase report, final clinical pathology phase report, email correspondence generated for the clinical pathology phase and printed copy of original signed final pathology phase report (copy 1/1) for life time. The study data file will be archived for at least 9 years following the completion of the study phase. Archiving beyond 9 years will be decided after consulting the sponsor.

#### 8. REPORT DISTRIBUTION

An electronic PDF copy (1/1) of clinical pathology phase report generated at the Test Site will be sent to the study director/Test Facility (PSL). The original signed final clinical pathology phase report (1/1) will be archived at the Test site (Eurofins Advinus).



## 9. TABLES

DRAFT PHASE REPORT



TABLE 1. Summary of Hematology Parameters – Males<sup>1</sup>

Refer [Appendix 1](#)

Sex: Male			Group 1	Group 2	Group 3	Group 4
Day(s) Relative to Start Date			0 CFU	1.668E+10 CFU	3.337E+10 CFU	1.001E+11 CFU
RBC (x10 <sup>6</sup> /μL)	31 []	Mean	8.48	8.54	8.09	8.33
		SD	0.66	0.30	0.43	0.32
		N	10	9	10	10
		%Diff		0.7	-4.6	-1.8
HGB (g/dL)	31 [ 1]	Mean	15.6	15.5	14.8 *	15.4
		SD	0.7	0.5	0.7	0.6
		N	10	9	10	10
		%Diff		-0.6	-5.1	-1.6
HCT (%)	31 [ 1]	Mean	49.3	47.9	45.7 *	47.6
		SD	2.5	1.8	2.1	1.7
		N	10	9	10	10
		%Diff		-2.7	-7.2	-3.5
MCV (fL)	31 [ 1]	Mean	58.3	56.1	56.5	57.2
		SD	3.9	2.1	1.9	1.1
		N	10	9	10	10
		%Diff		-3.7	-3.1	-2.0
MCH (pg)	31 [ 1]	Mean	18.5	18.2	18.4	18.5
		SD	0.8	0.7	0.7	0.3
		N	10	9	10	10
		%Diff		-1.6	-0.8	-0.2
MCHC (g/dL)	31 [ 1]	Mean	31.8	32.5	32.5	32.3
		SD	1.4	0.8	1.1	0.6
		N	10	9	10	10
		%Diff		2.1	2.1	1.5
RDW (%)	31 [ 1]	Mean	13.0	12.9	13.1	13.0
		SD	0.9	0.4	0.6	0.7
		N	10	9	10	10
		%Diff		-1.0	0.8	0.4
PLT (x10 <sup>3</sup> /μL)	31 [ 1]	Mean	952	919	852	830
		SD	159	148	282	304
		N	10	9	10	10
		%Diff		-3.5	-10.5	-12.8

[] - Anova & Dunnett

[ 1] - Dunnett: \* = p < 0.05

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.



TABLE 1 contd. Summary of Hematology Parameters – Males<sup>1</sup>

Refer [Appendix 1](#)

Sex: Male			Group 1	Group 2	Group 3	Group 4
Day(s) Relative to Start Date			0 CFU	1.668E+10 CFU	3.337E+10 CFU	1.001E+11 CFU
WBC (x10 <sup>3</sup> /μL)	31 []	Mean	8.77	10.75	11.91	10.58
		SD	2.03	3.43	3.75	2.68
		N	10	9	10	10
		%Diff		22.6	35.8	20.6
ANEU (x10 <sup>3</sup> /μL)	31 []	Mean	1.38	1.81	2.08 *	1.45
		SD	0.47	0.39	0.77	0.31
		N	10	9	10	10
		%Diff		31.1	50.3	5.3
ALYM (x10 <sup>3</sup> /μL)	31 []	Mean	6.98	8.39	9.22	8.70
		SD	1.71	2.95	3.18	2.41
		N	10	9	10	10
		%Diff		20.2	32.2	24.6
AMON (x10 <sup>3</sup> /μL)	31 []	Mean	0.17	0.23	0.29	0.21
		SD	0.09	0.13	0.18	0.14
		N	10	9	10	10
		%Diff		29.5	67.3	20.6
AEOS (x10 <sup>3</sup> /μL)	31 []	Mean	0.15	0.18	0.18	0.14
		SD	0.05	0.06	0.07	0.04
		N	10	9	10	10
		%Diff		20.5	21.8	-6.6
ABAS (x10 <sup>3</sup> /μL)	31 []	Mean	0.06	0.11	0.09	0.04
		SD	0.03	0.10	0.07	0.03
		N	10	9	10	10
		%Diff		82.3	56.2	-28.9
ALUC (x10 <sup>3</sup> /μL)	31 []	Mean	0.04	0.05	0.05	0.04
		SD	0.02	0.03	0.02	0.02
		N	10	9	10	10
		%Diff		28.5	47.2	16.5
ARET (x10 <sup>3</sup> /μL)	31 []	Mean	225.4	232.4	224.3	233.2
		SD	31.7	30.5	43.8	18.9
		N	10	9	10	10
		%Diff		3.1	-0.5	3.5

[] - Dunnett: \* = p < 0.05

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.



TABLE 2. Summary of Hematology Parameters – Females<sup>1</sup>

Refer [Appendix 2](#)

Sex: Female			Group 1	Group 2	Group 3	Group 4
Day(s) Relative to Start Date			0 CFU	1.668E+10 CFU	3.337E+10 CFU	1.001E+11 CFU
RBC (x10 <sup>6</sup> /μL)	31 []	Mean	8.60	8.35	8.11	8.35
		SD	0.38	0.58	0.71	0.27
		N	9	10	9	9
		%Diff		-3.0	-5.8	-3.0
HGB (g/dL)	31 [ 1]	Mean	15.6	15.3	15.0	15.4
		SD	0.6	0.9	1.2	0.5
		N	9	10	9	9
		%Diff		-2.4	-4.0	-1.5
HCT (%)	31 [ 1]	Mean	49.0	46.0	45.0 *	46.4
		SD	3.2	3.6	3.8	1.7
		N	9	10	9	9
		%Diff		-6.1	-8.1	-5.2
MCV (fL)	31 [ 1]	Mean	56.9	55.1	55.6	55.7
		SD	2.6	1.5	2.1	2.3
		N	9	10	9	9
		%Diff		-3.3	-2.4	-2.2
MCH (pg)	31 [ 1]	Mean	18.2	18.3	18.5	18.5
		SD	0.5	0.6	0.5	0.6
		N	9	10	9	9
		%Diff		0.6	1.8	1.4
MCHC (g/dL)	31 [ 1]	Mean	32.0	33.3	33.4	33.2
		SD	1.9	1.1	0.9	1.0
		N	9	10	9	9
		%Diff		3.9	4.2	3.6
RDW (%)	31 [ 1]	Mean	12.3	12.1	12.1	11.8
		SD	0.7	0.3	0.4	0.5
		N	9	10	9	9
		%Diff		-1.5	-1.4	-4.1
PLT (x10 <sup>3</sup> /μL)	31 [ 1]	Mean	1059	1048	1126	939
		SD	233	183	194	130
		N	9	10	9	9
		%Diff		-1.0	6.4	-11.4

[] - Anova & Dunnett

[ 1] - Dunnett: \* = p < 0.05

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.



TABLE 2 contd. Summary of Hematology Parameters – Females<sup>1</sup>

Refer [Appendix 2](#)

Sex: Female			Group 1	Group 2	Group 3	Group 4
Day(s) Relative to Start Date			0 CFU	1.668E+10 CFU	3.337E+10 CFU	1.001E+11 CFU
WBC (x10 <sup>3</sup> /μL)	31 □	Mean	7.28	6.67	7.24	5.90
		SD	2.34	1.35	2.40	1.65
		N	9	10	9	9
		%Diff		-8.3	-0.5	-18.9
ANEU (x10 <sup>3</sup> /μL)	31 □	Mean	0.72	0.65	0.69	0.54
		SD	0.24	0.22	0.35	0.16
		N	9	10	9	9
		%Diff		-9.9	-4.6	-25.5
ALYM (x10 <sup>3</sup> /μL)	31 □	Mean	6.22	5.67	6.25	5.07
		SD	2.18	1.26	2.27	1.50
		N	9	10	9	9
		%Diff		-8.8	0.5	-18.5
AMON (x10 <sup>3</sup> /μL)	31 □	Mean	0.10	0.13	0.12	0.13
		SD	0.05	0.06	0.07	0.06
		N	9	10	9	9
		%Diff		22.1	11.0	21.1
AEOS (x10 <sup>3</sup> /μL)	31 □	Mean	0.15	0.16	0.13	0.11
		SD	0.10	0.10	0.03	0.04
		N	9	10	9	9
		%Diff		3.3	-18.7	-29.3
ABAS (x10 <sup>3</sup> /μL)	31 □	Mean	0.03	0.03	0.02	0.02
		SD	0.02	0.02	0.01	0.01
		N	9	10	9	9
		%Diff		-19.0	-33.3	-43.2
ALUC (x10 <sup>3</sup> /μL)	31 □	Mean	0.04	0.03	0.04	0.03
		SD	0.02	0.02	0.02	0.01
		N	9	10	9	9
		%Diff		-9.6	-4.1	-18.0
ARET (x10 <sup>3</sup> /μL)	31 □	Mean	188.8	176.7	194.5	193.6
		SD	41.3	34.3	53.8	45.5
		N	9	10	9	9
		%Diff		-6.4	3.0	2.5

□ - Dunnett

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.



**TABLE 3. Summary of Coagulation Parameters – Males<sup>1</sup>**

Refer [Appendix 3](#)

Sex: Male			0 CFU Group 1	1.668E+10 CFU Group 2	3.337E+10 CFU Group 3	1.001E+11 CFU Group 4
Week(s) Relative to Start Date						
APTT (seconds)	5 [a]	Mean	17.17	18.76	18.90	18.33
		SD	2.20	5.55	2.23	2.75
		N	10	9	10	9
		%Diff		9.23	10.08	6.78
PT (seconds)	5 [a1]	Mean	10.18	10.14	10.20	10.17
		SD	0.36	0.56	0.43	0.24
		N	10	9	10	9
		%Diff		-0.35	0.20	-0.13

[a] - Anova & Dunnett(Rank)

[a1] - Anova & Dunnett(Log)

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.



TABLE 4. Summary of Coagulation Parameters – Females<sup>1</sup>

Refer [Appendix 4](#)

Sex: Female			0 CFU Group 1	1.668E+10 CFU Group 2	3.337E+10 CFU Group 3	1.001E+11 CFU Group 4
Week(s) Relative to Start Date						
APTT (seconds)	5 [a]	Mean	19.12	17.48	17.94	17.96
		SD	3.54	4.07	2.17	1.90
		N	10	9	10	9
		%Diff	-	-8.59	-6.17	-6.09
PT (seconds)	5 [a1]	Mean	9.83	9.76	10.02	9.91
		SD	0.26	0.81	0.33	0.37
		N	8	9	10	9
		%Diff	-	-0.71	1.98	0.88

[a] - Anova & Dunnett

[a1] - Anova & Dunnett(Rank)

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.



TABLE 5. Summary of Clinical Chemistry Parameters – Males<sup>1</sup>

Refer [Appendix 5](#)

Sex: Male			0 CFU Group 1	1.668E+10 CFU Group 2	3.337E+10 CFU Group 3	1.001E+11 CFU Group 4
Week(s) Relative to Start Date						
ALT (U/L)	5 [a]	Mean	32.9	54.3	32.7	44.9
		SD	6.8	67.5	5.5	44.6
		N	10	9	10	10
		%Diff		65.1	-0.6	36.5
ALB (g/dL)	5 [a1]	Mean	4.17	4.08	4.18	4.13
		SD	0.24	0.28	0.28	0.31
		N	10	9	10	10
		%Diff		-2.21	0.24	-0.96
ALKP (U/L)	5 [a1]	Mean	122.3	126.3	121.1	125.4
		SD	17.5	18.1	24.8	27.2
		N	10	9	10	10
		%Diff		3.3	-1.0	2.5
AST (U/L)	5 [a]	Mean	84.6	124.9	89.9	110.9
		SD	9.4	111.1	16.2	74.0
		N	10	9	10	10
		%Diff		47.6	6.3	31.1
CALC (mg/dL)	5 [a1]	Mean	11.45	11.29	11.41	11.40
		SD	0.50	0.34	0.49	0.48
		N	10	9	10	10
		%Diff		-1.41	-0.35	-0.44
CL (mmol/L)	5 [a1]	Mean	101.80	101.72	100.97	101.84
		SD	1.91	1.45	1.28	1.28
		N	10	9	10	10
		%Diff		-0.08	-0.82	0.04
CHOL (mg/dL)	5 [a2]	Mean	66.2	60.3	58.1	57.6
		SD	19.3	17.7	9.1	8.1
		N	10	9	10	10
		%Diff		-8.9	-12.2	-13.0
CREA (mg/dL)	5 [a]	Mean	0.182	0.189	0.202	0.187
		SD	0.018	0.030	0.039	0.022
		N	10	9	10	10
		%Diff		3.785	10.989	2.747

[a] - Anova & Dunnett(Rank)

[a1] - Anova & Dunnett

[a2] - Anova & Dunnett(Log)

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.



TABLE 5 contd. Summary of Clinical Chemistry Parameters – Males<sup>1</sup>

Refer [Appendix 5](#)

Sex: Male			0 CFU Group 1	1.668E+10 CFU Group 2	3.337E+10 CFU Group 3	1.001E+11 CFU Group 4
Week(s) Relative to Start Date						
GGT (U/L)	5 [l]	Mean	3.000n	3.000n	3.000n	3.000n
		SD	0.000	0.000	0.000	0.000
		N	10	9	10	10
		%Diff		0.000	0.000	0.000
GLOB (g/dL)	5 [a]	Mean	1.91	2.00	1.88	1.91
		SD	0.20	0.24	0.14	0.22
		N	10	9	10	10
		%Diff		4.71	-1.57	0.00
GLUC (mg/dL)	5 [a]	Mean	162.0	152.4	155.7	178.0
		SD	18.4	30.5	24.7	20.1
		N	10	9	10	10
		%Diff		-5.9	-3.9	9.9
IPHS (mg/dL)	5 [a]	Mean	10.42	10.02	10.12	10.02
		SD	0.94	0.64	1.23	1.07
		N	10	9	10	10
		%Diff		-3.82	-2.88	-3.84
K (mmol/L)	5 [a1]	Mean	7.361	7.746	7.351	7.639
		SD	0.568	0.541	1.209	1.702
		N	10	9	10	10
		%Diff		5.224	-0.136	3.777
NA (mmol/L)	5 [a]	Mean	144.30	143.56	142.90	143.60
		SD	2.31	2.88	2.69	2.41
		N	10	9	10	10
		%Diff		-0.52	-0.97	-0.49
SDH (U/L)	5 [a1]	Mean	10.98	20.57	16.84	21.24
		SD	4.60	29.39	10.80	23.91
		N	10	9	10	10
		%Diff		87.31	53.37	93.44
BILI (mg/dL)	5 [a2]	Mean	0.110	0.106	0.111	0.119
		SD	0.015	0.026	0.031	0.019
		N	10	9	10	10
		%Diff		-4.040	0.909	8.182

[l] - n - Inappropriate for statistics  
[a] - Anova & Dunnett  
[a1] - Anova & Dunnett(Rank)  
[a2] - Anova & Dunnett(Log)

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.



TABLE 5 contd. Summary of Clinical Chemistry Parameters – Males<sup>1</sup>

Refer [Appendix 5](#)

Sex: Male			0 CFU Group 1	1.668E+10 CFU Group 2	3.337E+10 CFU Group 3	1.001E+11 CFU Group 4
Week(s) Relative to Start Date						
TP (g/dL)	5 [a]	Mean	6.08	6.08	6.06	6.04
		SD	0.27	0.36	0.26	0.20
		N	10	9	10	10
		%Diff		-0.04	-0.33	-0.66
TRIG (mg/dL)	5 [a1]	Mean	51.6	58.2	46.5	51.7
		SD	26.9	22.2	15.2	22.4
		N	10	9	10	10
		%Diff		12.8	-9.9	0.2
BUN (mg/dL)	5 [a]	Mean	14.7	14.7	14.1	15.8
		SD	2.2	1.5	1.3	2.1
		N	10	9	10	10
		%Diff		-0.2	-4.1	7.5

[a] - Anova & Dunnett

[a1] - Anova & Dunnett(Log)

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.



TABLE 6. Summary of Clinical Chemistry Parameters – Females<sup>1</sup>

Refer [Appendix 6](#)

Sex: Female			0 CFU Group 1	1.668E+10 CFU Group 2	3.337E+10 CFU Group 3	1.001E+11 CFU Group 4
Week(s) Relative to Start Date						
ALT (U/L)	5 [a]	Mean	29.2	33.1	27.7	31.6
		SD	7.2	17.2	4.4	12.2
		N	10	10	10	9
		%Diff		13.4	-5.1	8.1
ALB (g/dL)	5 [a1]	Mean	5.15	5.16	4.97	5.20
		SD	0.44	0.37	0.38	0.36
		N	10	10	10	9
		%Diff		0.19	-3.50	0.97
ALKP (U/L)	5 [a1]	Mean	65.1	65.6	69.9	60.1
		SD	20.3	9.4	14.1	14.9
		N	10	10	10	9
		%Diff		0.8	7.4	-7.7
AST (U/L)	5 [a2]	Mean	94.8	86.5	80.2	80.0
		SD	17.3	14.8	11.5	16.6
		N	10	10	10	9
		%Diff		-8.8	-15.4	-15.6
CALC (mg/dL)	5 [a1]	Mean	11.42	11.55	11.45	11.59
		SD	0.64	0.72	0.46	0.57
		N	10	10	10	9
		%Diff		1.14	0.26	1.48
CL (mmol/L)	5 [a1]	Mean	100.75	101.14	101.95	102.33
		SD	1.96	2.73	1.89	2.12
		N	10	10	10	9
		%Diff		0.39	1.19	1.57
CHOL (mg/dL)	5 [a1]	Mean	79.8	73.6	75.4	75.7
		SD	14.9	18.6	20.4	11.4
		N	10	10	10	9
		%Diff		-7.8	-5.5	-5.2
CREA (mg/dL)	5 [a1]	Mean	0.231	0.269	0.267	0.281*
		SD	0.028	0.043	0.050	0.032
		N	10	10	10	9
		%Diff		16.450	15.584	21.693

[a] - Anova & Dunnett(Rank)

[a1] - Anova & Dunnett: \* = p < 0.05

[a2] - Anova & Dunnett(Log)

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.



TABLE 6 contd. Summary of Clinical Chemistry Parameters – Females<sup>1</sup>

Refer [Appendix 6](#)

Sex: Female			0 CFU Group 1	1.668E+10 CFU Group 2	3.337E+10 CFU Group 3	1.001E+11 CFU Group 4
Week(s) Relative to Start Date						
GGT (U/L)	5 [l]	Mean	3.000n	3.000n	3.000n	3.000n
		SD	0.000	0.000	0.000	0.000
		N	10	10	10	9
		%Diff		0.000	0.000	0.000
GLOB (g/dL)	5 [a]	Mean	1.77	1.75	1.87	1.68
		SD	0.29	0.24	0.22	0.33
		N	10	10	10	9
		%Diff		-1.13	5.65	-5.21
GLUC (mg/dL)	5 [a]	Mean	116.8	163.5	129.8	129.9
		SD	28.4	55.2	37.5	29.4
		N	10	10	10	9
		%Diff		40.0	11.1	11.2
IPHS (mg/dL)	5 [a]	Mean	9.03	8.91	8.85	8.91
		SD	0.97	0.83	0.74	0.77
		N	10	10	10	9
		%Diff		-1.33	-1.99	-1.32
K (mmol/L)	5 [a]	Mean	7.342	7.300	7.025	7.554
		SD	1.064	1.367	1.264	2.017
		N	10	10	10	9
		%Diff		-0.572	-4.318	2.894
NA (mmol/L)	5 [a]	Mean	142.70	144.00	143.90	144.33
		SD	2.21	2.79	2.28	3.57
		N	10	10	10	9
		%Diff		0.91	0.84	1.14
SDH (U/L)	5 [a1]	Mean	10.94	12.67	10.57	12.00
		SD	6.42	5.52	4.74	4.03
		N	10	10	10	9
		%Diff		15.81	-3.38	9.69
BILI (mg/dL)	5 [a2]	Mean	0.120	0.116	0.100	0.121
		SD	0.030	0.030	0.018	0.024
		N	10	10	10	9
		%Diff		-3.333	-16.667	0.926

[l] - n - Inappropriate for statistics  
[a] - Anova & Dunnett  
[a1] - Anova & Dunnett(Rank)  
[a2] - Anova & Dunnett(Log)

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.



TABLE 6 contd. Summary of Clinical Chemistry Parameters – Females<sup>1</sup>

Refer [Appendix 6](#)

Sex: Female			0 CFU Group 1	1.668E+10 CFU Group 2	3.337E+10 CFU Group 3	1.001E+11 CFU Group 4
Week(s) Relative to Start Date						
TP (g/dL)	5 [a]	Mean	6.92	6.91	6.84	6.88
		SD	0.46	0.48	0.34	0.60
		N	10	10	10	9
		%Diff		-0.14	-1.16	-0.61
TRIG (mg/dL)	5 [a1]	Mean	44.2	45.9	42.2	41.6
		SD	12.3	13.4	6.9	10.0
		N	10	10	10	9
		%Diff		3.8	-4.5	-6.0
BUN (mg/dL)	5 [a2]	Mean	15.1	16.7	16.0	16.2
		SD	1.5	2.7	2.1	1.0
		N	10	10	10	9
		%Diff		10.6	6.0	7.4

[a] - Anova & Dunnett  
[a1] - Anova & Dunnett(Log)  
[a2] - Anova & Dunnett(Rank)

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.



TABLE 7. Summary of Clinical Analysis of Urine – Males<sup>1</sup>

Refer [Appendix 7](#)

Sex: Male			0 CFU Group 1	1.668E+10 CFU Group 2	3.337E+10 CFU Group 3	1.001E+11 CFU Group 4
Week(s) Relative to Start Date						
Urine Volume (ml)	5 [a]	Mean	10.55	9.17	7.45	12.60
		SD	5.52	8.02	8.51	8.67
		N	10	9	10	10
		%Diff		-13.11	-29.38	19.43
pH	5 [a1]	Mean	6.85	6.67	6.70	6.70
		SD	0.58	0.43	0.35	0.35
		N	10	9	10	10
		%Diff		-2.68	-2.19	-2.19
Urine Glucose (mg/dL)	5 [a1]	Mean	0.0	0.0	20.0	0.0
		SD	0.0	0.0	42.2	0.0
		N	10	9	10	10
		%Diff				
Urine Ketone (mmol/L)	5 [a1]	Mean	10.0	10.6	10.0	7.0
		SD	5.3	5.3	5.3	4.2
		N	10	9	10	10
		%Diff		5.6	0.0	-30.0
Urine Protein (mg/dL)	5 [a1]	Mean	51.0	63.9	83.5	29.5
		SD	87.8	43.1	84.4	25.9
		N	10	9	10	10
		%Diff		25.3	63.7	-42.2
Specific Gravity	5 [a1]	Mean	1.0230	1.0261	1.0270	1.0230
		SD	0.0059	0.0049	0.0042	0.0054
		N	10	9	10	10
		%Diff		0.3041	0.3910	0.0000
Urobilinogen (EU/dL)	5 [a1]	Mean	0.28	0.20	0.28	0.20
		SD	0.25	0.00	0.25	0.00
		N	10	9	10	10
		%Diff		-28.57	0.00	-28.57

[a] - Anova & Dunnett(Log)

[a1] - Anova & Dunnett(Rank)

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.



**TABLE 8. Summary of Clinical Analysis of Urine – Females<sup>1</sup>**

Refer [Appendix 8](#)

Sex: Female			0 CFU Group 1	1.668E+10 CFU Group 2	3.337E+10 CFU Group 3	1.001E+11 CFU Group 4
Week(s) Relative to Start Date						
Urine Volume (ml)	5 [a]	Mean	6.95	7.15	4.05	3.40
		SD	6.13	7.35	4.15	3.25
		N	10	10	10	10
		%Diff		2.88	-41.73	-51.08
pH	5 [a1]	Mean	6.55	6.25	6.65	6.45
		SD	0.93	0.54	1.25	0.44
		N	10	10	10	10
		%Diff		-4.58	1.53	-1.53
Urine Glucose (mg/dL)	5 [a1]	Mean	10.0	0.0	10.0	0.0
		SD	31.6	0.0	31.6	0.0
		N	10	10	10	10
		%Diff		-100.0	0.0	-100.0
Urine Ketone (mmol/L)	5 [a1]	Mean	0.5	0.0	0.5	1.0
		SD	1.6	0.0	1.6	2.1
		N	10	10	10	10
		%Diff		-100.0	0.0	100.0
Urine Protein (mg/dL)	5 [a1]	Mean	39.0	29.0	79.0	64.5
		SD	43.5	38.6	88.1	46.6
		N	10	10	10	10
		%Diff		-25.6	102.6	65.4
Specific Gravity	5 [a1]	Mean	1.0240	1.0245	0.9743	1.0260
		SD	0.0084	0.0072	0.1656	0.0057
		N	10	10	10	10
		%Diff		0.0488	-4.8535	0.1953
Urobilinogen (EU/dL)	5 [a1]	Mean	0.28	0.20	0.52	0.36
		SD	0.25	0.00	0.41	0.34
		N	10	10	10	10
		%Diff		-28.57	85.71	28.57

[a] - Anova & Dunnett(Log)

[a1] - Anova & Dunnett(Rank)

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

## 10. APPENDICES

DRAFT PHASE REPORT

**APPENDIX 1. Individual Animal Hematology Parameters – Males<sup>1</sup>**

Sex: Male Day(s) Relative to Start Date							
Group 1	Hematology						
	RBC	HGB	HCT	MCV	MCH	MCHC	RDW
	(x10 <sup>6</sup> /μL)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	(%)
	31	31	31	31	31	31	31
3801	7.42	14.7	46.4	62.6	19.8	31.6	11.9
3802	9.20	16.2	54.9	59.7	17.6	29.5	13.5
3803	8.41	15.4	50.0	59.4	18.3	30.8	11.9
3804	7.74	14.7	48.1	62.1	19.1	30.7	13.8
3805	7.83	15.1	50.2	64.1	19.3	30.2	13.0
3806	8.91	15.7	46.7	52.4	17.6	33.6	14.8
3807	8.32	15.6	47.1	56.6	18.8	33.2	13.1
3808	9.40	16.5	50.1	53.3	17.6	33.0	12.4
3809	8.68	16.3	49.3	56.7	18.8	33.1	13.1
3810	8.88	16.2	49.9	56.2	18.3	32.5	12.3

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

APPENDIX 1 contd. Individual Animal Hematology Parameters – Males<sup>1</sup>

Sex: Male Day(s) Relative to Start Date

Group 1 0 CFU	Hematology						
	PLT	WBC	ANEU	ALYM	AMON	AEOS	ABAS
	(x10 <sup>3</sup> /μL)						
	31	31	31	31	31	31	31
3801	766	3.60	0.58	2.81	0.04	0.13	0.03
3802	1176	9.02	1.57	7.13	0.09	0.13	0.07
3803	915	7.90	1.29	6.38	0.11	0.09	0.02
3804	1067	10.12	2.29	7.41	0.15	0.17	0.05
3805	1116	9.30	1.16	7.75	0.12	0.16	0.09
3806	868	8.64	1.72	6.33	0.26	0.16	0.12
3807	900	8.32	1.38	6.42	0.23	0.17	0.08
3808	923	10.64	1.64	8.28	0.36	0.24	0.05
3809	689	9.72	0.86	8.48	0.19	0.11	0.04
3810	1101	10.47	1.33	8.78	0.18	0.09	0.04

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

APPENDIX 1 contd. Individual Animal Hematology Parameters – Males<sup>1</sup>

Sex: Male Day(s) Relative to Start Date

Group 1 0 CFU	ALUC	ARET
	(x10 <sup>3</sup> /μL)	(x10 <sup>3</sup> /μL)
	31	31
3801	0.01	196.6
3802	0.03	255.3
3803	0.02	189.5
3804	0.05	249.4
3805	0.02	257.6
3806	0.04	248.1
3807	0.03	182.7
3808	0.06	188.9
3809	0.04	251.6
3810	0.05	234.4

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

APPENDIX 1 contd. Individual Animal Hematology Parameters – Males<sup>1</sup>

Sex: Male Day(s) Relative to Start Date

Group 2 1.668E+10 CFU	Hematology						
	RBC	HGB	HCT	MCV	MCH	MCHC	RDW
	(x10 <sup>6</sup> /μL)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	(%)
	31	31	31	31	31	31	31
3821	8.70	15.5	48.7	56.0	17.8	31.8	12.4
3822	8.91	16.4	51.6	57.9	18.5	31.9	12.6
3823	8.03	15.5	48.5	60.4	19.3	32.0	12.7
3824	8.56 <sup>a</sup>	14.6 <sup>a</sup>	46.8 <sup>a</sup>	54.7 <sup>a</sup>	17.0 <sup>a</sup>	31.1 <sup>a</sup>	13.3 <sup>a</sup>
3825	8.81	15.8	47.5	53.9	17.9	33.3	12.5
3826	8.66	15.3	46.7	53.9	17.7	32.9	12.7
3827	8.66	16.0	49.2	56.8	18.5	32.5	13.1
3828	8.14	15.4	46.1	56.6	18.9	33.5	12.9
3830	8.38	15.4	46.2	55.1	18.4	33.3	13.5

<sup>a</sup> [SC:QNS during rerun attempt]

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

APPENDIX 1 contd. Individual Animal Hematology Parameters – Males<sup>1</sup>

Sex: Male Day(s) Relative to Start Date

Group 2 1.668E+10 CFU	Hematology						
	PLT	WBC	ANEU	ALYM	AMON	AEOS	ABAS
	(x10 <sup>3</sup> /μL)						
	31	31	31	31	31	31	31
3821	890	7.06	1.91	4.77	0.07	0.16	0.13
3822	976	13.26	2.04	10.49	0.15	0.17	0.36
3823	944	7.15	1.52	5.36	0.09	0.13	0.04
3824	1127 <sup>a</sup>	7.17 <sup>a</sup>	1.22	5.46	0.31	0.11	0.04
3825	578	11.06	1.90	8.51	0.28	0.25	0.09
3826	961	13.11	1.84	10.66	0.29	0.21	0.05
3827	984	16.85	2.59	13.31	0.47	0.27	0.10
3828	948	12.17	1.63	10.05	0.17	0.15	0.11
3830	861	8.94	1.63	6.88	0.21	0.13	0.05

<sup>a</sup> [SC:QNS during rerun attempt]

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

APPENDIX 1 contd. Individual Animal Hematology Parameters – Males<sup>1</sup>

Sex: Male Day(s) Relative to Start Date		
Group 2	ALUC	ARET
1.668E+10 CFU	(x10 <sup>3</sup> /μL)	(x10 <sup>3</sup> /μL)
	31	31
3821	0.01	245.9
3822	0.07	260.9
3823	0.02	215.8
3824	0.03	285.7
3825	0.03	201.3
3826	0.05	187.5
3827	0.10	216.8
3828	0.06	235.6
3830	0.04	242.1

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

APPENDIX 1 contd. Individual Animal Hematology Parameters – Males<sup>1</sup>

Sex: Male Day(s) Relative to Start Date							
Group 3 3.337E+10 CFU	Hematology						
	RBC	HGB	HCT	MCV	MCH	MCHC	RDW
	(x10 <sup>6</sup> /μL)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	(%)
	31	31	31	31	31	31	31
3841	8.25	15.3	47.8	57.9	18.6	32.0	13.4
3842	8.05	14.9	46.5	57.8	18.6	32.1	12.3
3843	8.55	15.9	49.3	57.6	18.6	32.2	12.5
3844	8.48	14.9	46.1	54.3	17.6	32.4	13.0
3845	7.43	13.1	43.2	58.1	17.6	30.3	13.3
3846	8.28	15.4	45.4	54.8	18.6	34.0	13.4
3847	8.61	15.0	47.1	54.8	17.5	31.9	13.8
3848	7.58	14.3	42.4	55.9	18.8	33.7	12.1
3849	8.16	14.8	44.5	54.5	18.2	33.3	13.3
3850	7.54	14.8	44.9	59.5	19.6	32.9	13.8

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

APPENDIX 1 contd. Individual Animal Hematology Parameters – Males<sup>1</sup>

Sex: Male Day(s) Relative to Start Date

Group 3 3.337E+10 CFU	Hematology						
	PLT	WBC	ANEU	ALYM	AMON	AEOS	ABAS
	(x10 <sup>3</sup> /μL)						
	31	31	31	31	31	31	31
3841	548	9.33	2.16	6.36	0.27	0.30	0.19
3842	928	10.11	1.31	8.40	0.15	0.15	0.05
3843	878	15.34	3.02	11.69	0.23	0.14	0.20
3844	931	10.92	2.18	8.38	0.09	0.19	0.04
3845	205	6.05	1.89	3.67	0.10	0.18	0.19
3846	897	19.73	3.51	15.19	0.67	0.16	0.10
3847	942	14.30	1.37	12.05	0.41	0.30	0.06
3848	886	11.89	2.38	8.98	0.31	0.14	0.04
3849	1134	10.82	1.92	8.44	0.27	0.13	0.02
3850	1169	10.62	1.01	9.04	0.41	0.08	0.04

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

APPENDIX 1 contd. Individual Animal Hematology Parameters – Males<sup>1</sup>

Sex: Male Day(s) Relative to Start Date

Group 3 3.337E+10 CFU	ALUC	ARET
	(x10 <sup>3</sup> /μL)	(x10 <sup>3</sup> /μL)
	31	31
3841	0.05	193.2
3842	0.04	208.7
3843	0.06	253.2
3844	0.04	272.4
3845	0.02	171.6
3846	0.10	251.9
3847	0.09	194.0
3848	0.04	168.2
3849	0.05	296.4
3850	0.04	233.6

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

**APPENDIX 1 contd. Individual Animal Hematology Parameters – Males<sup>1</sup>**

Sex: Male Day(s) Relative to Start Date

Group 4 1.001E+11 CFU	Hematology						
	RBC	HGB	HCT	MCV	MCH	MCHC	RDW
	(x10 <sup>6</sup> /μL)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	(%)
	31	31	31	31	31	31	31
3861	8.08	15.2	46.4	57.5	18.8	32.7	12.6
3862	8.00	14.9	46.5	58.2	18.6	31.9	13.4
3863	8.86	15.8	49.8	56.2	17.9	31.8	11.8
3864	8.08	14.7	46.3	57.3	18.2	31.8	13.4
3865	8.37	15.4	49.4	59.0	18.4	31.1	12.2
3866	8.14	15.0	45.5	55.9	18.4	32.9	13.5
3867	8.47	15.6	47.6	56.2	18.4	32.8	13.4
3868	8.84	16.7	50.6	57.3	18.9	32.9	12.4
3869	8.07	15.3	47.0	58.2	18.9	32.5	13.6
3870	8.34	15.3	46.6	55.9	18.3	32.7	14.0

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

**APPENDIX 1 contd. Individual Animal Hematology Parameters – Males<sup>1</sup>**

Sex: Male Day(s) Relative to Start Date

Group 4 1.001E+11 CFU	Hematology						
	PLT (x10 <sup>3</sup> /μL)	WBC (x10 <sup>3</sup> /μL)	ANEU (x10 <sup>3</sup> /μL)	ALYM (x10 <sup>3</sup> /μL)	AMON (x10 <sup>3</sup> /μL)	AEOS (x10 <sup>3</sup> /μL)	ABAS (x10 <sup>3</sup> /μL)
	31	31	31	31	31	31	31
3861	1067	7.13	1.79	5.15	0.04	0.12	0.01
3862	681	6.00	1.17	4.61	0.10	0.10	0.01
3863	1000	9.47	1.44	7.67	0.10	0.19	0.04
3864	1079	11.01	1.49	9.16	0.12	0.17	0.02
3865	978	13.59	1.88	11.02	0.43	0.15	0.04
3866	902	11.76	1.51	9.87	0.18	0.14	0.02
3867	1019	13.40	1.78	10.97	0.36	0.19	0.05
3868	582	10.70	1.17	9.06	0.25	0.11	0.06
3869	100	9.10	0.92	7.79	0.14	0.12	0.10
3870	891	13.68	1.41	11.66	0.38	0.08	0.05

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

APPENDIX 1 contd. Individual Animal Hematology Parameters – Males<sup>1</sup>

Sex: Male Day(s) Relative to Start Date

Group 4 1.001E+11 CFU	ALUC	ARET
	(x10 <sup>3</sup> /μL)	(x10 <sup>3</sup> /μL)
	31	31
3861	0.01	259.4
3862	0.01	222.2
3863	0.03	208.1
3864	0.04	256.1
3865	0.07	244.0
3866	0.04	230.4
3867	0.04	215.7
3868	0.05	212.0
3869	0.05	231.4
3870	0.08	252.6

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

**APPENDIX 2. Individual Animal Hematology Parameters – Females<sup>1</sup>**

Sex: Female Day(s) Relative to Start Date

Group 1 0 CFU	Hematology						
	RBC (x10 <sup>6</sup> /μL)	HGB (g/dL)	HCT (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)	RDW (%)
	31	31	31	31	31	31	31
3811	8.54	15.9	52.1	61.0	18.7	30.6	11.8
3812	8.71 <sup>a</sup>	15.1 <sup>a</sup>	52.7 <sup>a</sup>	60.5 <sup>a</sup>	17.4 <sup>a</sup>	28.7 <sup>a</sup>	14.0 <sup>a</sup>
3813	8.85	15.5	50.9	57.5	17.5	30.5	11.9
3814	8.75	15.9	50.4	57.6	18.2	31.6	12.4
3815	8.36	15.3	48.2	57.7	18.3	31.7	11.8
3816	9.22	16.8	50.5	54.8	18.2	33.2	11.9
3817	NP	NP	NP	NP	NP	NP	NP
3818	8.02	14.9	43.2	53.9	18.6	34.5	11.8
3819	8.15	15.1	45.0	55.2	18.6	33.6	12.5
3820	8.83	16.2	47.7	54.0	18.3	33.8	12.5

<sup>a</sup> [SC:QNS to Rerun]

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

APPENDIX 2 contd. Individual Animal Hematology Parameters – Females<sup>1</sup>

Sex: Female Day(s) Relative to Start Date

Group 1 0 CFU	Hematology						
	PLT	WBC	ANEU	ALYM	AMON	AEOS	ABAS
	(x10 <sup>3</sup> /μL)						
	31	31	31	31	31	31	31
3811	1225	11.17	1.05	9.66	0.21	0.10	0.07
3812	816 <sup>a</sup>	9.83 <sup>a</sup>	0.92	8.52	0.16	0.13	0.04
3813	1349	8.13	0.62	7.26	0.05	0.13	0.03
3814	638	6.01	0.97	4.49	0.09	0.40	0.04
3815	1231	6.14	0.91	4.91	0.08	0.20	0.01
3816	1184	6.84	0.47	6.03	0.11	0.15	0.04
3817	NP	NP	.	.	.	.	.
3818	1065	6.03	0.37	5.48	0.07	0.07	0.01
3819	877	3.28	0.55	2.52	0.05	0.12	0.02
3820	1144	8.06	0.63	7.13	0.12	0.09	0.05

<sup>a</sup> [SC:QNS to Rerun]

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

APPENDIX 2 contd. Individual Animal Hematology Parameters – Females<sup>1</sup>

Sex: Female Day(s) Relative to Start Date		
Group 1	ALUC	ARET
	(x10 <sup>3</sup> /μL)	(x10 <sup>3</sup> /μL)
	31	31
3811	0.07	212.0
3812	0.05	190.2
3813	0.04	230.4
3814	0.02	230.4
3815	0.02	167.3
3816	0.05	112.3
3817	.	.
3818	0.03	161.7
3819	0.02	232.4
3820	0.04	162.7

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

**APPENDIX 2 contd. Individual Animal Hematology Parameters – Females<sup>1</sup>**

Sex: Female Day(s) Relative to Start Date

Group 2 1.668E+10 CFU	Hematology						
	RBC	HGB	HCT	MCV	MCH	MCHC	RDW
	(x10 <sup>6</sup> /μL)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	(%)
	31	31	31	31	31	31	31
3831	8.29	15.0	46.6	56.2	18.1	32.2	12.1
3832	7.29	13.6	40.7	55.7	18.6	33.4	12.1
3833	9.35 <sup>a</sup>	16.7 <sup>a</sup>	52.9 <sup>a</sup>	56.6 <sup>a</sup>	17.9 <sup>a</sup>	31.5 <sup>a</sup>	12.4 <sup>a</sup>
3834	9.09	16.0	49.5	54.5	17.6	32.4	11.4
3835	8.42	15.7	47.6	56.5	18.7	33.1	12.3
3836	8.27	15.8	47.1	57.0	19.1	33.5	12.2
3837	8.00	15.3	43.3	54.1	19.2	35.5	11.8
3838	8.49	15.2	45.2	53.2	17.8	33.5	12.2
3839	8.41	14.9	45.1	53.6	17.8	33.2	12.4
3840	7.87	14.4	41.8	53.1	18.3	34.4	12.1

<sup>a</sup> [SC:QNS to repeat]

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

APPENDIX 2 contd. Individual Animal Hematology Parameters – Females<sup>1</sup>

Sex: Female Day(s) Relative to Start Date

Group 2 1.668E+10 CFU	Hematology						
	PLT	WBC	ANEU	ALYM	AMON	AEOS	ABAS
	(x10 <sup>3</sup> /μL)						
	31	31	31	31	31	31	31
3831	1237	8.36	0.57	7.52	0.10	0.09	0.03
3832	1240	6.73	0.77	5.69	0.11	0.11	0.01
3833	965 <sup>a</sup>	7.09 <sup>a</sup>	0.76	5.95	0.17	0.11	0.07
3834	995	5.59	0.96	4.24	0.07	0.25	0.03
3835	914	4.94	0.48	4.22	0.08	0.09	0.04
3836	1325	8.42	1.05	6.77	0.08	0.40	0.05
3837	1083	6.80	0.42	6.11	0.14	0.09	0.01
3838	1112	6.44	0.57	5.53	0.20	0.11	0.01
3839	779	7.84	0.42	6.94	0.24	0.18	0.02
3840	831	4.50	0.51	3.75	0.08	0.15	0.01

<sup>a</sup> [SC:QNS to repeat]

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

APPENDIX 2 contd. Individual Animal Hematology Parameters – Females<sup>1</sup>

Sex: Female Day(s) Relative to Start Date		
Group 2	ALUC	ARET
1.668E+10 CFU	(x10 <sup>3</sup> /μL)	(x10 <sup>3</sup> /μL)
	31	31
3831	0.05	210.9
3832	0.04	138.8
3833	0.03	191.8
3834	0.04	209.2
3835	0.01	218.5
3836	0.06	193.9
3837	0.03	131.0
3838	0.02	147.8
3839	0.05	188.1
3840	0.00	137.0

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

APPENDIX 2 contd. Individual Animal Hematology Parameters – Females<sup>1</sup>

Sex: Female Day(s) Relative to Start Date

Group 3 3.337E+10 CFU	Hematology						
	RBC	HGB	HCT	MCV	MCH	MCHC	RDW
	(x10 <sup>6</sup> /μL)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	(%)
	31	31	31	31	31	31	31
3851	8.13	14.9	47.1	57.9	18.3	31.6	12.3
3852	6.54	12.6	37.9	58.0	19.3	33.3	11.9
3853	NP	NP	NP	NP	NP	NP	NP
3854	7.67	14.0	41.9	54.6	18.3	33.5	12.4
3855	8.52	16.2	49.7	58.3	19.0	32.5	11.5
3856	8.89	15.6	46.6	52.4	17.5	33.5	11.8
3857	7.85	14.4	42.0	53.6	18.4	34.3	11.9
3858	8.36	15.3	45.9	54.9	18.3	33.3	12.0
3859	8.20	15.6	45.1	54.9	19.0	34.5	12.6
3860	8.80	16.5	48.8	55.5	18.7	33.7	12.7

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

**APPENDIX 2 contd. Individual Animal Hematology Parameters – Females<sup>1</sup>**

Sex: Female Day(s) Relative to Start Date

Group 3 3.337E+10 CFU	Hematology						
	PLT (x10 <sup>3</sup> /μL)	WBC (x10 <sup>3</sup> /μL)	ANEU (x10 <sup>3</sup> /μL)	ALYM (x10 <sup>3</sup> /μL)	AMON (x10 <sup>3</sup> /μL)	AEOS (x10 <sup>3</sup> /μL)	ABAS (x10 <sup>3</sup> /μL)
	31	31	31	31	31	31	31
3851	1090	7.39	1.49	5.63	0.09	0.13	0.02
3852	1403	4.33	0.34	3.84	0.05	0.08	0.01
3853	NP	NP	.	.	.	.	.
3854	989	4.20	0.73	3.31	0.05	0.09	0.00
3855	1158	7.16	0.34	6.59	0.06	0.10	0.03
3856	1059	9.38	0.66	8.22	0.23	0.20	0.04
3857	1300	6.66	0.83	5.50	0.17	0.13	0.02
3858	1294	11.66	0.76	10.42	0.22	0.14	0.03
3859	1089	8.56	0.40	7.88	0.09	0.13	0.01
3860	754	5.83	0.65	4.89	0.08	0.13	0.04

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

APPENDIX 2 contd. Individual Animal Hematology Parameters – Females<sup>1</sup>

Sex: Female Day(s) Relative to Start Date		
Group 3 3.337E+10 CFU	ALUC	ARET
	(x10 <sup>3</sup> /μL)	(x10 <sup>3</sup> /μL)
	31	31
3851	0.02	214.8
3852	0.01	186.5
3853	.	.
3854	0.01	261.7
3855	0.04	265.8
3856	0.05	159.8
3857	0.03	131.0
3858	0.07	114.6
3859	0.05	185.0
3860	0.03	231.5

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

**APPENDIX 2 contd. Individual Animal Hematology Parameters – Females<sup>1</sup>**

Sex: Female Day(s) Relative to Start Date

Group 4 1.001E+11 CFU	Hematology						
	RBC	HGB	HCT	MCV	MCH	MCHC	RDW
	(x10 <sup>6</sup> /μL)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	(%)
	31	31	31	31	31	31	31
3871	8.10	14.5	46.1	56.9	17.8	31.3	11.9
3872	8.38	15.5	47.7	56.9	18.5	32.5	11.4
3874	8.38	15.5	47.8	57.1	18.5	32.3	12.1
3875	8.28	15.9	48.3	58.3	19.2	32.9	11.4
3876	8.48	16.0	47.4	55.9	18.9	33.8	11.5
3877	8.23	15.1	44.6	54.3	18.4	33.9	12.8
3878	8.73	16.1	47.5	54.3	18.4	33.9	11.5
3879	8.68	15.0	44.0	50.7	17.3	34.2	11.9
3880	7.87	15.0	44.5	56.5	19.1	33.7	11.6

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

**APPENDIX 2 contd. Individual Animal Hematology Parameters – Females<sup>1</sup>**

Sex: Female Day(s) Relative to Start Date

Group 4 1.001E+11 CFU	Hematology						
	PLT	WBC	ANEU	ALYM	AMON	AEOS	ABAS
	(x10 <sup>3</sup> /μL)						
	31	31	31	31	31	31	31
3871	839	7.44	0.54	6.65	0.11	0.07	0.04
3872	857	4.52	0.28	4.10	0.05	0.07	0.01
3874	924	3.67	0.40	3.08	0.05	0.09	0.01
3875	815	6.98	0.58	6.14	0.10	0.10	0.03
3876	995	7.77	0.59	6.80	0.19	0.12	0.03
3877	860	5.18	0.64	4.24	0.09	0.19	0.01
3878	1236	7.82	0.67	6.70	0.20	0.16	0.02
3879	1003	4.03	0.38	3.37	0.16	0.09	0.02
3880	918	5.67	0.77	4.59	0.19	0.10	0.01

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

APPENDIX 2 contd. Individual Animal Hematology Parameters – Females<sup>1</sup>

Sex: Female Day(s) Relative to Start Date

Group 4 1.001E+11 CFU	ALUC	ARET
	(x10 <sup>3</sup> /μL)	(x10 <sup>3</sup> /μL)
	31	31
3871	0.03	258.2
3872	0.02	222.8
3874	0.03	222.5
3875	0.03	202.4
3876	0.05	174.2
3877	0.02	236.7
3878	0.05	153.0
3879	0.02	126.0
3880	0.02	146.7

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

**APPENDIX 3. Individual Animal Coagulation Parameters – Males<sup>1</sup>**

Sex: Male Week(s) Relative to Start Date

0 CFU Group 1	APTT	PT
	(seconds)	(seconds)
	5	5
3801	15.4	10.1
3802	17.0	10.2
3803	16.3	10.0
3804	16.2	10.1
3805	15.7	10.2
3806	22.0	10.4
3807	16.6	10.2
3808	19.2	11.0
3809	14.6	10.0
3810	18.7	9.6
Mean	17.17	10.18
SD	2.20	0.36
N	10	10

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

APPENDIX 3 contd. Individual Animal Coagulation Parameters – Males<sup>1</sup>

Sex: Male Week(s) Relative to Start Date

1.668E+10 CFU Group 2	APTT	PT
	(seconds)	(seconds)
	5	5
3821	14.4	10.5
3822	17.7	10.2
3823	16.5	9.9
3824	16.1	9.9
3825	32.3	11.4
3826	22.1	9.8
3827	18.5	9.4
3828	15.6	10.2
3830	15.6	10.0
Mean	18.76	10.14
SD	5.55	0.56
N	9	9
%Diff	9.23	-0.35

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

**APPENDIX 3 contd. Individual Animal Coagulation Parameters – Males<sup>1</sup>**

Sex: Male Week(s) Relative to Start Date

3.337E+10 CFU Group 3	APTT	PT
	(seconds)	(seconds)
	5	5
3841	18.0	10.5
3842	14.7	9.3
3843	17.8	10.2
3844	16.6	10.9
3845	19.0	9.9
3846	18.6	10.3
3847	20.5	10.4
3848	21.6	10.3
3849	21.2	10.3
3850	21.0	9.9
Mean	18.90	10.20
SD	2.23	0.43
N	10	10
%Diff	10.08	0.20

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

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APPENDIX 3 contd. Individual Animal Coagulation Parameters – Male's

Sex: Male Week(s) Relative to Start Date		
1.001E+11 CFU Group 4	APTT	PT
	(seconds)	(seconds)
	5	5
3861	16.7	9.8
3862	17.5	10.3
3863	19.1	10.5
3864	14.3	9.9
3865	14.7	10.3
3866	19.3	10.2
3867	21.8	9.9
3868	19.8	10.4
3869	ERR	ERR
3870	21.8	10.2
Mean	18.33	10.17
SD	2.75	0.24
N	9	9
%Diff	6.78	-0.13

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

**APPENDIX 4. Individual Animal Coagulation Parameters – Females<sup>1</sup>**

Sex: Female Week(s) Relative to Start Date

0 CFU Group 1	APTT	PT
	(seconds)	(seconds)
	5	5
3811	16.3	10.0
3812	26.8	ERR
3813	16.3	9.6
3814	17.8	ERR
3815	16.1	9.5
3816	22.8	10.2
3817	18.2	10.0
3818	21.2	9.9
3819	19.4	9.9
3820	16.3	9.5
Mean	19.12	9.83
SD	3.54	0.26
N	10	8

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

APPENDIX 4 contd. Individual Animal Coagulation Parameters – Females<sup>1</sup>

Sex: Female Week(s) Relative to Start Date		
1.668E+10 CFU Group 2	APTT	PT
	(seconds)	(seconds)
	5	5
3831	21.9	10.0
3832	17.3	9.6
3833	16.3	9.3
3834	13.5	8.7
3835	11.7	9.3
3836	ERR	ERR
3837	25.3	10.4
3838	17.4	9.6
3839	17.4	9.4
3840	16.5	11.5
Mean	17.48	9.76
SD	4.07	0.81
N	9	9
%Diff	-8.59	-0.71

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

APPENDIX 4 contd. Individual Animal Coagulation Parameters – Females<sup>1</sup>

Sex: Female Week(s) Relative to Start Date		
3.337E+10 CFU Group 3	APTT	PT
	(seconds)	(seconds)
	5	5
3851	17.8	10.0
3852	16.9	9.9
3853	14.1	9.4
3854	15.7	10.3
3855	17.0	10.5
3856	20.7	10.0
3857	18.8	10.0
3858	21.0	10.0
3859	17.8	9.7
3860	19.6	10.4
Mean	17.94	10.02
SD	2.17	0.33
N	10	10
%Diff	-6.17	1.98

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

APPENDIX 4 contd. Individual Animal Coagulation Parameters – Females<sup>1</sup>

Sex: Female Week(s) Relative to Start Date		
1.001E+11 CFU Group 4	APTT	PT
	(seconds)	(seconds)
	5	5
3871	21.8	10.1
3872	16.5	9.9
3873	ERR	ERR
3874	16.7	9.0
3875	18.9	9.9
3876	18.4	10.1
3877	17.6	9.9
3878	18.0	9.9
3879	18.7	10.2
3880	15.0	10.2
Mean	17.96	9.91
SD	1.90	0.37
N	9	9
%Diff	-6.09	0.88

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

**APPENDIX 5. Individual Animal Clinical Chemistry Parameters – Males<sup>1</sup>**

Sex: Male Week(s) Relative to Start Date							
0 CFU Group 1	ALT	ALB	ALKP	AST	CALC	CL	CHOL
	(U/L)	(g/dL)	(U/L)	(U/L)	(mg/dL)	(mmol/L)	(mg/dL)
	5	5	5	5	5	5	5
3801	31	3.9	106	93	10.4	104.1	66
3802	41	4.0	111	84	11.7	100.1	42
3803	26	4.0	105	86	11.0	98.7	94
3804	37	4.0	112	87	11.6	102.0	67
3805	32	4.0	111	83	11.4	100.5	38
3806	44	4.5	137	101	12.2	100.4	93
3807	28	4.2	113	73	11.5	102.7	48
3808	30	4.3	147	75	11.4	105.0	71
3809	24	4.2	129	92	11.3	102.3	66
3810	38	4.6	152	72	12.0	102.2	77
Mean	32.9	4.17	122.3	84.6	11.45	101.80	66.2
SD	6.8	0.24	17.5	9.4	0.50	1.91	19.3
N	10	10	10	10	10	10	10

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

**APPENDIX 5 contd. Individual Animal Clinical Chemistry Parameters – Males<sup>1</sup>**

Sex: Male Week(s) Relative to Start Date							
0 CFU Group 1	CREA	GGT	GLOB	GLUC	IPHS	K	NA
	(mg/dL)	(U/L)	(g/dL)	(mg/dL)	(mg/dL)	(mmol/L)	(mmol/L)
	5	5	5	5	5	5	5
3801	0.17	3.00	1.8	132	8.5	6.62	143.0
3802	0.17	3.00	2.0	174	11.5	7.42	144.0
3803	0.22	3.00	1.9	194	9.9	6.88	140.0
3804	0.17	3.00	2.3	144	9.9	7.27	142.0
3805	0.17	3.00	1.8	151	10.8	7.49	143.0
3806	0.18	3.00	2.0	169	11.9	8.55	146.0
3807	0.17	3.00	1.6	167	10.2	7.14	145.0
3808	0.18	3.00	2.0	161	10.1	7.38	147.0
3809	0.18	3.00	2.0	149	10.7	7.99	146.0
3810	0.21	3.00	1.7	179	10.7	6.87	147.0
Mean	0.182	3.000	1.91	162.0	10.42	7.361	144.30
SD	0.018	0.000	0.20	18.4	0.94	0.568	2.31
N	10	10	10	10	10	10	10

The Limit of Quantitation (LOQ for GGT is 3.0

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

APPENDIX 5 contd. Individual Animal Clinical Chemistry Parameters – Males<sup>1</sup>

Sex: Male Week(s) Relative to Start Date

0 CFU Group 1	SDH	BILI	TP	TRIG	BUN
	(U/L)	(mg/dL)	(g/dL)	(mg/dL)	(mg/dL)
	5	5	5	5	5
3801	8.8	0.11	5.7	36	13
3802	7.7	0.11	6.0	38	14
3803	5.2	0.12	5.9	117	16
3804	12.9	0.08	6.3	31	12
3805	9.5	0.11	5.8	32	12
3806	15.0	0.11	6.5	78	15
3807	13.7	0.14	5.8	37	16
3808	12.2	0.10	6.3	43	16
3809	5.1	0.11	6.2	50	14
3810	19.7	0.11	6.3	54	19
Mean	10.98	0.110	6.08	51.6	14.7
SD	4.60	0.015	0.27	26.9	2.2
N	10	10	10	10	10

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

**APPENDIX 5 contd. Individual Animal Clinical Chemistry Parameters – Males<sup>1</sup>**

Sex: Male Week(s) Relative to Start Date

1.668E+10 CFU Group 2	ALT	ALB	ALKP	AST	CALC	CL	CHOL
	(U/L)	(g/dL)	(U/L)	(U/L)	(mg/dL)	(mmol/L)	(mg/dL)
	5	5	5	5	5	5	5
3821	28	3.9	128	91	10.8	101.4	55
3822	41	4.3	140	88	11.6	100.1	49
3823	27	4.3	119	80	11.4	103.0	74
3824	38	4.1	117	117	11.1	100.8	48
3825	32	4.5	154	98	11.7	104.0	39
3826	29	3.8	103	79	11.0	100.6	75
3827	234	3.6	149	419	11.6	100.5	95
3828	31	4.0	105	76	10.9	101.5	49
3830	29	4.2	122	76	11.5	103.6	59
Mean	54.3	4.08	126.3	124.9	11.29	101.72	60.3
SD	67.5	0.28	18.1	111.1	0.34	1.45	17.7
N	9	9	9	9	9	9	9
%Diff	65.1	-2.21	3.3	47.6	-1.41	-0.08	-8.9

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

**APPENDIX 5 contd. Individual Animal Clinical Chemistry Parameters – Males<sup>1</sup>**

Sex: Male Week(s) Relative to Start Date

1.668E+10 CFU Group 2	CREA	GGT	GLOB	GLUC	IPHS	K	NA
	(mg/dL)	(U/L)	(g/dL)	(mg/dL)	(mg/dL)	(mmol/L)	(mmol/L)
	5	5	5	5	5	5	5
3821	0.17	3.00	1.6	148	9.1	8.33	141.0
3822	0.17	3.00	1.9	169	10.5	7.98	142.0
3823	0.17	3.00	1.9	114	10.0	7.18	144.0
3824	0.17	3.00	2.1	164	10.1	7.49	142.0
3825	0.25	3.00	2.3	105	11.4	7.92	149.0
3826	0.18	3.00	2.0	150	9.6	7.80	140.0
3827	0.19	3.00	2.4	151	9.8	7.31	144.0
3828	0.23	3.00	1.9	209	9.9	8.66	143.0
3830	0.17	3.00	1.9	162	9.8	7.04	147.0
Mean	0.189	3.000	2.00	152.4	10.02	7.746	143.56
SD	0.030	0.000	0.24	30.5	0.64	0.541	2.88
N	9	9	9	9	9	9	9
%Diff	3.785	0.000	4.71	-5.9	-3.82	5.224	-0.52

The Limit of Quantitation (LOQ for GGT is 3.0

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.



**APPENDIX 5 contd. Individual Animal Clinical Chemistry Parameters – Males<sup>1</sup>**

Sex: Male Week(s) Relative to Start Date							
3.337E+10 CFU Group 3	ALT	ALB	ALKP	AST	CALC	CL	CHOL
	(U/L)	(g/dL)	(U/L)	(U/L)	(mg/dL)	(mmol/L)	(mg/dL)
	5	5	5	5	5	5	5
3841	45	4.0	153	98	10.7	101.0	48
3842	32	3.9	114	121	11.1	100.1	50
3843	36	4.3	96	99	11.3	100.5	54
3844	27	4.3	132	73	11.3	100.6	65
3845	35	4.1	79	73	11.9	100.8	59
3846	32	4.4	140	107	11.7	100.8	61
3847	27	4.5	117	87	12.1	102.0	74
3848	27	3.8	124	82	10.9	103.1	58
3849	31	3.9	101	73	11.1	102.3	45
3850	35	4.6	155	86	12.0	98.5	67
Mean	32.7	4.18	121.1	89.9	11.41	100.97	58.1
SD	5.5	0.28	24.8	16.2	0.49	1.28	9.1
N	10	10	10	10	10	10	10
%Diff	-0.6	0.24	-1.0	6.3	-0.35	-0.82	-12.2

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

**APPENDIX 5 contd. Individual Animal Clinical Chemistry Parameters – Males<sup>1</sup>**

Sex: Male Week(s) Relative to Start Date							
3.337E+10 CFU Group 3	CREA	GGT	GLOB	GLUC	IPHS	K	NA
	(mg/dL)	(U/L)	(g/dL)	(mg/dL)	(mg/dL)	(mmol/L)	(mmol/L)
	5	5	5	5	5	5	5
3841	0.18	3.00	1.9	160	8.4	5.98	142.0
3842	0.17	3.00	1.9	161	9.1	6.86	139.0
3843	0.22	3.00	1.7	124	11.0	7.25	143.0
3844	0.17	3.00	1.7	178	9.4	7.44	141.0
3845	0.20	3.00	1.9	167	9.9	5.89	144.0
3846	0.22	3.00	2.0	137	11.8	8.17	147.0
3847	0.29	3.00	2.0	198	11.1	7.74	147.0
3848	0.17	3.00	1.9	171	9.3	7.21	142.0
3849	0.17	3.00	2.1	121	9.3	6.83	144.0
3850	0.23	3.00	1.7	140	11.9	10.14	140.0
Mean	0.202	3.000	1.88	155.7	10.12	7.351	142.90
SD	0.039	0.000	0.14	24.7	1.23	1.209	2.69
N	10	10	10	10	10	10	10
%Diff	10.989	0.000	-1.57	-3.9	-2.88	-0.136	-0.97

The Limit of Quantitation (LOQ) for GGT is 3.0

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

APPENDIX 5 contd. Individual Animal Clinical Chemistry Parameters – Males<sup>1</sup>

Sex: Male Week(s) Relative to Start Date

3.337E+10 CFU Group 3	SDH	BILI	TP	TRIG	BUN
	(U/L)	(mg/dL)	(g/dL)	(mg/dL)	(mg/dL)
	5	5	5	5	5
3841	19.9	0.12	5.9	53	16
3842	16.0	0.11	5.8	44	14
3843	8.2	0.11	6.0	38	14
3844	10.7	0.14	6.0	75	14
3845	12.4	0.07	6.0	28	16
3846	45.3	0.10	6.4	58	14
3847	12.4	0.09	6.5	62	15
3848	19.9	0.10	5.7	30	12
3849	8.9	0.09	6.0	34	13
3850	14.7	0.18	6.3	43	13
Mean	16.84	0.111	6.06	46.5	14.1
SD	10.80	0.031	0.26	15.2	1.3
N	10	10	10	10	10
%Diff	53.37	0.909	-0.33	-9.9	-4.1

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

**APPENDIX 5 contd. Individual Animal Clinical Chemistry Parameters – Males<sup>1</sup>**

Sex: Male Week(s) Relative to Start Date							
1.001E+11 CFU Group 4	ALT	ALB	ALKP	AST	CALC	CL	CHOL
	(U/L)	(g/dL)	(U/L)	(U/L)	(mg/dL)	(mmol/L)	(mg/dL)
	5	5	5	5	5	5	5
3861	27	4.1	116	73	11.1	101.3	67
3862	24	3.8	122	85	10.5	101.9	52
3863	32	4.1	120	119	11.2	102.8	58
3864	29	4.2	84	77	11.2	101.3	56
3865	41	4.0	136	114	11.6	100.5	52
3866	28	4.0	93	72	11.4	100.0	69
3867	171	3.6	126	316	11.2	101.7	66
3868	31	4.5	182	95	11.9	103.8	44
3869	36	4.5	147	84	11.7	103.8	51
3870	30	4.5	128	74	12.2	101.3	61
Mean	44.9	4.13	125.4	110.9	11.40	101.84	57.6
SD	44.6	0.31	27.2	74.0	0.48	1.28	8.1
N	10	10	10	10	10	10	10
%Diff	36.5	-0.96	2.5	31.1	-0.44	0.04	-13.0

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

APPENDIX 5 contd. Individual Animal Clinical Chemistry Parameters – Males<sup>1</sup>

Sex: Male Week(s) Relative to Start Date							
1.001E+11 CFJ Group 4	CREA	GGT	GLOB	GLUC	IPHS	K	NA
	(mg/dL)	(U/L)	(g/dL)	(mg/dL)	(mg/dL)	(mmol/L)	(mmol/L)
	5	5	5	5	5	5	5
3861	0.22	3.00	1.8	204	9.0	6.87	142.0
3862	0.17	3.00	1.9	176	8.3	6.24	141.0
3863	0.17	3.00	1.7	175	9.7	7.63	141.0
3864	0.17	3.00	2.0	184	9.5	7.34	142.0
3865	0.17	3.00	2.1	203	10.4	7.64	144.0
3866	0.18	3.00	2.0	190	9.2	5.98	143.0
3867	0.20	3.00	2.4	142	10.5	6.91	145.0
3868	0.23	3.00	1.7	152	10.8	6.93	148.0
3869	0.18	3.00	1.7	186	11.9	11.86	143.0
3870	0.18	3.00	1.8	168	10.9	8.99	147.0
Mean	0.187	3.000	1.91	178.0	10.02	7.639	143.60
SD	0.022	0.000	0.22	20.1	1.07	1.702	2.41
N	10	10	10	10	10	10	10
%Diff	2.747	0.000	0.00	9.9	-3.84	3.777	-0.49

The

Limit of Quantitation (LOQ) for GGT is 3.0.

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

APPENDIX 5 contd. Individual Animal Clinical Chemistry Parameters – Males<sup>1</sup>

Sex: Male Week(s) Relative to Start Date

1.001E+11 CFU Group 4	SDH	BILI	TP	TRIG	BUN
	(U/L)	(mg/dL)	(g/dL)	(mg/dL)	(mg/dL)
	5	5	5	5	5
3861	9.2	0.13	5.9	48	14
3862	11.2	0.13	5.7	33	16
3863	8.4	0.12	5.8	40	15
3864	11.9	0.11	6.2	62	14
3865	27.2	0.09	6.1	107	15
3866	11.3	0.14	6.0	44	14
3867	87.6	0.13	6.0	33	17
3868	15.5	0.11	6.2	63	21
3869	15.1	0.14	6.2	34	17
3870	15.0	0.09	6.3	53	15
Mean	21.24	0.119	6.04	51.7	15.8
SD	23.91	0.019	0.20	22.4	2.1
N	10	10	10	10	10
%Diff	93.44	8.182	-0.66	0.2	7.5

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

**APPENDIX 6. Individual Animal Clinical Chemistry Parameters – Females<sup>1</sup>**

Sex: Female Week(s) Relative to Start Date

0 CFU Group 1	ALT	ALB	ALP	AST	CALC	CL	CHOL
	(U/L)	(g/dL)	(U/L)	(U/L)	(mg/dL)	(mmol/L)	(mg/dL)
	5	5	5	5	5	5	5
3811	27	4.6	95	78	11.7	101.0	71
3812	33	5.9	27	107	12.6	96.6	85
3813	23	5.3	66	121	11.8	99.5	85
3814	34	4.7	96	86	11.4	102.0	66
3815	23	4.9	56	93	11.3	101.7	78
3816	46	5.5	65	112	11.6	102.9	82
3817	26	5.3	61	79	11.2	102.6	66
3818	22	5.6	56	81	11.7	101.8	108
3819	28	4.7	75	115	10.4	100.7	60
3820	30	5.0	54	76	10.5	98.7	97
Mean	29.2	5.15	65.1	94.8	11.42	100.75	79.8
SD	7.2	0.44	20.3	17.3	0.64	1.96	14.9
N	10	10	10	10	10	10	10

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

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APPENDIX 6 contd. Individual Animal Clinical Chemistry Parameters – Females<sup>1</sup>

Sex: Female Week(s) Relative to Start Date

0 CFU Group 1	CREA	GGT	GLOB	GLUC	IPHS	K	NA
	(mg/dL)	(U/L)	(g/dL)	(mg/dL)	(mg/dL)	(mmol/L)	(mmol/L)
	5	5	5	5	5	5	5
3811	0.19	3.00	2.0	129	9.5	8.07	143.0
3812	0.22	3.00	2.0	129	9.3	8.51	138.0
3813	0.27	3.00	1.9	150	9.3	7.35	143.0
3814	0.26	3.00	2.3	80	10.4	8.10	142.0
3815	0.22	3.00	1.8	112	8.2	6.20	143.0
3816	0.23	3.00	1.4	79	9.5	8.02	144.0
3817	0.22	3.00	1.4	149	8.2	6.53	145.0
3818	0.26	3.00	1.7	131	7.7	5.58	146.0
3819	0.25	3.00	1.6	77	10.3	8.56	142.0
3820	0.19	3.00	1.6	132	7.9	6.50	141.0
Mean	0.231	3.000	1.77	116.8	9.03	7.342	142.70
SD	0.028	0.000	0.29	28.4	0.97	1.064	2.21
N	10	10	10	10	10	10	10

The Limit of Quantitation (LOQ) for GGT is 3.0

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

APPENDIX 6 contd. Individual Animal Clinical Chemistry Parameters – Females<sup>1</sup>

Sex: Female Week(s) Relative to Start Date

0 CFU Group 1	SDH	BILI	TP	TRIG	BUN
	(U/L)	(mg/dL)	(g/dL)	(mg/dL)	(mg/dL)
	5	5	5	5	5
3811	14.0	0.16	6.6	43	14
3812	20.6	0.18	7.9	73	18
3813	5.2	0.10	7.2	34	15
3814	12.1	0.10	7.0	32	15
3815	8.9	0.09	6.7	42	14
3816	21.8	0.11	6.9	41	17
3817	7.4	0.14	6.7	35	14
3818	7.3	0.10	7.3	45	15
3819	1.7	0.12	6.3	40	16
3820	10.4	0.10	6.6	57	13
Mean	10.94	0.120	6.92	44.2	15.1
SD	6.42	0.030	0.46	12.3	1.5
N	10	10	10	10	10

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

APPENDIX 6 contd. Individual Animal Clinical Chemistry Parameters – Females<sup>1</sup>

Sex: Female Week(s) Relative to Start Date							
1.668E+10 CFU Group 2	ALT	ALB	ALKP	AST	CALC	CL	CHOL
	(U/L)	(g/dL)	(U/L)	(U/L)	(mg/dL)	(mmol/L)	(mg/dL)
	5	5	5	5	5	5	5
3831	26	5.6	79	80	12.1	99.2	69
3832	23	4.7	75	66	11.6	98.6	86
3833	75	5.4	64	121	12.2	97.6	81
3834	25	5.5	56	79	12.3	98.9	109
3835	42	5.1	72	91	11.4	100.1	60
3836	26	5.2	65	87	11.6	104.7	63
3837	21	5.1	68	78	11.8	104.4	65
3838	21	5.3	47	77	11.1	102.3	87
3839	47	5.3	61	94	11.6	100.8	75
3840	25	4.4	69	92	9.8	104.8	41
Mean	33.1	5.16	65.6	86.5	11.55	101.14	73.6
SD	17.2	0.37	9.4	14.8	0.72	2.73	18.6
N	10	10	10	10	10	10	10
%Diff	13.4	0.19	0.8	-8.8	1.14	0.39	-7.8

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

**APPENDIX 6 contd. Individual Animal Clinical Chemistry Parameters – Females<sup>1</sup>**

Sex: Female Week(s) Relative to Start Date							
1.668E+10 CFU Group 2	CREA	GGT	GLOB	GLUC	IPHS	K	NA
	(mg/dL)	(U/L)	(g/dL)	(mg/dL)	(mg/dL)	(mmol/L)	(mmol/L)
	5	5	5	5	5	5	5
3831	0.29	3.00	1.9	189	8.0	6.28	142.0
3832	0.21	3.00	2.1	150	8.8	6.27	141.0
3833	0.24	3.00	1.6	166	10.0	9.06	141.0
3834	0.32	3.00	2.0	203	8.5	5.97	143.0
3835	0.27	3.00	1.9	160	8.7	9.44	143.0
3836	0.32	3.00	1.8	159	8.7	7.09	150.0
3837	0.24	3.00	1.6	99	10.2	7.89	147.0
3838	0.23	3.00	1.4	104	9.0	6.24	144.0
3839	0.33	3.00	1.8	287	9.6	8.75	144.0
3840	0.24	3.00	1.4	118	7.6	6.01	145.0
Mean	0.269	3.000	1.75	163.5	8.91	7.300	144.00
SD	0.043	0.000	0.24	55.2	0.83	1.367	2.79
N	10	10	10	10	10	10	10
%Diff	16.450	0.000	-1.13	40.0	-1.33	-0.572	0.91

The Limit of Quantitation (LOQ) for GGT is 3.0

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

APPENDIX 6 contd. Individual Animal Clinical Chemistry Parameters – Females<sup>1</sup>

Sex: Female Week(s) Relative to Start Date

1.668E+10 CFU Group 2	SDH	BILI	TP	TRIG	BUN
	(U/L)	(mg/dL)	(g/dL)	(mg/dL)	(mg/dL)
	5	5	5	5	5
3831	15.2	0.15	7.5	41	19
3832	8.5	0.11	6.8	44	16
3833	24.1	0.12	7.0	76	15
3834	11.9	0.11	7.5	39	21
3835	14.9	0.17	7.0	40	15
3836	10.5	0.07	7.0	38	16
3837	8.2	0.11	6.7	49	19
3838	13.3	0.11	6.7	42	12
3839	16.2	0.13	7.1	61	15
3840	3.9	0.08	5.8	29	19
Mean	12.67	0.116	6.91	45.9	16.7
SD	5.52	0.030	0.48	13.4	2.7
N	10	10	10	10	10
%Diff	15.81	-3.333	-0.14	3.8	10.6

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

**APPENDIX 6 contd. Individual Animal Clinical Chemistry Parameters – Females<sup>1</sup>**

Sex: Female Week(s) Relative to Start Date							
3.337E+10 CFU Group 3	ALT	ALB	ALKP	AST	CALC	CL	CHOL
	(U/L)	(g/dL)	(U/L)	(U/L)	(mg/dL)	(mmol/L)	(mg/dL)
	5	5	5	5	5	5	5
3851	26	4.5	90	89	11.4	99.3	35
3852	22	5.2	76	85	12.2	100.9	57
3853	31	4.3	66	85	11.6	100.5	90
3854	26	5.2	83	69	11.3	100.9	103
3855	23	4.8	61	66	11.6	101.4	100
3856	37	5.0	77	101	11.6	105.2	82
3857	31	5.3	70	74	10.8	101.2	70
3858	26	4.7	38	85	11.7	104.0	71
3859	26	5.5	67	81	11.7	101.9	80
3860	29	5.2	71	87	10.6	104.2	66
Mean	27.7	4.97	69.9	80.2	11.45	101.95	75.4
SD	4.4	0.38	14.1	11.5	0.46	1.89	20.4
N	10	10	10	10	10	10	10
%Diff	-5.1	-3.50	7.4	-15.4	0.26	1.19	-5.5

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

**APPENDIX 6 contd. Individual Animal Clinical Chemistry Parameters – Females<sup>1</sup>**

Sex: Female Week(s) Relative to Start Date							
3.337E+10 CFU Group 3	CREA	GGT	GLOB	GLUC	IPHS	K	NA
	(mg/dL)	(U/L)	(g/dL)	(mg/dL)	(mg/dL)	(mmol/L)	(mmol/L)
	5	5	5	5	5	5	5
3851	0.24	3.00	2.0	199	9.2	6.43	141.0
3852	0.22	3.00	1.7	144	10.0	7.00	143.0
3853	0.24	3.00	2.1	123	8.8	5.88	144.0
3854	0.18	3.00	1.6	167	7.5	6.10	141.0
3855	0.34	3.00	2.2	165	8.7	6.44	144.0
3856	0.34	3.00	1.7	105	9.8	7.17	148.0
3857	0.27	3.00	1.8	91	8.5	5.85	144.0
3858	0.27	3.00	1.9	97	9.3	8.64	146.0
3859	0.28	3.00	2.1	89	8.5	7.28	146.0
3860	0.29	3.00	1.6	118	8.1	9.66	142.0
Mean	0.267	3.000	1.87	129.8	8.85	7.025	143.90
SD	0.050	0.000	0.22	37.5	0.74	1.264	2.28
N	10	10	10	10	10	10	10
%Diff	15.584	0.000	5.65	11.1	-1.99	-4.318	0.84

The Limit of Quantitation (LOQ) for GGT is 3.0

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

APPENDIX 6 contd. Individual Animal Clinical Chemistry Parameters – Females<sup>1</sup>

Sex: Female Week(s) Relative to Start Date					
3.337E+10 CFU Group 3	SDH	BILI	TP	TRIG	BUN
	(U/L)	(mg/dL)	(g/dL)	(mg/dL)	(mg/dL)
	5	5	5	5	5
3851	7.4	0.09	6.5	44	15
3852	7.5	0.08	6.9	46	15
3853	7.1	0.09	6.4	34	17
3854	7.1	0.10	6.8	55	12
3855	12.8	0.10	7.0	39	15
3856	13.1	0.09	6.7	50	18
3857	7.7	0.14	7.1	33	20
3858	13.9	0.12	6.6	42	16
3859	7.6	0.10	7.6	38	16
3860	21.5	0.09	6.8	41	16
Mean	10.57	0.100	6.84	42.2	16.0
SD	4.74	0.018	0.34	6.9	2.1
N	10	10	10	10	10
%Diff	-3.38	-16.667	-1.16	-4.5	6.0

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

**APPENDIX 6 contd. Individual Animal Clinical Chemistry Parameters – Females<sup>1</sup>**

Sex: Female Week(s) Relative to Start Date							
1.001E+11 CFU Group 4	ALT	ALB	ALKP	AST	CALC	CL	CHOL
	(U/L)	(g/dL)	(U/L)	(U/L)	(mg/dL)	(mmol/L)	(mg/dL)
	5	5	5	5	5	5	5
3871	38	4.7	52	107	11.7	101.5	51
3872	25	5.0	87	75	12.2	99.4	85
3874	56	5.6	41	97	11.6	101.3	82
3875	40	5.9	48	63	12.6	99.1	90
3876	24	5.3	55	66	11.5	103.7	80
3877	20	4.9	78	78	11.4	105.2	78
3878	23	5.1	64	68	11.6	103.9	74
3879	38	5.1	51	99	11.0	103.2	73
3880	20	5.2	65	67	10.7	103.7	68
Mean	31.6	5.20	60.1	80.0	11.59	102.33	75.7
SD	12.2	0.36	14.9	16.6	0.57	2.12	11.4
N	9	9	9	9	9	9	9
%Diff	8.1	0.97	-7.7	-15.6	1.48	1.57	-5.2

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

**APPENDIX 6 contd. Individual Animal Clinical Chemistry Parameters – Females<sup>1</sup>**

Sex: Female Week(s) Relative to Start Date

1.001E+11 CFU Group 4	CREA	GGT	GLOB	GLUC	IPHS	K	NA
	(mg/dL)	(U/L)	(g/dL)	(mg/dL)	(mg/dL)	(mmol/L)	(mmol/L)
	5	5	5	5	5	5	5
3871	0.27	3.00	1.8	174	9.3	8.46	142.0
3872	0.22	3.00	1.7	165	9.6	7.63	141.0
3874	0.27	3.00	1.9	129	8.5	11.47	139.0
3875	0.26	3.00	2.3	138	8.6	9.18	142.0
3876	0.29	3.00	1.6	130	8.1	5.82	149.0
3877	0.28	3.00	1.8	145	9.2	6.68	148.0
3878	0.31	3.00	1.3	97	10.4	8.04	144.0
3879	0.30	3.00	1.5	94	8.1	5.51	148.0
3880	0.33	3.00	1.2	97	8.4	5.20	146.0
Mean	0.281	3.000	1.68	129.9	8.91	7.554	144.33
SD	0.032	0.000	0.33	29.4	0.77	2.017	3.57
N	9	9	9	9	9	9	9
%Diff	21.693	0.000	-5.21	11.2	-1.32	2.894	1.14

The Limit of Quantitation (LOQ) for GGT is 3.0

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

APPENDIX 6 contd. Individual Animal Clinical Chemistry Parameters – Females<sup>1</sup>

Sex: Female Week(s) Relative to Start Date

1.001E+11 CFU Group 4	SDH	BILI	TP	TRIG	BUN
	(U/L)	(mg/dL)	(g/dL)	(mg/dL)	(mg/dL)
	5	5	5	5	5
3871	15.1	0.11	6.5	28	16
3872	9.9	0.11	6.7	35	15
3874	16.5	0.15	7.5	50	17
3875	8.3	0.12	8.2	53	15
3876	15.7	0.09	6.9	57	16
3877	6.9	0.11	6.7	43	16
3878	7.1	0.10	6.4	32	16
3879	16.3	0.14	6.6	40	17
3880	12.2	0.16	6.4	36	18
Mean	12.00	0.121	6.88	41.6	16.2
SD	4.03	0.024	0.60	10.0	1.0
N	9	9	9	9	9
%Diff	9.69	0.926	-0.61	-6.0	7.4

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

**APPENDIX 7. Individual Animal Clinical Analysis of Urine – Males<sup>1</sup>**

Sex: Male Week(s) Relative to Start Date

0 CFU Group 1	Urine Volume (ml)	pH	Specific Gravity	Urine Glucose (mg/dL)	Urine Ketone (mmol/L)	Urine Protein (mg/dL)	Urobilinogen (EU/dL)
	5	5	5	5	5	5	5
3801	7.0 <sup>1</sup>	7.0	1.025	0	15	30	0.2
3802	16.0 <sup>2</sup>	7.0	1.020	0	5	15	0.2
3803	7.0 <sup>1</sup>	6.5	1.030	0	5	30	0.2
3804	10.0 <sup>1</sup>	6.5	1.025	0	15	30	0.2
3805	2.0 <sup>3</sup>	5.5	1.030	0	5	300	1.0
3806	12.0 <sup>4</sup>	7.5	1.015	0	15	15	0.2
3807	14.0 <sup>5</sup>	7.0	1.020	0	15	15	0.2
3808	20.0 <sup>5</sup>	7.5	1.015	0	5	15	0.2
3809	13.0 <sup>4</sup>	7.0	1.020	0	15	30	0.2
3810	4.5 <sup>4</sup>	7.0	1.030	0	5	30	0.2
Mean	10.55	6.85	1.0230	0.0	10.0	51.0	0.28
SD	5.52	0.58	0.0059	0.0	5.3	87.8	0.25
N	10	10	10	10	10	10	10

<sup>1</sup> [RC:Hair Contamination, Possible Fecal Contamination.]

<sup>2</sup> [RC:Hair Contamination, Possible Fecal Contamination. Possible Water Contamination.]

<sup>3</sup> [RC:Possible Fecal Contamination.]

<sup>4</sup> [RC:Hair Contamination. Possible Fecal Contamination.]

<sup>5</sup> [RC:Hair Contamination. Possible Fecal Contamination. Possible Water Contamination.]

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

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**APPENDIX 7 contd. Individual Animal Clinical Analysis of Urine – Males<sup>1</sup>**

Sex: Male Week(s) Relative to Start Date							
0 CFU	Urine Bilirubin	Urine Blood	Urine Clarity	Urine Color	Urine Quality	Urine Sediment	Sediment (Abnormal)
Group 1							
	5	5	5	5	5	5	5
3801	NEGATIVE	NEGATIVE	CLEAR	BROWN	MEDIUM <sup>1</sup>	WNL <sup>1</sup>	NONE <sup>1</sup>
3802	NEGATIVE	NEGATIVE	CLEAR	LT. YELLOW	LIGHT <sup>2</sup>	WNL <sup>2</sup>	NONE <sup>2</sup>
3803	NEGATIVE	NEGATIVE	CLEAR	YELLOW	MEDIUM <sup>1</sup>	WNL <sup>1</sup>	NONE <sup>1</sup>
3804	NEGATIVE	NEGATIVE	CLEAR	YELLOW	MEDIUM <sup>1</sup>	WNL <sup>1</sup>	NONE <sup>1</sup>
3805	SMALL	NEGATIVE	CLEAR	DK. YELLOW	MEDIUM <sup>3</sup>	WNL <sup>3</sup>	NONE <sup>3</sup>
3806	NEGATIVE	TR-INTACT	CLEAR	YELLOW	MEDIUM <sup>4</sup>	WNL <sup>4</sup>	NONE <sup>4</sup>
3807	NEGATIVE	TR-INTACT	CLEAR	LT. YELLOW	LIGHT <sup>5</sup>	WNL <sup>5</sup>	NONE <sup>5</sup>
3808	NEGATIVE	NEGATIVE	CLEAR	LT. YELLOW	LIGHT <sup>5</sup>	WNL <sup>5</sup>	NONE <sup>5</sup>
3809	NEGATIVE	TR-INTACT	CLEAR	YELLOW	MEDIUM <sup>4</sup>	WNL <sup>4</sup>	NONE <sup>4</sup>
3810	NEGATIVE	TR-INTACT	CLEAR	YELLOW	MEDIUM <sup>4</sup>	WNL <sup>4</sup>	NONE <sup>4</sup>
Mean	-	-	-	-	-	-	-
SD	-	-	-	-	-	-	-
N	-	-	-	-	-	-	-

<sup>1</sup> [RC:Hair Contamination, Possible Fecal Contamination.]

<sup>2</sup> [RC:Hair Contamination, Possible Fecal Contamination, Possible Water Contamination.]

<sup>3</sup> [RC:Possible Fecal Contamination.]

<sup>4</sup> [RC:Hair Contamination, Possible Fecal Contamination.]

<sup>5</sup> [RC:Hair Contamination, Possible Fecal Contamination, Possible Water Contamination.]

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

**APPENDIX 7 contd. Individual Animal Clinical Analysis of Urine – Males<sup>1</sup>**

Sex: Male Week(s) Relative to Start Date

1.668E+10 CFU Group 2	Urine Volume (ml)	pH	Specific Gravity	Urine Glucose (mg/dL)	Urine Ketone (mmol/L)	Urine Protein (mg/dL)	Urobilinogen (EU/dL)
	5	5	5	5	5	5	5
3821	3.0 <sup>1</sup>	6.0	1.030	0	5	100	0.2
3822	6.0 <sup>1</sup>	6.5	1.030	0	15	30	0.2
3823	3.5 <sup>1</sup>	6.5	1.030	0	15	100	0.2
3824	17.0 <sup>2</sup>	7.5	1.020	0	5	15	0.2
3825	3.5 <sup>3</sup>	7.0	1.025	0	15	100	0.2
3826	20.0 <sup>4</sup>	6.5	1.020	0	15	15	0.2
3827	3.5 <sup>3</sup>	6.5	1.030	0	15	100	0.2
3828	4.0 <sup>3</sup>	6.5	1.030	0	5	100	0.2
3830	22.0 <sup>4</sup>	7.0	1.020	0	5	15	0.2
Mean	9.17	6.67	1.0261	0.0	10.6	63.9	0.20
SD	8.02	0.43	0.0049	0.0	5.3	43.1	0.00
N	9	9	9	9	9	9	9
%Diff	-13.11	-2.68	0.3041	-	5.6	25.3	-28.57

<sup>1</sup> [RC:Hair Contamination, Possible Fecal Contamination.]

<sup>2</sup> [RC:Hair Contamination, Possible Fecal Contamination. Possible Water Contamination.]

<sup>3</sup> [RC:Hair Contamination, Possible Fecal Contamination.]

<sup>4</sup> [RC:Hair Contamination, Possible Fecal Contamination. Possible Water Contamination.]

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

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**APPENDIX 7 contd. Individual Animal Clinical Analysis of Urine – Males<sup>1</sup>**

Sex: Male		Week(s) Relative to Start Date					
1.688E+10 CFJ Group 2	Urine Bilirubin	Urine Blood	Urine Clarity	Urine Color	Urine Quality	Urine Sediment	Sediment (Abnormal)
	5	5	5	5	5	5	5
	3321	NEGATIVE	NEGATIVE	CLEAR	YELLOW	MEDIUM <sup>1</sup>	WNL <sup>1</sup>
3322	NEGATIVE	NEGATIVE	CLEAR	YELLOW	MEDIUM <sup>1</sup>	WNL <sup>1</sup>	NONE <sup>1</sup>
3323	NEGATIVE	NEGATIVE	CLEAR	YELLOW	MEDIUM <sup>1</sup>	WNL <sup>1</sup>	NONE <sup>1</sup>
3324	NEGATIVE	NEGATIVE	CLEAR	LT. YELLOW	LIGHT <sup>2</sup>	WNL <sup>2</sup>	NONE <sup>2</sup>
3325	NEGATIVE	NEGATIVE	CLEAR	YELLOW	MEDIUM <sup>3</sup>	WNL <sup>3</sup>	NONE <sup>3</sup>
3326	NEGATIVE	NEGATIVE	CLEAR	LT. YELLOW	LIGHT <sup>4</sup>	WNL <sup>4</sup>	NONE <sup>4</sup>
3327	SMALL	TR-INTEGRAL	CLEAR	DK. YELLOW	MEDIUM <sup>3</sup>	WNL <sup>3</sup>	NONE <sup>3</sup>
3328	SMALL	NEGATIVE	CLEAR	BROWN	MEDIUM <sup>3</sup>	WNL <sup>3</sup>	NONE <sup>3</sup>
3330	NEGATIVE	NEGATIVE	CLEAR	LT. YELLOW	LIGHT <sup>4</sup>	WNL <sup>4</sup>	NONE <sup>4</sup>
Mean	-	-	-	-	-	-	-
SD	-	-	-	-	-	-	-
N	-	-	-	-	-	-	-
%Diff	-	-	-	-	-	-	-

<sup>1</sup> [RC:Hair Contamination, Possible Fecal Contamination.]

<sup>2</sup> [RC:Hair Contamination, Possible Fecal Contamination, Possible Water Contamination.]

<sup>3</sup> [RC:Hair Contamination, Possible Fecal Contamination.]

<sup>4</sup> [RC:Hair Contamination, Possible Fecal Contamination, Possible Water Contamination.]

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

**APPENDIX 7 contd. Individual Animal Clinical Analysis of Urine – Males<sup>1</sup>**

Sex: Male Week(s) Relative to Start Date							
3.337E+10 CFU Group 3	Urine Volume (ml)	pH	Specific Gravity	Urine Glucose (mg/dL)	Urine Ketone (mmol/L)	Urine Protein (mg/dL)	Urobilinogen (EU/dL)
	5	5	5	5	5	5	5
3841	4.0 <sup>1</sup>	6.5	1.030	0	5	100	0.2
3842	11.0 <sup>1</sup>	7.0	1.025	0	5	30	0.2
3843	9.5 <sup>2</sup>	6.5	1.025	0	15	30	0.2
3844	1.0 <sup>3</sup>	7.5	1.020	100	15	300	1.0
3845	30.0 <sup>2</sup>	7.0	1.020	0	5	15	0.2
3846	4.0 <sup>4</sup>	6.5	1.030	0	5	30	0.2
3847	3.0 <sup>4</sup>	6.5	1.030	100	15	100	0.2
3848	3.0 <sup>4</sup>	6.5	1.030	0	15	100	0.2
3849	3.0 <sup>4</sup>	6.5	1.030	0	5	100	0.2
3850	6.0 <sup>4</sup>	6.5	1.030	0	15	30	0.2
Mean	7.45	6.70	1.0270	20.0	10.0	83.5	0.28
SD	8.51	0.35	0.0042	42.2	5.3	84.4	0.25
N	10	10	10	10	10	10	10
%Diff	-29.38	-2.19	0.3910		0.0	63.7	0.00

<sup>1</sup> [RC:Hair Contamination, Possible Fecal Contamination.]

<sup>2</sup> [RC:Hair Contamination, Possible Fecal Contamination, Possible Water Contamination.]

<sup>3</sup> [RC:Possible Fecal Contamination.]

<sup>4</sup> [RC:Hair Contamination, Possible Fecal Contamination.]

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

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**APPENDIX 7 contd. Individual Animal Clinical Analysis of Urine – Males<sup>1</sup>**

Sex: Male Week(s) Relative to Start Date							
3.337E+10 CFU Group 3	Urine Bilirubin	Urine Blood	Urine Clarity	Urine Color	Urine Quality	Urine Sediment	Sediment (Abnormal)
	5	5	5	5	5	5	5
	3841	NEGATIVE	TR-LYSED	CLEAR	YELLOW	MEDIUM <sup>1</sup>	WNL <sup>1</sup>
3842	NEGATIVE	TR-INTACT	CLEAR	YELLOW	MEDIUM <sup>1</sup>	WNL <sup>1</sup>	NONE <sup>1</sup>
3843	NEGATIVE	NEGATIVE	CLEAR	YELLOW	LIGHT <sup>2</sup>	WNL <sup>2</sup>	NONE <sup>2</sup>
3844	MODERATE	TR-INTACT	CLEAR	DK. YELLOW	DARK <sup>3</sup>	WNL <sup>3</sup>	NONE <sup>3</sup>
3845	NEGATIVE	TR-INTACT	CLEAR	LT. YELLOW	LIGHT <sup>2</sup>	WNL <sup>2</sup>	BACT <sup>2</sup>
3846	NEGATIVE	NEGATIVE	CLEAR	YELLOW	MEDIUM <sup>4</sup>	WNL <sup>4</sup>	NONE <sup>4</sup>
3847	SMALL	NEGATIVE	CLEAR	DK. YELLOW	MEDIUM <sup>4</sup>	WNL <sup>4</sup>	NONE <sup>4</sup>
3848	SMALL	NEGATIVE	CLEAR	DK. BROWN	MEDIUM <sup>4</sup>	WNL <sup>4</sup>	NONE <sup>4</sup>
3849	SMALL	MODERATE	CLEAR	DK. YELLOW	MEDIUM <sup>4</sup>	WNL <sup>4</sup>	NONE <sup>4</sup>
3850	NEGATIVE	NEGATIVE	CLEAR	YELLOW	MEDIUM <sup>4</sup>	WNL <sup>4</sup>	NONE <sup>4</sup>
Mean	-	-	-	-	-	-	-
SD	-	-	-	-	-	-	-
N	-	-	-	-	-	-	-
%Diff	-	-	-	-	-	-	-

<sup>1</sup> [RC:Hair Contamination, Possible Fecal Contamination.]

<sup>2</sup> [RC:Hair Contamination, Possible Fecal Contamination. Possible Water Contamination.]

<sup>3</sup> [RC:Possible Fecal Contamination.]

<sup>4</sup> [RC:Hair Contamination. Possible Fecal Contamination.]

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

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APPENDIX 7 contd. Individual Animal Clinical Analysis of Urine – Males<sup>1</sup>

Sex: Male Week(s) Relative to Start Date

1.001E+11 CFU Group 4	Urine Volume (ml)	pH	Specific Gravity	Urine Glucose (mg/dL)	Urine Ketone (mmol/L)	Urine Protein (mg/dL)	Urobilinogen (EU/dL)
	5	5	5	5	5	5	5
3861	5.0 <sup>1</sup>	6.5	1.030	0	5	30	0.2
3862	2.0 <sup>1</sup>	6.0	1.030	0	5	100	0.2
3863	7.0 <sup>1</sup>	7.0	1.020	0	5	30	0.2
3864	29.0 <sup>2</sup>	7.0	1.015	0	5	15	0.2
3865	13.0 <sup>2</sup>	6.5	1.025	0	15	30	0.2
3866	12.5 <sup>3</sup>	7.0	1.020	0	5	15	0.2
3867	13.0 <sup>3</sup>	6.5	1.020	0	5	15	0.2
3868	14.0 <sup>3</sup>	7.0	1.020	0	5	15	0.2
3869	5.5 <sup>4</sup>	6.5	1.030	0	5	30	0.2
3870	25.0 <sup>3</sup>	7.0	1.020	0	15	15	0.2
Mean	12.60	6.70	1.0230	0.0	7.0	29.5	0.20
SD	8.67	0.35	0.0054	0.0	4.2	25.9	0.00
N	10	10	10	10	10	10	10
%Diff	19.43	-2.19	0.0000		-30.0	-42.2	-28.57

<sup>1</sup> [RC:Hair Contamination, Possible Fecal Contamination.]

<sup>2</sup> [RC:Hair Contamination, Possible Fecal Contamination. Possible Water Contamination.]

<sup>3</sup> [RC:Hair Contamination. Possible Fecal Contamination. Possible Water Contamination.]

<sup>4</sup> [RC:Hair Contamination. Possible Fecal Contamination.]

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

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APPENDIX 7 contd. Individual Animal Clinical Analysis of Urine – Males<sup>1</sup>

Sex: Male Weeks) Relative to Start Date							
1.001E+11 CFU Group 4	Urine Bilirubin	Urine Blood	Urine Clarity	Urine Color	Urine Quality	Urine Sediment	Sediment (Abnormal)
	5	5	5	5	5	5	5
3861	NEGATIVE	NEGATIVE	CLEAR	YELLOW	LIGHT <sup>1</sup>	WNL <sup>1</sup>	NONE <sup>1</sup>
3862	SMALL	NEGATIVE	CLEAR	DK. YELLOW	MEDIUM <sup>1</sup>	WNL <sup>1</sup>	NONE <sup>1</sup>
3863	NEGATIVE	SMALL	CLEAR	YELLOW	MEDIUM <sup>1</sup>	WNL <sup>1</sup>	NONE <sup>1</sup>
3864	NEGATIVE	TR-INTACT	CLEAR	LT. YELLOW	LIGHT <sup>2</sup>	WNL <sup>2</sup>	NONE <sup>2</sup>
3865	NEGATIVE	NEGATIVE	CLEAR	YELLOW	LIGHT <sup>2</sup>	WNL <sup>2</sup>	NONE <sup>2</sup>
3866	NEGATIVE	TR-INTACT	CLEAR	YELLOW	LIGHT <sup>3</sup>	WNL <sup>3</sup>	NONE <sup>3</sup>
3867	NEGATIVE	NEGATIVE	CLEAR	LT. YELLOW	LIGHT <sup>3</sup>	WNL <sup>3</sup>	NONE <sup>3</sup>
3868	NEGATIVE	NEGATIVE	CLEAR	LT. YELLOW	LIGHT <sup>3</sup>	WNL <sup>3</sup>	NONE <sup>3</sup>
3869	NEGATIVE	NEGATIVE	CLEAR	YELLOW	MEDIUM <sup>4</sup>	WNL <sup>4</sup>	NONE <sup>4</sup>
3870	NEGATIVE	NEGATIVE	CLEAR	LT. YELLOW	LIGHT <sup>3</sup>	WNL <sup>3</sup>	NONE <sup>3</sup>
Mean	-	-	-	-	-	-	-
SD	-	-	-	-	-	-	-
N	-	-	-	-	-	-	-
%Diff	-	-	-	-	-	-	-

<sup>1</sup> [RC:Hair Contamination, Possible Fecal Contamination.]

<sup>2</sup> [RC:Hair Contamination, Possible Fecal Contamination. Possible Water Contamination.]

<sup>3</sup> [RC:Hair Contamination, Possible Fecal Contamination. Possible Water Contamination.]

<sup>4</sup> [RC:Hair Contamination, Possible Fecal Contamination.]

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

**APPENDIX 8. Individual Animal Clinical Analysis of Urine – Females<sup>1</sup>**

Sex: Female Week(s) Relative to Start Date

Group 1	Urine Volume (ml)	pH	Specific Gravity	Urine Glucose (mg/dL)	Urine Ketone (mmol/L)	Urine Protein (mg/dL)	Urobilinogen (EU/dL)
	5	5	5	5	5	5	5
3811	4.0 <sup>1</sup>	6.5	1.030	0	0	30	0.2
3812	5.0 <sup>2</sup>	6.5	1.030	0	0	30	0.2
3813	5.5 <sup>1</sup>	6.5	1.030	0	0	0	0.2
3814	6.0 <sup>1</sup>	7.0	1.020	0	5	15	0.2
3815	1.0	5.0	1.030	0	0	100	1.0
3816	1.0 <sup>3</sup>	5.5	1.030	100	0	100	0.2
3817	2.5 <sup>3</sup>	6.5	1.030	0	0	100	0.2
3818	10.5 <sup>4</sup>	6.5	1.020	0	0	0	0.2
3819	14.0 <sup>3</sup>	8.5	1.010	0	0	15	0.2
3820	20.0 <sup>4</sup>	7.0	1.010	0	0	0	0.2
Mean	6.95	6.55	1.0240	10.0	0.5	39.0	0.28
SD	6.13	0.93	0.0084	31.6	1.6	43.5	0.25
N	10	10	10	10	10	10	10

<sup>1</sup> [RC:Hair Contamination, Possible Fecal Contamination.]

<sup>2</sup> [RC:Possible Fecal Contamination.]

<sup>3</sup> [RC:Hair Contamination, Possible Fecal Contamination.]

<sup>4</sup> [RC:Hair Contamination, Possible Fecal Contamination, Possible Water Contamination.]

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

**APPENDIX 8 contd. Individual Animal Clinical Analysis of Urine – Females<sup>1</sup>**

Sex: Female Week(s) Relative to Start Date							
0 CFU Group 1	Urine Bilirubin	Urine Blood	Urine Clarity	Urine Color	Urine Quality	Urine Sediment	Sediment (Abnormal)
	5	5	5	5	5	5	5
	3811	NEGATIVE	NEGATIVE	CLEAR	YELLOW	MEDIUM <sup>1</sup>	WNL <sup>1</sup>
3812	NEGATIVE	NEGATIVE	CLEAR	YELLOW	MEDIUM <sup>2</sup>	WNL <sup>2</sup>	NONE <sup>2</sup>
3813	NEGATIVE	NEGATIVE	CLEAR	YELLOW	LIGHT <sup>1</sup>	WNL <sup>1</sup>	NONE <sup>1</sup>
3814	NEGATIVE	SMALL	CLEAR	YELLOW	LIGHT <sup>1</sup>	WNL <sup>1</sup>	NONE <sup>1</sup>
3815	MODERATE	NEGATIVE	CLEAR	DK. YELLOW	MEDIUM	WNL	NONE
3816	SMALL	NEGATIVE	CLEAR	DK. YELLOW	MEDIUM <sup>3</sup>	WNL <sup>3</sup>	NONE <sup>3</sup>
3817	NEGATIVE	NEGATIVE	CLEAR	YELLOW	MEDIUM <sup>3</sup>	WNL <sup>3</sup>	NONE <sup>3</sup>
3818	NEGATIVE	NEGATIVE	CLEAR	LT. YELLOW	LIGHT <sup>4</sup>	WNL <sup>4</sup>	NONE <sup>4</sup>
3819	NEGATIVE	MODERATE	CLEAR	YELLOW	MEDIUM <sup>3</sup>	WNL <sup>3</sup>	NONE <sup>3</sup>
3820	NEGATIVE	NEGATIVE	CLEAR	LT. YELLOW	LIGHT <sup>4</sup>	WNL <sup>4</sup>	NONE <sup>4</sup>
Mean	-	-	-	-	-	-	-
SD	-	-	-	-	-	-	-
N	-	-	-	-	-	-	-

<sup>1</sup> [RC:Hair Contamination, Possible Fecal Contamination.]

<sup>2</sup> [RC:Possible Fecal Contamination.]

<sup>3</sup> [RC:Hair Contamination, Possible Fecal Contamination.]

<sup>4</sup> [RC:Hair Contamination, Possible Fecal Contamination, Possible Water Contamination.]

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

**APPENDIX 8 contd. Individual Animal Clinical Analysis of Urine – Females<sup>1</sup>**

Sex: Female Week(s) Relative to Start Date							
1.668E+10 CFU Group 2	Urine Volume (ml)	pH	Specific Gravity	Urine Glucose (mg/dL)	Urine Ketone (mmol/L)	Urine Protein (mg/dL)	Urobilinogen (EU/dL)
	5	5	5	5	5	5	5
	3831	2.5 <sup>1</sup>	6.5	1.030	0	0	15
3832	13.0 <sup>2</sup>	5.5	1.020	0	0	0	0.2
3833	2.5 <sup>1</sup>	6.5	1.030	0	0	30	0.2
3834	1.5 <sup>1</sup>	7.0	1.030	0	0	100	0.2
3835	0.5 <sup>3</sup>	5.5	1.030	0	0	100	0.2
3836	4.0 <sup>4</sup>	6.5	1.025	0	0	15	0.2
3837	20.0 <sup>5</sup>	6.5	1.010	0	0	0	0.2
3838	4.5 <sup>4</sup>	6.5	1.025	0	0	15	0.2
3839	4.0 <sup>4</sup>	6.5	1.030	0	0	15	0.2
3840	19.0 <sup>5</sup>	5.5	1.015	0	0	0	0.2
Mean	7.15	6.25	1.0245	0.0	0.0	29.0	0.20
SD	7.35	0.54	0.0072	0.0	0.0	38.6	0.00
N	10	10	10	10	10	10	10
%Diff	2.88	-4.56	0.0488	-100.0	-100.0	-25.6	-28.57

<sup>1</sup> [RC:Hair Contamination, Possible Fecal Contamination.]

<sup>2</sup> [RC:Hair Contamination, Possible Fecal Contamination. Possible Water Contamination.]

<sup>3</sup> [RC:Hair Contamination.]

<sup>4</sup> [RC:Hair Contamination. Possible Fecal Contamination.]

<sup>5</sup> [RC:Hair Contamination. Possible Fecal Contamination. Possible Water Contamination.]

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

**APPENDIX 8 contd. Individual Animal Clinical Analysis of Urine – Females<sup>1</sup>**

Sex: Female Week(s) Relative to Start Date

1.668E+10 CFU Group 2	Urine	Urine	Urine	Urine	Urine	Urine	Sediment
	Bilirubin	Blood	Clarity	Color	Quality	Sediment	(Abnormal)
	5	5	5	5	5	5	5
3831	NEGATIVE	NEGATIVE	CLEAR	YELLOW	LIGHT <sup>1</sup>	WNL <sup>1</sup>	NONE <sup>1</sup>
3832	NEGATIVE	NEGATIVE	CLEAR	LT. YELLOW	LIGHT <sup>2</sup>	WNL <sup>2</sup>	NONE <sup>2</sup>
3833	SMALL	MODERATE	CLEAR	DK. YELLOW	MEDIUM <sup>1</sup>	WNL <sup>1</sup>	NONE <sup>1</sup>
3834	SMALL	TR-INTACT	CLEAR	DK. YELLOW	MEDIUM <sup>1</sup>	WNL <sup>1</sup>	BACT <sup>1</sup>
3835	SMALL	NEGATIVE	CLEAR	DK. YELLOW	MEDIUM <sup>3</sup>	WNL <sup>3</sup>	NONE <sup>3</sup>
3836	NEGATIVE	NEGATIVE	CLEAR	YELLOW	LIGHT <sup>4</sup>	WNL <sup>4</sup>	NONE <sup>4</sup>
3837	NEGATIVE	NEGATIVE	CLEAR	LT. YELLOW	LIGHT <sup>5</sup>	WNL <sup>5</sup>	NONE <sup>5</sup>
3838	NEGATIVE	NEGATIVE	CLEAR	YELLOW	LIGHT <sup>4</sup>	WNL <sup>4</sup>	NONE <sup>4</sup>
3839	NEGATIVE	NEGATIVE	CLEAR	YELLOW	LIGHT <sup>4</sup>	WNL <sup>4</sup>	NONE <sup>4</sup>
3840	NEGATIVE	NEGATIVE	CLEAR	LT. YELLOW	LIGHT <sup>5</sup>	WNL <sup>5</sup>	NONE <sup>5</sup>
Mean	-	-	-	-	-	-	-
SD	-	-	-	-	-	-	-
N	-	-	-	-	-	-	-
%Diff	-	-	-	-	-	-	-

<sup>1</sup> [RC:Hair Contamination, Possible Fecal Contamination.]

<sup>2</sup> [RC:Hair Contamination, Possible Fecal Contamination. Possible Water Contamination.]

<sup>3</sup> [RC:Hair Contamination.]

<sup>4</sup> [RC:Hair Contamination. Possible Fecal Contamination.]

<sup>5</sup> [RC:Hair Contamination. Possible Fecal Contamination. Possible Water Contamination.]

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

**APPENDIX 8 contd. Individual Animal Clinical Analysis of Urine – Females<sup>1</sup>**

Sex: Female Week(s) Relative to Start Date							
3.337E+10 CFU Group 3	Urine Volume (ml)	pH	Specific Gravity	Urine Glucose (mg/dL)	Urine Ketone (mmol/L)	Urine Protein (mg/dL)	Urobilinogen (EU/dL)
	5	5	5	5	5	5	5
	3851	5.0 <sup>1</sup>	9.0	0.503	0	0	30
3852	7.5 <sup>1</sup>	6.5	1.025	0	0	15	0.2
3853	3.0 <sup>1</sup>	6.0	1.030	0	0	30	0.2
3854	4.5 <sup>1</sup>	6.0	1.025	0	0	15	0.2
3855	1.0 <sup>1</sup>	6.5	1.030	0	0	300	0.2
3856	1.0 <sup>2</sup>	5.5	1.030	0	0	100	1.0
3857	3.0 <sup>3</sup>	8.5	1.020	0	5	100	1.0
3858	0.5 <sup>2</sup>	5.0	1.030	100	0	100	1.0
3859	1.0 <sup>2</sup>	6.5	1.030	0	0	100	1.0
3860	14.0 <sup>4</sup>	7.0	1.020	0	0	0	0.2
Mean	4.05	6.65	0.9743	10.0	0.5	79.0	0.52
SD	4.15	1.25	0.1656	31.6	1.6	88.1	0.41
N	10	10	10	10	10	10	10
%Diff	-41.73	1.53	-4.8535	0.0	0.0	102.6	85.7 <sup>1</sup>

<sup>1</sup> [RC:Hair Contamination, Possible Fecal Contamination.]

<sup>2</sup> [RC:Hair Contamination. Possible Fecal Contamination.]

<sup>3</sup> [RC:Possible Fecal Contamination.]

<sup>4</sup> [RC:Hair Contamination. Possible Fecal Contamination. Possible Water Contamination.]

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

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**APPENDIX 8 contd. Individual Animal Clinical Analysis of Urine – Females<sup>1</sup>**

Sex: Female Week(s) Relative to Start Date

3.337E+10 CFU Group 3	Urine Bilirubin	Urine Blood	Urine Clarity	Urine Color	Urine Quality	Urine Sediment	Sediment (Abnormal)
	5	5	5	5	5	5	5
3851	NEGATIVE	NEGATIVE	CLEAR	YELLOW	MEDIUM <sup>1</sup>	WNL <sup>1</sup>	NONE <sup>1</sup>
3852	NEGATIVE	TR:INTACT	CLEAR	YELLOW	MEDIUM <sup>1</sup>	WNL <sup>1</sup>	NONE <sup>1</sup>
3853	NEGATIVE	NEGATIVE	CLEAR	YELLOW	MEDIUM <sup>1</sup>	WNL <sup>1</sup>	NONE <sup>1</sup>
3854	NEGATIVE	NEGATIVE	CLEAR	LT. YELLOW	LIGHT <sup>1</sup>	WNL <sup>1</sup>	NONE <sup>1</sup>
3855	SMALL	NEGATIVE	CLEAR	DK. YELLOW	LIGHT <sup>1</sup>	WNL <sup>1</sup>	NONE <sup>1</sup>
3856	MODERATE	NEGATIVE	CLEAR	DK. YELLOW	MEDIUM <sup>2</sup>	WNL <sup>2</sup>	NONE <sup>2</sup>
3857	SMALL	SMALL	CLEAR	DK. ORANGE	DARK <sup>3</sup>	WNL <sup>3</sup>	NONE <sup>3</sup>
3858	SMALL	NEGATIVE	CLEAR	DK. YELLOW	MEDIUM <sup>2</sup>	WNL <sup>2</sup>	NONE <sup>2</sup>
3859	SMALL	MODERATE	CLEAR	DK. YELLOW	DARK <sup>2</sup>	WNL <sup>2</sup>	NONE <sup>2</sup>
3860	NEGATIVE	NEGATIVE	CLEAR	LT. YELLOW	LIGHT <sup>4</sup>	WNL <sup>4</sup>	NONE <sup>4</sup>
Mean	-	-	-	-	-	-	-
SD	-	-	-	-	-	-	-
N	-	-	-	-	-	-	-
%Diff	-	-	-	-	-	-	-

<sup>1</sup> [RC:Hair Contamination, Possible Fecal Contamination.]

<sup>2</sup> [RC:Hair Contamination, Possible Fecal Contamination.]

<sup>3</sup> [RC:Possible Fecal Contamination.]

<sup>4</sup> [RC:Hair Contamination, Possible Fecal Contamination, Possible Water Contamination.]

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

**PSL Study No.: 55164**

**Eurofins Advinus Study Phase No.: G23206\_Clin\_PATH/Clinical Pathology Phase Report**

**Copy No. 1/1**

**APPENDIX 8 contd. Individual Animal Clinical Analysis of Urine – Females<sup>1</sup>**

Sex: Female Week(s) Relative to Start Date

1.001E+11 CFU Group 4	Urine Volume (ml)	pH	Specific Gravity	Urne Glucose (mg/dL)	Urine Ketone (mmol/L)	Urine Protein (mg/dL)	Urobilinogen (EU/dL)
	5	5	5	5	5	5	5
3871	1.0 <sup>1</sup>	6.5	1.030	0	0	100	0.2
3872	1.0 <sup>1</sup>	6.0	1.030	0	0	100	0.2
3873	2.0 <sup>2</sup>	6.5	1.030	0	0	30	0.2
3874	2.0 <sup>1</sup>	6.5	1.030	0	0	100	1.0
3875	1.0 <sup>2</sup>	6.5	1.030	0	5	100	1.0
3876	1.5 <sup>3</sup>	6.5	1.030	0	0	100	0.2
3877	10.0 <sup>3</sup>	6.0	1.020	0	0	15	0.2
3878	8.5 <sup>3</sup>	6.5	1.015	0	0	0	0.2
3879	3.0 <sup>2</sup>	7.5	1.020	0	5	100	0.2
3880	4.0 <sup>3</sup>	6.0	1.025	0	0	0	0.2
Mean	3.40	6.45	1.0260	0.0	1.0	64.5	0.36
SD	3.25	0.44	0.0057	0.0	2.1	46.6	0.34
N	10	10	10	10	10	10	10
%Diff	-51.08	-1.53	0.1953	-100.0	100.0	65.4	28.57

<sup>1</sup> [RC:Hair Contamination, Possible Fecal Contamination.]

<sup>2</sup> [RC:Possible Fecal Contamination.]

<sup>3</sup> [RC:Hair Contamination, Possible Fecal Contamination.]

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.

**PSL Study No.: 55164**
**Eurofins Advinus Study Phase No.: G23206\_Clin\_PATH/Clinical Pathology Phase Report**
**Copy No. 1/1**
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**APPENDIX 8 contd. Individual Animal Clinical Analysis of Urine – Females<sup>1</sup>**

Sex: Female Week(s) Relative to Start Date

1.001E+11 CFU Group 4	Urine Bilirubin	Urine Blood	Urine Clarity	Urine Color	Urine Quality	Urine Sediment	Sediment (Abnormal)
	5	5	5	5	5	5	5
3871	SMALL	NEGATIVE	CLEAR	DK. YELLOW	MEDIUM <sup>1</sup>	WNL <sup>1</sup>	NONE <sup>1</sup>
3872	SMALL	TR-INTACT	CLEAR	DK. YELLOW	MEDIUM <sup>1</sup>	WNL <sup>1</sup>	NONE <sup>1</sup>
3873	SMALL	SMALL	CLEAR	DK. YELLOW	DARK <sup>2</sup>	WNL <sup>2</sup>	NONE <sup>2</sup>
3874	SMALL	SMALL	CLEAR	DK. YELLOW	MEDIUM <sup>1</sup>	WNL <sup>1</sup>	BACT <sup>1</sup>
3875	SMALL	SMALL	CLEAR	DK. YELLOW	DARK <sup>2</sup>	WNL <sup>2</sup>	NONE <sup>2</sup>
3876	SMALL	NEGATIVE	CLEAR	DK. YELLOW	MEDIUM <sup>3</sup>	WNL <sup>3</sup>	NONE <sup>3</sup>
3877	NEGATIVE	NEGATIVE	CLEAR	LT. YELLOW	LIGHT <sup>3</sup>	WNL <sup>3</sup>	NONE <sup>3</sup>
3878	NEGATIVE	NEGATIVE	CLEAR	LT. YELLOW	LIGHT <sup>3</sup>	WNL <sup>3</sup>	NONE <sup>3</sup>
3879	NEGATIVE	MODERATE	CLEAR	DK. ORANGE	DARK <sup>2</sup>	WNL <sup>2</sup>	NONE <sup>2</sup>
3880	NEGATIVE	NEGATIVE	CLEAR	YELLOW	LIGHT <sup>3</sup>	WNL <sup>3</sup>	NONE <sup>3</sup>
Mean	..	..	..	..	..	..	..
SD	..	..	..	..	..	..	..
N	..	..	..	..	..	..	..
%Diff	..	..	..	..	..	..	..

<sup>1</sup> [RC:Hair Contamination, Possible Fecal Contamination.]

<sup>2</sup> [RC:Possible Fecal Contamination.]

<sup>3</sup> [RC:Hair Contamination. Possible Fecal Contamination.]

<sup>1</sup> The doses listed are the nominal doses for each strain in terms of CFU/kg bw/day.



## 11. ANNEXURES

DRAFT PHASE REPORT



**ANNEXURE 1. GLP Certificate**

The summary of GLP accreditations received by the test facility from multiple Monitoring Authorities and the GLP certificates issued by the Indian National GLP Compliance Monitoring Authority are given below:

**Summary of Accreditations Received by the Test Facility from Multiple GLP Monitoring Authorities**

<b>GLP Monitoring Authority</b>	<b>Accreditation received in the year</b>
Germany	1992, 1997, 2001, 2005 and 2010.
Netherlands	1999, 2003, 2007 and 2009.
India	2005, 2008, 2012, 2014, 2017, 2020 and 2021

Note:

1. The test facility was inspected / monitored as per the OECD GLP system by the respective Monitoring Authorities stated above, and maintained the accreditations continuously.
2. India accepted the OECD Council invitation and received the Full Adherence status for Mutual Acceptance of Data (MAD) in March 2011, and also became a member of the OECD GLP Working Group. As per the OECD provisions, the Monitoring Authorities in OECD member countries as well as those in Full Adherent countries would inspect test facilities in the respective countries for the purpose of monitoring and accreditation. Accordingly, since 2011, the test facility was inspected only by the Indian National GLP Compliance Monitoring Authority (NGCMA) for monitoring and accreditation.
3. The NGCMA issued a revised GLP Certificate in March 2020 for the earlier accreditation received in 2017. In the revised GLP Certificate, the NGCMA rationalized the system of inclusion of areas of expertise, test systems and medical devices applicable for non-clinical studies.



ANNEXURE 1. GLP Certificate (contd.)

**National Good Laboratory Practice Compliance  
Monitoring Authority**

**Certificate of GLP Compliance**



GOVERNMENT OF INDIA  
Department of Science and Technology  
Technology Bhawan, New Mehrauli Road, New Delhi-110016  
[www.dst.gov.in/ngcma](http://www.dst.gov.in/ngcma)



ANNEXURE 1. GLP Certificate (contd.)

  
  
राष्ट्रीय उत्तम प्रयोगशाला पद्धति (जी एल पी) अनुपालन निगरानी प्राधिकरण (एन जी सी एम ए)  
विज्ञान और प्रौद्योगिकी विभाग  
भारत सरकार

**जी एल पी अनुपालन प्रमाण-पत्र**  
प्रमाणित किया जाता है कि

**यूरोफिन्स एडविन्स लिमिटेड**  
प्लॉट नं. 21 एवं 22, फेज-II, पोस्ट बॉक्स नं.- 5813  
पीन्य इंडस्ट्रियल एरिया, बंगलुरु - 560058, कर्नाटक (भारत)

एनजीसीएमए की प्रलेख संख्या जीएलपी-101 "जाँच सुविधा केंद्र द्वारा जीएलपी प्रमाणीकरण की प्राप्ति एवं अनुरक्षण से संबंधित एनजीसीएमए के निबंधन एवं शर्तों" और जीएलपी के ऑइसीडी के सिद्धांतों का अनुपालन करने वाला जीएलपी प्रमाणित जाँच सुविधा केंद्र है।

यह जाँच सुविधा केंद्र निम्नलिखित जाँच/अध्ययन संचालित करता है:

- भौतिक-रासायनिक जाँच (पाँच वेच के विश्लेषण सहित)
- विमाकता अध्ययन
- उत्पत्ति-निर्णयता अध्ययन
- जलीय एवं स्थलीय जीवों के संबंध में पर्यावरणीय विषाक्तता अध्ययन
- जल, मृदा और वायु में व्यवहार संबंधी अध्ययन: जैवसंवयन
- अवशेष अध्ययन
- विश्लेषणात्मक एवं नैदानिक रासायनिक जाँच
- अन्य

विशेषज्ञता के विशिष्ट क्षेत्रों, जाँच मदों और जाँच प्रणालियों की सूची अनुलग्नक में दी गई है।  
वैधता की अवधि: 7 नवम्बर, 2020 - 6 नवम्बर, 2023

प्रमाण पत्र सं.: जी एल पी/सी-155/2021  
जारी करने की तारीख: 13-01-2021

  
(डॉ. नीरज शर्मा)  
प्रमुख, एनजीसीएमए



ANNEXURE 1. GLP Certificate (contd.)





ANNEXURE 1. GLP Certificate (contd.)

National GLP Compliance Monitoring Authority (NGCMA)

**Annexure to Certificate of GLP Compliance No. GLP/C-155/2021**

**Areas of Expertise:**

• **Physical-chemical Testing (Including Five Batch Analysis)**

• **Toxicity Studies**

- o Acute Toxicity
- o Carcinogenicity
- o Dermal Toxicity
- o Developmental and Reproductive Toxicity
- o Eye Irritation
- o Inhalation Toxicity
- o Repeated Dose Toxicity
- o Skin Irritation/ Corrosion
- o Skin Sensitization

• **Mutagenicity Studies**

- o Bacterial Reverse Mutation (AMES) Test
- o Cell Gene Mutation Test
- o Chromosomal Aberration Test (*in vitro* and *in vivo*)
- o Micronucleus Test (*in vitro* and *in vivo*)

• **Environment Toxicity Studies on Aquatic and Terrestrial Organisms**

• **Studies on Behavior in Water, Soil and Air; Bioaccumulation**

• **Residue Studies**

• **Analytical and Clinical Chemistry Testing**

• **Others**

- o Bioanalysis
- o Drug Metabolism & Pharmacokinetic (DMPK)
- o Safety pharmacology
- o Toxicokinetics and Immunogenicity analysis of Biologics

**Test Item (s) :** Agrochemicals, Cosmetics Products, Feed Additives, Food Additives, Industrial Chemicals, Medical Devices (*Applicable only for Bio-compatibility, not applicable for Batch Release parameters required as per MDR, 2017*) and Pharmaceuticals (Human and Veterinary).

**Test System (s) :** Algae, Cell Lines, Chicken, Daphnia, Dog, Earthworm, *Escherichia coli*, Fresh Water Fish, Goat, Guinea Pig, Honey Bee, Mice, Pigeon, Quail, Rabbit, Rat, *Salmonella typhimurium*.



**(Dr. Neeraj Sharma)**  
Head, NGCMA



**ANNEXURE 2. Historical Control Data**

**HISTORICAL CONTROL DATA FOR CLINICAL PATHOLOGY PARAMETERS**

**Hematology - Males**

Laboratory		PSL <sup>1</sup>			CRL <sup>2</sup>		
Test	Unit	N	Mean	Range	N	Mean	Range
Red Blood Cell Count (RBC)	x 10 <sup>6</sup> /µL	202	8.93	7.73-10.08	-	-	-
Hemoglobin (HGB)	g/dL	202	15.9	13.7-19.1	464	15.35	14.70-16.60
Hematocrit (HCT)	%	202	49.5	43.9-55.3	464	43.25	28.30-49.20
Mean Corpuscular (cell) volume (MCV)	fL	202	55.6	50.4-62.4	464	54.01	51.70-58.40
Mean Corpuscular (cell) hemoglobin (MCH)	pg	202	17.8	15.4-21.6	464	18.43	17.70-19.00
Mean Corpuscular (cell) hemoglobin concentration (MCHC)	g/dL	202	32.0	29.9-36.9	-	-	-
Red Cell Distribution Width (RDW)	%	202	13.5	10.9-17.2	-	-	-
Platelet Count (PLT)	x 10 <sup>3</sup> /µL	202	1095	650-1517	-	-	-
White Blood Cell Count (WBC)	x 10 <sup>3</sup> /µL	202	12.26	5.66-24.27	-	-	-
Absolute Neutrophil (ANEU)	x 10 <sup>3</sup> /µL	202	1.88	0.65-8.79	464	1.33	0.91-1.65
Absolute Lymphocyte (ALYM)	x 10 <sup>3</sup> /µL	202	9.64	4.17-20.00	464	9.21	8.10-10.65
Absolute Monocyte (AMON)	x 10 <sup>3</sup> /µL	202	0.34	0.10-0.83	464	0.27	0.14-0.52
Absolute Eosinophil (AEOS)	x 10 <sup>3</sup> /µL	202	0.17	0.04-0.64	464	0.14	0.06-0.20
Absolute Basophil (ABAS)	x 10 <sup>3</sup> /µL	202	0.12	0.01-0.32	464	0.04	0.00-0.06
Absolute Large Unstained Cell (ALUC)	x 10 <sup>3</sup> /µL	202	0.11	0.01-0.50	266	0.18	0.13-0.33
Absolute Reticulocyte Count (ARET)	x 10 <sup>3</sup> /µL	202	219.24	43.90-414.70	-	-	-

(-) = No data available

<sup>1</sup> PSL historical control data from CD(SD) rats at approximately 11-22 weeks of age; September 2018 – June 2019.

<sup>2</sup> Charles River Laboratories historical control data from CRL:CD(SD) Rats at 13-22 weeks of age.



ANNEXURE 2 contd. Historical Control Data

**HISTORICAL CONTROL DATA FOR CLINICAL PATHOLOGY PARAMETERS**

**Hematology - Females**

Laboratory Test	Unit	N	PSL <sup>1</sup>		CRL <sup>2</sup>		
			Mean	Range	N	Mean	Range
Red Blood Cell Count (RBC)	x 10 <sup>6</sup> /µL	203	8.34	6.74-9.74	-	-	-
Hemoglobin (HGB)	g/dL	203	15.3	12.5-17.8	479	14.64	13.50-15.50
Hematocrit (HCT)	%	203	46.9	39.4-52.0	479	42.24	39.60-45.90
Mean Corpuscular (cell) volume (MCV)	fL	203	56.3	51.2-61.5	479	55.14	53.50-58.30
Mean Corpuscular (cell) hemoglobin (MCH)	pg	203	18.4	16.4-21.3	479	19.10	18.50-19.50
Mean Corpuscular (cell) hemoglobin concentration (MCHC)	g/dL	203	32.7	30.6-36.1	-	-	-
Red Cell Distribution Width (RDW)	%	203	11.6	10.1-15.8	-	-	-
Platelet Count (PLT)	x 10 <sup>3</sup> /µL	203	1033.9	698.0-1641.0	-	-	-
White Blood Cell Count (WBC)	x 10 <sup>3</sup> /µL	203	7.66	2.75-17.16	-	-	-
Absolute Neutrophil (ANEU)	x 10 <sup>3</sup> /µL	203	1.19	0.31-7.26	479	1.60	0.58-8.10
Absolute Lymphocyte (ALYM)	x 10 <sup>3</sup> /µL	203	6.00	2.1-12.09	479	7.27	5.80-9.25
Absolute Monocyte (AMON)	x 10 <sup>3</sup> /µL	203	0.21	0.04-0.81	479	0.18	0.10-0.25
Absolute Eosinophil (AEOS)	x 10 <sup>3</sup> /µL	203	0.13	0.03-0.34	479	0.11	0.06-0.15
Absolute Basophil (ABAS)	x 10 <sup>3</sup> /µL	203	0.06	0.00-0.23	479	0.03	0.00-0.05
Absolute Large Unstained Cell (ALUC)	x 10 <sup>3</sup> /µL	203	0.07	0.01-0.31	265	0.13	0.07-0.19
Absolute Reticulocyte Count (ARET)	x 10 <sup>3</sup> /µL	203	158.96	2.30-542.70	-	-	-

(-) – No data available

<sup>1</sup> PSL historical control data from CD(SD) rats at approximately 11-22 weeks of age; September 2018 – June 2019.

<sup>2</sup> Charles River Laboratories historical control data from CRL:CD(SD) Rats at 13-22 weeks of age.



ANNEXURE 2 contd. Historical Control Data

**HISTORICAL CONTROL DATA FOR CLINICAL PATHOLOGY PARAMETERS**

**Coagulation**

Males		PSL <sup>1</sup>		
Test	Unit	N	Mean	Range
Prothrombin Time (PT)	sec	162	9.7	8.5-10.7
Activated Partial Thromboplastin Time (APTT)	sec	162	19.9	14.1-37.6
Fibrinogen	mg/dL	15	224.9	192.0-248.0

Females		PSL <sup>1</sup>		
Test	Unit	N	Mean	Range
Prothrombin Time (PT)	sec	162	9.1	8.3-11.0
Activated Partial Thromboplastin Time (APTT)	sec	162	17.6	11.2-30.5
Fibrinogen	mg/dL	15	179.5	163.0-213.0

<sup>1</sup> PSL historical control data from CD(SD) rats at approximately 11-22 weeks of age; September 2018 – June 2019.



ANNEXURE 2 contd. Historical Control Data

**HISTORICAL CONTROL DATA FOR CLINICAL PATHOLOGY PARAMETERS**

**Clinical Chemistry - Males**

Laboratory		PSL <sup>1</sup>			CRL <sup>2</sup>		
Test	Unit	N	Mean	Range	N	Mean	Range
Alanine Aminotransferase (ALT)	U/L	260	35	16-161	666	35.08	27.00-46.00
Albumin (ALB)	g/dL	260	3.8	2.8-4.6	661	3.74	3.30-4.60
Alkaline Phosphates (ALKP)	U/I	260	74	36-143	646	124.67	104.00-160.00
Aspartate Aminotransferase (AST)	U/I	260	83	47-266	666	91.00	77.00-110.00
Calcium (CALC)	mg/dL	260	10.6	9.1-13.4	661	10.17	9.60-10.90
Chloride (CL)	mmol/L	260	101.4	93.1-112.8	658	103.75	101.00-107.00
Cholesterol (CHOL)	mg/dL	260	74	36-163	666	65.42	55.00-89.00
Creatinine (CREA)	mg/dL	260	0.20	0.06-0.47	661	0.57	0.40-0.60
Globulin (GLOB)	g/dL	260	155	77-365	-	-	-
Glucose (GLUC)	mg/dL	260	155	77-365	661	157.33	121.00-197.00
High Density Lipoprotein (HDL)	mmol/L	89	1.0	0.5-2.6	-	-	-
Inorganic Phosphorous (PHOS)	mg/dL	260	7.4	4.6-11.7	636	7.68	7.00-9.50
Low Density Lipoprotein (LDL)	mmol/L	89	0.2	0.1-0.5	-	-	-
Potassium (K)	mmol/L	260	6.16	3.73-11.38	658	5.26	4.60-6.10
Sodium (NA)	mmol/L	260	143	131-157	658	144.83	141.00-149.00
Sorbitol Dehydrogenase (SDH)	U/L	245	10.2	0.2-60.3	-	-	-
Total Bilirubin (TBIL)	mg/dL	260	0.10	0.02-0.90	666	0.60	0.20-1.00
Total Bile Acids (TBA)	µmol/L	103	24	2-163	-	-	-
Total Protein (TP)	g/dL	260	6.3	4.9-7.7	661	6.43	6.00-7.10
Triglycerides (TRIG)	mg/dL	260	98	18-376	661	75.67	62.00-92.00
Urea Nitrogen (BUN)	mg/dL	260	14	8-24	661	13.42	10.00-16.00

<sup>1</sup> PSL historical control data from CD(SD) rats at approximately 11-22 weeks of age; September 2018 – June 2020.

<sup>2</sup> Charles River Laboratories historical control data from CRL:CD(SD) Rats at 13-22 weeks of age.



ANNEXURE 2 contd. Historical Control Data

**HISTORICAL CONTROL DATA FOR CLINICAL PATHOLOGY PARAMETERS**

**Clinical Chemistry - Females**

Laboratory Test	Unit	PSL <sup>1</sup>			CRI <sup>2</sup>		
		N	Mean	Range	N	Mean	Range
Alanine Aminotransferase (ALT)	U/L	248	35	13-182	678	32.33	25.00-45.00
Albumin (ALB)	g/dL	248	4.9	2.6-6.4	673	4.17	3.50-5.30
Alkaline Phosphates (ALKP)	U/L	248	38	15-115	658	82.83	65.00-117.00
Aspartate Aminotransferase (AST)	U/L	248	86	42-341	678	92.83	72.00-116.00
Calcium (CALC)	mg/dL	248	10.7	7.7-15.5	673	10.28	9.60-11.20
Chloride (CL)	mmol/L	248	100.7	89.1-114.6	667	104.83	101.00-108.00
Cholesterol (CHOL)	mg/dL	248	90.4	28.0-249.0	678	77.67	66.00-97.00
Creatinine (CREA)	mg/dL	248	0.26	0.11-0.53	673	0.58	0.40-0.70
Globulin (GLOB)	g/dL	247	2.09	1.10-3.60			
Glucose (GLUC)	mg/dL	248	145	87-364	673	159.33	120.00-186.00
High Density Lipoprotein (HDL)	mmol/L	89	1.70	0.59-2.71	-	-	-
Inorganic Phosphorous (PHOS)	mg/dL	248	6.1	2.4-12.4	649	6.57	5.60-8.60
Low Density Lipoprotein (LDL)	mmol/L	89	0.19	0.10-0.38	-	-	-
Potassium (K)	mmol/L	248	5.46	3.49-12.96	667	4.87	4.30-5.90
Sodium (NA)	mmol/L	248	142	128-159	667	143.33	141.00-148.00
Sorbitol Dehydrogenase (SDH)	U/L	244	10.5	0.5-81.1			
Total Bilirubin (BILI)	mg/dL	248	0.09	0.00-0.22	678	1.10	0.20-2.00
Total Bile Acids (TBA)	µmol/L	90	30	3-124	-	-	-
Total Protein (TP)	g/dL	248	7.0	5.1-9.0	673	6.73	6.40-7.50
Triglycerides (TRIG)	mg/dL	248	75	24-934	673	60.75	51.00-75.00
Urea Nitrogen (BUN)	mg/dL	248	15	8-28	673	13.17	11.00-17.00

<sup>1</sup> PSL historical control data from CD(SD) rats at approximately 11-22 weeks of age; September 2018 – June 2020.

<sup>2</sup> Charles River Laboratories historical control data from CRL:CD(SD) Rats at 13-22 weeks of age.



ANNEXURE 2 contd. Historical Control Data

**HISTORICAL CONTROL DATA FOR CLINICAL PATHOLOGY PARAMETERS**

**Urinalysis**

Males		PSL <sup>1</sup>		
Test (Unit)	Unit	N	Mean	Range
Volume (UVOL)	mL	160.0	7.3	0.5-30.0
Log. of Reciprocal of Hydrogen Ion Concentration (pH)	-	190	6.5	5.0-8.5
Specific Gravity (SG)	-	190	1.019	0.503-1.030
Urobilinogen (URO)	EU/dL	190	0.3	0.2-2.0
Protein (UMTP)	mg/dL	120	67	30-300
Ketones (KET)	mmol/L	64	13	5-40

Females		PSL <sup>1</sup>		
Test (Unit)	Unit	N	Mean	Range
Volume (UVOL)	mL	147	6.0	0.5-21.0
Log. of Reciprocal of Hydrogen Ion Concentration (pH)	-	184	6.6	5.0-9.0
Specific Gravity (SG)	-	184	0.997	0.503-1.030
Urobilinogen (URO)	EU/dL	184	0.3	0.2-4.0
Protein (UMTP)	mg/dL	78	75	30-300
Ketones (KET)	mmol/L	3	8	5-15

<sup>1</sup> PSL historical control data from CD(SD) rats at approximately 11-22 weeks of age; September 2018 – June 2019.

## **APPENDIX L: TRANSLOCATION REPORT**

### **PRODUCT IDENTIFICATION**

*L. reuteri* 3630 & *L. reuteri* 3632

Submitted By:  
BioPrimate  
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Study 51122

Translocation Report

September 8, 2021

For: Product Safety Laboratory (in support of Product Safety Laboratory study 55164)  
Raghavendra Gowda

By: BioPrimate

Frank R. Burns, PhD

**Purpose:**

The overall purpose of the study was to determine the safety of two probiotic *Limosiloactobacillus reuteri* (*L. reuteri*) preparations, labeled 1D (strain *L. reuteri* 3630) and 2D (strain *L. reuteri* 3632).

This portion of the study was designed to determine level of bacterial translocation from the intestinal tract to the mesenteric lymph nodes, liver, and blood and if the translocated bacteria were derived from either of two test strains.

**Materials received:** (from Product Safety Labs, Dayton, NJ)

Two Lyophilized test strains were received, refrigerated in 50ML conical tubes. MRS agar plates that were spread plated following homogenization of the tissues at necropsy. Plates were received in anaerobic chambers immediately following 48 hours of incubation at 37 °C. Plates were held overnight at 4 °C maintained under anaerobic conditions and processed the following morning.

**Work performed by BioPrimate.**

Colony morphology was assessed for six characteristics (see appendix one) for all colonies present and colonies were picked and replated. If there were more than 5 colonies of a particular morphology on plates from a single sample only 5 of that morphology were used for further analysis. Colonies were streaked on new MRS agar plates and incubated anaerobically at 37°C for 48 hours (see appendix). Material from the regrown colonies was processed for DNA extraction and the DNA subjected to amplification of the 16s ribosomal RNA gene variable region 4 using the standard primers and methods described by the earth microbiome project (<http://www.earthmicrobiome.org/protocols-and-standards/16s/>). Amplicon libraries were sequenced on an Illumina MiSeq instrument and a taxonomic designation was assigned for each isolate using the Mothur 16s MiSeq analysis pipeline (Kozich et al. Applied and Environmental Microbiology. 79(17):5112-20). By 16S V4 sequence analysis, *L. reuteri* can be differentiated from other species (Figure 1). The 16S sequences from the lyophilized test materials and all *L. reuteri* identified on the plated tissue samples generated identical 16S V4 sequences.

For each tissue sample of origin, morphology was assessed, taxa assigned based on 16S V4, or for *L. reuteri* isolates further refined based on *dlTA* gene sequence and random amplification of polymorphic DNA (RAPD) profiles as shown in Appendix 1 and described below.

select all 100 sequences selected

GenBank Graphics Distance tree of results

Description	Scientific Name	Max Score	Query Cover	E value	Per. Ident	Accession
Lactobacillus reuteri JCM 1112 16S ribosomal RNA gene, partial sequence	Lactobacillus reuteri JCM 1112	464	100%	5e-128	100.00%	MN865144.1
Lactobacillus reuteri JCM 1112 16S ribosomal RNA gene, partial sequence	Lactobacillus reuteri JCM 1112	464	100%	5e-128	100.00%	MN587974.1
Lactobacillus antri JCM 15950 gene for 16S ribosomal RNA, partial sequence	Limosilactobacillus antri	464	100%	5e-128	100.00%	LC480809.1
Lactobacillus frumenti JCM 11122 gene for 16S ribosomal RNA, partial sequence	Limosilactobacillus frumenti	464	100%	5e-128	100.00%	LC480798.1
Lactobacillus panis gene for 16S ribosomal RNA, partial sequence, strain: JCM 11053	Limosilactobacillus panis	464	100%	5e-128	100.00%	LC145560.1
Lactobacillus reuteri gene for 16S ribosomal RNA, partial sequence, strain: JCM 1112	Lactobacillus reuteri JCM 1112	464	100%	5e-128	100.00%	LC145550.1
Lactobacillus caviae strain MOZM2 16S ribosomal RNA, partial sequence	Limosilactobacillus caviae	464	100%	5e-128	100.00%	NR_157747.1
Lactobacillus reuteri complete genome, strain ATCC 53608	Limosilactobacillus reuteri subsp. suis	464	100%	5e-128	100.00%	LN906634.1
Lactobacillus reuteri DSM 20016 16S ribosomal RNA, partial sequence	Limosilactobacillus reuteri subsp. re...	464	100%	5e-128	100.00%	NR_075036.1
Limosilactobacillus reuteri 3c6 16S ribosomal RNA gene, partial sequence	Limosilactobacillus reuteri subsp. p...	464	100%	5e-128	100.00%	MW367860.1
Limosilactobacillus reuteri DSM 20016 16S ribosomal RNA gene, partial sequence	Limosilactobacillus reuteri subsp. re...	464	100%	5e-128	100.00%	MW367846.1
Limosilactobacillus reuteri 100-23 16S ribosomal RNA gene, partial sequence	Limosilactobacillus reuteri subsp. ro...	464	100%	5e-128	100.00%	MW367780.1
Lactobacillus reuteri strain NBRC 15892 16S ribosomal RNA, partial sequence	Limosilactobacillus reuteri	464	100%	5e-128	100.00%	NR_113820.1
Limosilactobacillus sp. c9Ua_26 M 16S ribosomal RNA gene, partial sequence	Limosilactobacillus urinaemulienis	464	100%	5e-128	100.00%	MW016377.1
Limosilactobacillus sp. c11Ua_112 M 16S ribosomal RNA gene, partial sequence	Limosilactobacillus portuensis	464	100%	5e-128	100.00%	MW016036.1
Lactobacillus reuteri DSM 20016 16S ribosomal RNA gene, partial sequence	Limosilactobacillus reuteri subsp. re...	464	100%	5e-128	100.00%	MN038048.1
Limosilactobacillus sp. AP3 16S ribosomal RNA gene, partial sequence	Limosilactobacillus reuteri subsp. ki...	464	100%	5e-128	100.00%	MT823192.1
Limosilactobacillus sp. STM3_1 16S ribosomal RNA gene, partial sequence	Limosilactobacillus rudii	464	100%	5e-128	100.00%	MT823182.1
Limosilactobacillus sp. Lr3000 16S ribosomal RNA gene, partial sequence	Limosilactobacillus albertensis	464	100%	5e-128	100.00%	MT823181.1
Limosilactobacillus sp. WF-MTS-A 16S ribosomal RNA gene, partial sequence	Limosilactobacillus agrestis	464	100%	5e-128	100.00%	MT823179.1
Limosilactobacillus sp. BG-AF3-A 16S ribosomal RNA gene, partial sequence	Limosilactobacillus balticus	464	100%	5e-128	100.00%	MT823145.1
Lactobacillus reuteri JCM 1112 DNA, complete genome	Lactobacillus reuteri JCM 1112	464	100%	5e-128	100.00%	AP007281.1
Lactobacillus reuteri DSM 20016, complete genome	Limosilactobacillus reuteri subsp. re...	464	100%	5e-128	100.00%	CP000705.1
Lactobacillus antri strain Kx146A4 16S ribosomal RNA, partial sequence	Limosilactobacillus antri	464	100%	5e-128	100.00%	NR_027206.1
Lactobacillus frumenti strain TMW 1 666 16S ribosomal RNA, partial sequence	Limosilactobacillus frumenti	464	100%	5e-128	100.00%	NR_025371.1
Lactobacillus panis strain DSM 6035 16S ribosomal RNA, partial sequence	Limosilactobacillus panis	464	100%	5e-128	100.00%	NR_026310.1
Lactobacillus oris strain DSM 4864 16S ribosomal RNA, partial sequence	Limosilactobacillus oris	464	100%	5e-128	100.00%	NR_026309.1
Lactobacillus reuteri DSM 20016 16S ribosomal RNA, partial sequence	Limosilactobacillus reuteri subsp. re...	464	100%	5e-128	100.00%	NR_119069.1
Lactobacillus oris gene for 16S ribosomal RNA, partial sequence, strain: JCM 11028	Limosilactobacillus oris	460	100%	6e-127	99.60%	LC097079.1
Lactobacillus vaginalis gene for 16S ribosomal RNA, partial sequence, strain: JCM 9505	Limosilactobacillus vaginalis	459	100%	2e-126	99.60%	LC096217.1
Limosilactobacillus reuteri ATCC 53608 16S ribosomal RNA gene, partial sequence	Limosilactobacillus reuteri subsp. suis	459	100%	2e-126	99.60%	MW367845.1
Limosilactobacillus sp. WF-MOT-1 16S ribosomal RNA gene, partial sequence	Limosilactobacillus fastidiosus	453	100%	1e-124	99.20%	MT823190.1

Figure 1. By 16s V4 rRNA sequence analysis all *L. reuteri* isolates from this study (test article and tissue derived) were identical. Alignment of this sequence to the NCBI genebank data base shows some *L. reuteri* can be differentiated in this region by a single nucleotide substitution, most fall within a single sequence type indicated by the red box (100% identity)

A multilocus sequence typing (MLST) approach had been developed and the most discriminatory gene in the panel was the D-alanine-D-alanyl carrier protein ligase (*dltA*) gene. This gene clearly discriminates the monophyletic clades associated with host origin of the isolates (Oh et al 2009). Amplification and sequencing of a fragment of this gene was carried out on test article isolates as well as all tissue isolates identified as *L. reuteri* by 16s rRNA V4 sequence.

The two test article showed identical sequence over this region and were consistent with isolates of porcine origin, referred to going forward as genotype 1. By *dltA* gene sequence over half of the *L. reuteri* tissue isolates from the study were different from the test strain, but identical to each other and consistent with isolates of rodent origin. These two *dltA* sequence variants have over a dozen single nucleotide differences over the region sequenced (Figure 2).

Genotype 1 and 2 aligned



Figure 2. Alignment of two *dltA* genotypes found among *L. reuteri* isolates from this study. Genotype 1 is a match to Porcine derived isolates. Genotype 2 is a match to a rodent derived isolates.

**Genotype assignments for *L. reuteri* isolates:** We designated genotypes 1 and 2 based on *dlfA* gene sequence where type 1 represented porcine origin and was consistent with all test article isolates and genotype 2 was distinct and indicated rodent origin.

Taxa assignments of translocated bacteria.

A limitation of this study is that assignment of taxa when more than 5 colonies of a given morphological type were present on plates from a single sample, only 5 representative colonies were picked and analyzed further. The total number of colonies were assigned proportionally to the taxa found among the five representatives. For example, the second colony morphology for mesentery from animal 3826 (see Appendix 1) had a colony count of 15. Upon molecular characterization of five representative colonies 4 were found to be *Lactococcus* and one to be *L. reuteri* genotype 2. The 15 colonies were then 4/5 (12) to genus *Lactococcus* and 1/5 (3) to *L. reuteri* genotype 2. In the event the result is not a whole number, the number was rounded to the nearest whole number.

**Results:**

**Number of animals showing translocation by tissue and group.**

Five animals of each sex were analyzed from each dose group: group1 vehicle control, group 2 low dose, group 3 medium dose and group 4 high dose.

Table 1. Incidence of translocation of any bacteria to tissues by treatment and sex.

Group (treatment and sex) n= 5 for each group	Number of animals with translocated bacteria in blood	Number of animals with translocated bacteria in liver	Number of animals with translocated bacteria in mesentery	Number of animals showing any translocation
1 Male	0	2	4	5
1 Female	1	3	4	5
2 Male	1	1	3	4
2 Female	0	2	3	4
3 Male	0	3	3	4
3 Female	0	2	3	3
4 Male	1	3	5	5
4 Female	0	4	3 (of 4*)	5
Total All Groups	3	20	28	35

\*No evaluable plates received for this tissue from on animal in this group.

Blood

Translocated bacteria were found in one animal each from three groups. This included one vehicle control group. It is likely that these represent environmental contamination of the samples during necropsy or plating (absent clinical findings consistent with bacteremia).

Liver

Translocated bacteria in the liver were found in from one to four animals from each group including three animals from one of the vehicle control groups. Uptake of bacteria by Kupffer cells lining the sinusoids of the liver is a normal physiological response during bacterial translocation. Kupffer cells of the liver

represent 80-90% of all tissue macrophages and are well known to take up bacteria delivered via the portal circulation where they can help orchestrate tolerance or inflammation (Son et al 2010). Differences between vehicle control and other dose groups are not statistically significant.

#### Mesenteric lymph nodes

Translocated bacteria were identified in the mesenteric lymph nodes of both female and male rats from each treatment group with from three to five animals having translocated bacteria in the mesentery. Differences among the groups are not statistically significant with or without separating out animals by sex.

#### Number of animals with translocated bacteria: Overall result

Translocated bacteria were found among both males and females in each group, including vehicle control animals. The number of animals with translocated bacteria in each group of five animals (grouped by treatment and sex) ranged from 3 to 5. When both sexes within a treatment group are considered together translocations were observed in; 10 animals from the vehicle control group, 8 animals from the low dose treatment group and 7 animals from the medium dose treatment group and 10 animals from the high dose treatment group. The differences among groups, either as a whole or when each sex is considered, are not statistically significant.

#### Number of animals with translocated bacteria detected in the mesentery.

In each group of five animals, three to five animals had detectable bacteria in the mesentery. The differences among dose groups, either as a whole or when each sex is considered independently, are not statistically significant.

#### Number of animals with translocated bacteria detected in the Liver.

In each group of five animals, three to five animals at least one, and up to four, animals had detectable bacteria in the liver. The largest difference was between low dose (3 of 10) and high dose (7 of 10) animals. With no vehicle control (4 of 10) and medium dose (5 of 10). The differences among dose groups, either as a whole or when each sex is considered independently, are not statistically significant.

#### Number of animals with translocated bacteria detected in the Blood.

Three animals, one from a vehicle control group, one from the low dose group and one from the high dose group had colonies grow on the blood plates.

One animal from the vehicle control group (#3819) had 16 colonies identified as *Staphylococcus*.

One animal in the low dose group one (#3825) had four colonies, one *Lactobacillus*, two *L. reuteri* genotype 2 (of rodent origin, not test material related) and one of *L. reuteri* genotype 1, consistent with test article origin.

One animal in the high dose group (#3869) had a single colony on the blood plates which types as *Limosilactobacillus* genotype 1, consistent with the yellow phenotype colonies from test article.

Finding culturable bacteria in the blood is unusual. Absent any clinical findings, it is likely that the presence of these colonies on the blood plates are due to environmental contamination during necropsy or plating. These findings were rare (3 of 40 animals overall) and had no apparent association with treatment group.

**Enumeration of translocated bacteria, CFU per gram in tissues.**

Blood enumeration is described in the previous section. Enumeration of bacteria from liver and mesentery is summarized below.

Table 2. Mean and median detected CFU/gram of tissue by treatment and sex. When bacteria were detected the nominal CFU/gram is listed. In instances where no bacteria are detected the limit of detection based on the amount of tissue interrogated is also listed as < the 95% confidence limit of detection.

Group (treatment and sex) n= 5 for each group	Mean CFU/gram in liver	Median CFU/gram in liver	Mean CFU/gram in Mesentery	Median CFU/gram in Mesentery
1 Vehicle Control Male	12	None detected < 33	240	200
1 Vehicle Control Female	40	33	886	300
2 Low Dose Male	13	None detected <33	160	33
2 Low Dose Female	27	None detected <33	100	33
3 Mid Dose Male	53	33	5233	67
3 Mid Dose Female	53	None detected <33	460	267
4 High Dose Male	1067	133	33947*	3667
4 High Dose Female	67	33	3467**	2150**

\*Should be considered a minimum. One animal generated plates with colonies too numerous to accurately count, the count generated was based on identifiable single colonies and represents an estimated minimum.

\*\*Interpretable plates from only 4 animals were received.

**Low dose group comparison to vehicle control group.**

Low dose male and female groups showed equivalent to nominally lower levels of translocation to both mesentery and liver in comparison to vehicle control groups.

**Mid dose group comparison to vehicle control group.**

Mid dose groups showed values not significantly different from vehicle control with the exception of mean CFU in mesentery from mid dose male animals. Occasional findings of a large number of translocated bacteria in a tissue are not abnormal in these studies and they have been observed in vehicle control as well as test article administered groups (Mukherjee et al 2016). The high mean value in group 3 males is driven by such an event, as indicated by the elevated mean, and lack of elevated median value. This is due to the mesentery sample from a single male (#3846) that yielded 775 colonies on the three plates (representing 0.03 grams of tissue) for a CFU/gram of 25,833 for mesentery from that animal.

Taxonomic assignment of the colonies from this sample indicates that only 3 (0.38%) were consistent with a test strain (*L. reuteri* genotype 1) derived bacterium (Table 3 and Appendix 1).

Table 3. Enumeration by taxa of translocated bacteria from animal 3846 mesentery.

Taxa	Number of colonies	Extrapolated CFU/gram
<i>Escherichia/Shigella</i>	733	24,433
<i>Enterococcus</i>	41	1,367
<i>L. reuteri</i> genotype 1	1	33

Given the result from a single sample elevating the mean, the low level of contribution of test article derived bacteria to the translocated population and the finding of such events among vehicle controls in the past, this finding does not raise concerns.

**High dose group comparison to vehicle control group**

Male High Dose comparison to Male Vehicle control.

High dose males exhibit nominally higher CFU means and medians in both liver and mesentery when compared to vehicle control animals.

Table 4. Actual colonies counted by animal for tissues from Male Vehicle Control and Male High Dose Mesentery and Liver samples (see Appendix1).

Vehicle Control Male Mesentery	High Dose Male Mesentery	Vehicle Control Male Liver	High Dose Male Liver
11	110	0	4
6	10	1	0
4	4800	0	147
0	47	1	0
15	125	0	5

These results fail to find a significant difference between vehicle control and high dose groups, with the mesentery results showing a P value of 0.16 and the liver results also generating a P value of 0.16 (students T test). In light of the small N in this study and nominal increase in translocation seen in this group it is suggested that signs of clinical impact in high dose males, particularly animal 3868 (4800 mesentery and 147 liver counts) be carefully checked for. It should be noted that most translocated bacteria in the mesentery were not of test article origin and none of the translocated bacteria in the liver of this animal were of test article origin (Tables 5 and 6).

Table 5. Enumeration by taxa of translocated bacteria from animal 3868 mesentery.

Taxa	Number of colonies	Extrapolated CFU/gram
<i>L. reuteri</i> genotype 2 (not test article derived)	2580	86000
<i>Lactobacillus</i>	1720	57333
<i>L. reuteri</i> genotype 1	375	12500
<i>Ligilactobacillus</i>	120	4000

Table 6. Enumeration by taxa of translocated bacteria from animal 3868 liver:

Taxa	Number of colonies	Extrapolated CFU/gram
<i>Lactobacillus</i>	109	3633
<i>L. reuteri</i> genotype 2 (not test article derived)	28	933
<i>Escherichia/Shigella/</i>	2	67
<i>Ligilactobacillus</i>	1	33
<i>Enterococcus</i>	1	33

Female High Dose comparison to Female Vehicle control.

Table 7. Actual colonies counted by animal for tissues from Female Vehicle Control and Female High Dose Mesentery and Liver samples (see Appendix1).

Vehicle Control Female Mesentery	High Dose Female Mesentery	Vehicle Control Female Liver	High Dose Female Liver
0	92	0	5
4	37	3	3
90	No Plates	0	0
30	0	3	1
9	387	1	1

No statistically significant differences were observed between the female high dose and the female vehicle control group. Additionally, there were no nominal findings indicative of a need for enhanced scrutiny.

**Interpretation.**

Animals that are subject to either physical or chronic psychological stress experience extra intestinal bacterial translocation (Zareie et al 2006, Velin et al 2004, Neal et al 2006). The finding of translocated facultative anaerobes is not unexpected in animals subject to daily gavage over multiple rounds. The frequent finding of translocated bacteria across the vehicle control as well as treatment groups is consistent with expectations. The high levels of *L reuteri* test strains administered in this study, coupled with *Limosilactobacillus* being a commonly translocated genera, makes the finding of the apparent test strains contributing to the translocated bacteria not unexpected. Similar results have been seen in previous studies with high level dosing of frequently translocated genera (Mukerji et al 2016).

In no instances were test article treated group translocated bacterial colony counts significantly different than the counts seen in the same sex vehicle control group. The male high dose group results are nominally higher than the vehicle control group and given the high variance in this type of data as well as the small N for the study a careful evaluation for any clinical abnormality may be warranted.

The test strains *L. reuteri* (genotypes 1) did not translocate in a greater abundance than the endogenous *L. reuteri* (genotype 2).

A low incidence of bacteria found on plates from blood samples (3 of 40 animals) was not associated with treatment and likely resulted from environmental contamination during the study

Absent any pathological findings or other treatment related toxicity, the translocation findings would not indicate the test strains to be harmful.

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Date 07/27/2021

Part 1. Morphological differentiation and selection of isolates for further analysis.

Morphology  
Key

Morphology Key						
Size	Shape	Elevation	Margin	Surface	Opacity	Pigmentation
A Pinpoint	A Punctate	A Flat/invasi	A Entire	A Smooth	A Transparent	Color/clear
B Small	B Circular	B Raised	B Undulate	B Glistening	B Translucent	
C Medium	C Filamentoi	C Convex	C Lobate	C Rough	C Opaque	
D Large	D Irregular	D Pulvinate	D Erode	D Wrinkled		
	E Lobate	E Ulmbonate	E Filamentoi	E Dry		
	F Spindle	F Cratered	F Curled			

Group 1 Males		cfu total	size	shape	elevation	margin	surface	opacity	color	CFU
3806	mes ln	11	c	d	b	a	b	c	yellow	6
			b	b	b	a	b	b	white	2
			b	b	e	a	b	b	white	1
			d	b	b	a	b	c	white	1
			a	a	b	a	b	b	white	1
3806	liver	0								
3806	blood	0								
3807	mes ln	6	c	b	e	b	b	b	white	5
			b	b	b	a	b	c	white	1
3807	liver	1	c	b	e	c	e	b	white	1
3807	blood	0								
3808	mes ln	4	b	a	b	a	b	b	white	2
			b	d	a	b	c	b	white	1
			c	b	e	b	c	b	white	1
3808	liver	0								
3808	blood	0								
3809	mes ln	0								
3809	liver	1	b	b	b	a	b	c	white	1
3809	blood	0								

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3810	mes ln	15	d	b	e	a	b	b	white	4
			d	b	f	a	e	c	white	6
			b	b	e	a	b	c	white	5
3810	liver*	0	* Only 1 plate available for evaluation.							
3810	blood	0								

Group 1 Females

3816	mes ln	0								
3816	liver	0								
3816	blood	0								
3817	mes ln	4	b	b	b	a	b	b	white	3
			c	b	e	c	c	b	white	1
3817	liver	3	a	a	b	a	b	b	white	2
			b	b	b	a	b	c	white	1
3817	blood	0								
3818	mes ln	90	c	d	f	b	c	b	white	39
			b	b	b	a	b	c	orange	1
			c	d	f	c	c	b	white	14
			d	b	a	a	b	b	white	8
			b	b	e	a	a	b	white	24
			b	b	a	a	e	b	white	4
3818	liver	0								
3818	blood	0								
3819	mes ln	30	c	b	f	b	c	b	white	19
			c	b	e	a	a	c	white	10
			a	a	b	a	b	b	white	1
3819	liver	3	b	d	a	b	c	b	white	1
			b	b	b	a	b	c	white	0

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3819	blood	16	c	b	b	a	b	c	white with red center	16
3820	mes ln	9	b	b	b	a	b	b	white	3
			a	a	b	a	b	a	clear	3
			b	b	b	a	a	c	white	3
3820	liver	1	c	b	b	a	b	white	1	
3820	blood	0								

Group 2 Males

3825	mes ln	0								
3825	liver	0								
3825	blood	4	a	a	b	a	b	c	white	4
			Only 2 plates available for evaluation							
3826	mes ln	19	d	b	b	b	b	c	white	4
			c	b	b	a	b	c	white	15
3826	liver	2	a	a	a	a	b	b	white	2
3826	blood	0								
3827	mes ln	0								
3827	liver	0								
3827	blood	0								
3828	mes ln	4	b	b	b	a	a	b	white	2
			c	d	a	a	b	b	white	1
			c	b	e	c	c	b	white	1
3828	liver	0								
3828	blood	0								
3830	mes ln	1	c	b	e	b	e	b	white	1
3830	liver	0								
3830	blood	0								



**Group 2 Females**

3836	mes ln	10	a	b	c	a	a	b	white	5	
			a	a	a	a	a	c	white	3	
			b	b	b	a	b	c	white	2	
3836	liver	0									
3836	blood	0									
3837	mes ln	0									
3837	liver	0									
3837	blood	0									
3838	mes ln	0									
3838	liver	3	d	b	a	b	e	b	white	2	
			a	a	a	a	d	b	white	1	
3838	blood	0									
3839	mes ln	4	b	b	a	a	e	b	white	4	
			Only 2 plates available for evaluation								
3839	liver	0	Only 2 plates available for evaluation								
3839	blood	0									
3840	mes ln	1	c	b	e	a	b	b	white	1	
3840	liver	1	c	b	a	a	e	c	white	1	
3840	blood	0									

**Group 3 Males**

3840	mes ln	775	c	b	b	a	b	b	white	733
			c	b	b	a	b	c	white	41
			c	b	b	a	b	c	yellow	1
3840	liver	9	d	b	a	a	b	b	white	8
			b	b	b	a	e	b	white	1
3840	blood	0								

3847	mes ln	0								
3847	liver	0								
Only 2 plates available for evaluation										
3847	blood	0								
3848	mes ln	0								
3848	liver	1	b	b	e	a	c	b	white	1
3848	blood	0								
3849	mes ln	2	c	b	f	a	e	c	white	1
			d	b	b	a	b	c	white	1
3849	liver	0								
3849	blood	0								
3850	mes ln	8	b	b	e	c	c	b	white	5
			b	b	e	a	b	b	white	3
3850	liver	3	a	a	b	a	b	b	white	2
			c	b	e	c	e	b	white	1
3850	blood	0								

**Group 3 Females**

3856	mes ln	0								
3856	liver	0								
3856	blood	0								
3857	mes ln	20	a	a	a	a	b	b	white	1
			b	b	e	c	c	c	white	5
			c	c	a	c	c	b	white	13
			c	b	a	c	c	b	white	1
3857	liver	7	d	b	a	a	e	b	white	4
			c	b	b	a	b	c	white	3
3857	blood	0								
3858	mes ln	41	b	b	b	a	b	c	white	11

			d	b	b	a	b	b	white	13
			c	b	e	b	c	b	white	10
			b	b	b	b	b	b	white	7
3858	liver	0								
			* Only 1 plate available for evaluation.							
3858	blood	0								
3859	mes ln	0								
3859	liver	0								
3859	blood	0								
3860	mes ln	8	c	b	a	a	e	b	white	6
			c	b	b	a	b	c	white	2
3860	liver	1	d	b	a	a	e	b	white	1
3860	blood	0								

**Group 4 Males**

3866	mes ln	110	c	b	b	a	b	c	white	28
			d	b	b	a	b	c	yellow	2
			c	b	b	a	b	b	white	80
3866	liver	4	c	b	c	a	b	c	orange	3
									yellow	1
3866	blood	0								
			* Only 1 plate available for evaluation.							
3867	mes ln	10	c	b	a	c	e	b	white	4
			c	b	b	a	b	c	orange	3
			c	b	b	a	b	c	white	3
3867	liver	0								
			* Only 1 plate available for evaluation.							
3867	blood	0								
3868	mes ln	~4800	?	b	b	a	b	c	white	~120

	To numerous for accurate count		?	b	a	a	a	b	white	4300
			?	b	b	a	b	c	yellow	~375
3868	liver	147	d	b	c	a	b	c	yellow	5
			c	b	b	a	b	c	white	6
			d	b	b	a	b	c	white	136
3868	blood	0								
3869	mes ln	47	c	b	e	a	b	b	white	15
			c	b	b	a	b	c	white	1
			c	d	f	b	c	b	white	14
			a	a	b	a	b	c	white	1
			e	d	a	c	c	b	white	16
3869	liver	0								
3869	blood	1	b	b	a	a	b	c	red	1
3870	mes ln	125	d	b	c	a	b	c	white	5
			c	b	b	a	b	b	clear	120
3870	liver	5	c	b	b	a	b	c	white	2
			c	d	a	a	a	a	transparent	2
			c	b	b	a	b	a	transparent	1
3870	blood	0								

**Group 4 Females**

3876	mes ln	92	c	b	e	a	c	b	white	24
			a	a	b	a	b	b	white	35
			c	b	e	c	c	b	white	5
3876	liver	5	b	d	e	b	c	b	white	1
			c	b	b	a	b	b	white	1
			b	b	e	a	a	b	white	3
3876	blood	0								

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3877	mes ln	37	d	b	a	a	b	b	white	37
3877	liver	3	d	b	b	a	b	b	white	1
			c	d	b	a	b	b	white	1
			b	b	b	a	b	b	clear	1
3877	blood	0								
3878	mes ln	No plates available for evaluation.								
3878	liver	0								
3878	blood	0								
3879	mes ln	0								
3879	liver	1	b	a	b	a	b	b	white	1
3879	blood	0								
3880	mes ln	387	c	b	f	a	b	b	white	183
			c	b	b	a	b	b	white	36
			b	b	b	a	b	c	white	168
3880	liver	1	c	b	b	a	b	b	white	1
3880	blood	0								

Appendix Part 2. Taxonomic assignment based on molecular typing. Genus level with sub species genotype for *L. reuteri*.

3806	mes ln	6	<i>L. reuteri</i> Genotype 1A, 5 of 5				
		2	<i>Morganella</i> , 1 of 2	<i>Staphylococcus</i> 1 of 2			
		1	<i>Escherichia/Shigella</i>				
		1	<i>L. reuteri</i> Genotype 1B				
		1	<i>Staphylococcus</i>				
	liver						
	blood						
3807	mes ln	5	<i>L. reuteri</i> genotype 2, 3 of 5	<i>Lactobacillus</i> 2 of 5			
		1	<i>L. reuteri</i> genotype 2				
		1	<i>Lactobacillus</i>				
	liver						
	blood						
3808	mes ln	2	<i>Corynebacterium</i> , 2 of 2				
		1	<i>Lactobacillus</i>				
		1	<i>L. reuteri</i> genotype 2				
	liver						
	blood						
3809	mes ln	1	<i>Lactococcus</i>				
	liver						
	blood						
3810	mes ln	4	<i>Ligilactobacillus</i> 3 of 4	<i>L. reuteri</i> genotype 2, 1 of 4			
		6	<i>Lactococcus</i> 4 of 5	<i>L. reuteri</i> genotype 2, 1 of 5			
		5	<i>Lactobacillus</i> 1 of 5	Mixed sequences 1 of 5	<i>Lactobacillus</i> , 1 of 5	<i>Ligilactobacillus</i> , 1 of 5	<i>Streptococcus</i> 1 of 5
	liver*						
	* 1 plate available						
	blood						
<b>Group 1 Female</b>							
3816	mes ln						
	liver						
	blood						
3817	mes ln	3	<i>Lactococcus</i> , 1 of 3	<i>Streptococcus</i> 2 of 3			
		1	<i>Ligilactobacillus</i>				
		2	<i>Lactobacillus</i> 1 of 2	Mixed sequences 1 of 2			
		1	<i>Enterococcus</i>				
	liver						
	blood						
3818	mes ln	39	<i>Lactobacillus</i> 5 of 5				
		1	<i>L. reuteri</i> Genotype 1A				
		14	<i>Staphylococcus</i> , 2 of 3	<i>Lactobacillus</i> , 2 of 5	<i>L. reuteri</i> genotype 2, 1 of 5		
		8	<i>Escherichia/Shigella</i> , 5 of 5				

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		24	<i>Lactobacillus</i> 5 of 5		
		4	<i>Lactobacillus</i> 3 of 4	<i>Streptococcus</i> , 1 of 4	
	liver				
	blood				
3819	mes In	19	<i>Lactobacillus</i> 5 of 5		
		10	<i>Lactobacillus</i> 3 of 5	<i>L. reuteri</i> genotype 2, 2 of 5	
		1	<i>Streptococcus</i>		
	liver*	1	<i>Streptococcus</i>		
	* 2 plates available				
	blood	2	<i>Lactococcus</i> 1 of 2	<i>Streptococcus</i> , 1 of 2	
3820	mes In	16	<i>Staphylococcus</i> 5 of 5		
		3	<i>Bacteroides</i> 2 of 3	<i>Escherichia/Shigella</i> , 1 of 3	
		3	<i>Bacteroides</i> 3 of 3		
		3	<i>Enterococcus</i> 1 of 3	<i>Staphylococcus</i> 1 of 3	<i>Escherichia/Shigella</i> 1 of 3
	liver	1	<i>Morganella</i>		
	blood				
<b>Group 2 Male</b>					
3825	mes In				
	liver				
	blood*	4	<i>L. reuteri</i> genotype 2, 2 of 4	<i>Lactobacillus</i> , 1 of 4	<i>L. reuteri</i> genotype 1B, 1 of 4
	2 plates available				
3826	mes In	4	<i>Lactobacillus</i> 3 of 4	<i>Proteus</i> 1 of 4	
		15	<i>Lactococcus</i> 4 of 5	<i>L. reuteri</i> genotype 2, 1 of 5	
	liver	2	<i>Lactobacillus</i> 1 of 2	<i>Lactococcus</i> 1 of 2	
	blood				
3827	mes In				
	liver				
	blood				
3828	mes In	2	<i>Streptococcus</i> 2 of 2		
		1	<i>Morganella</i>		
		1	<i>L. reuteri</i> genotype 1B		
	liver				
	blood				
3830	mes In	1	<i>Bacillus</i>		
	liver				
	blood				
<b>Group 2 Female</b>					
3836	mes In	5	<i>Streptococcus</i> 4 of 5	<i>Lactococcus</i> 1 of 5	
		3	<i>Streptococcus</i> 2 of 3	<i>Enterococcus</i> , 1 of 3	
		2	<i>Enterococcus</i> 2 of 2		

	liver				
	blood				
3837	mes In				
	liver				
	blood				
3838	mes In				
	liver	2	<i>Morganella, 2 of 2</i>		
		1	<i>Streptococcus</i>		
	blood				
3839	mes In*	4	<i>Staphylococcus, 2 of 4</i>	<i>Streptococcus, 2 of 4</i>	
	* 2 plates available				
	liver*				
	* 2 plates available				
	blood				
3840	mes In	1	<i>L. reuteri genotype 2</i>		
	liver	1	<i>L. reuteri genotype 2</i>		
	blood				
<b>Group 3 Male</b>					
3846	mes In	733	<i>Escherichia/Shigella, 5 of 5</i>		
		41	<i>Enterococcus 5 of 5</i>		
		1	<i>L. reuteri Genotype 1A</i>		
	liver	8	<i>L. reuteri genotype 2, 1 of 5</i>	<i>L. reuteri genotype 1B, 1 of 5</i>	<i>Escherichia/Shigella, 3 of 5</i>
		1	<i>Lactococcus</i>		
	blood				
3847	mes In				
	liver*				
	* 2 plates available				
	blood				
3848	mes In				
	liver	1	<i>Streptococcus</i>		
	blood				
3849	mes In	1	<i>Lactobacillus</i>		
		1	<i>Escherichia/Shigella</i>		
	liver				
	blood				
3850	mes In	5	<i>Ligilactobacillus, 5 of 5</i>		
		3	<i>L. reuteri genotype 1B, 2 of 3</i>	<i>Streptococcus, 1 of 3</i>	
	liver	2	<i>Corynebacterium, 2 of 2</i>		
		1	<i>Proteus</i>		

blood				
<b>Group 3 Female</b>				
3856	mes In			
	liver			
	blood			
3857	mes In	1	<i>Lactococcus</i>	
		5	<i>Ligilactobacillus</i> , 2 of 5	<i>L. reuteri</i> genotype 2, 2 of 5
		13	<i>Lactobacillus</i> , 5 of 5	<i>Bacillus</i> , 1 of 5
		1	<i>Ligilactobacillus</i>	
	liver	4	<i>Lactobacillus</i> , 2 of 4	<i>Ligilactobacillus</i> , 1 of 4
		3	<i>Streptococcus</i> , 3 of 3	<i>Mixed sequences</i> , 1 of 4
	blood			
3858	mes In	11	<i>Enterococcus</i> , 3 of 5	<i>Lactobacillus</i> , 1 of 5
		13	<i>Escherichia/Shigella</i> ', 5 of 5	<i>L. reuteri</i> genotype 2, 1 of 5
		10	<i>Lactobacillus</i> , 4 of 5	<i>L. reuteri</i> genotype 2, 1 of 5
		7	<i>Lactobacillus</i> , 2 of 5	<i>Escherichia/Shigella</i> ', 3 of 5
	liver*			
	* 1 plate available			
	blood			
3859	mes In			
	liver			
	blood			
3860	mes In	6	<i>Morganella</i> 3 of 5	<i>Enterococcus</i> , 1 of 5
		2	<i>Enterococcus</i> 1 of 2	<i>Morganella</i> 1 of 2
	liver	1	<i>Lactobacillus</i>	<i>Escherichia/Shigella</i> ', 1 of 5
	blood			
<b>Group 4 Male</b>				
3866	mes In	28	<i>Enterococcus</i> , 4 of 5	<i>Streptococcus</i> , 1 of 5
		2	<i>L. reuteri</i> Genotype 1A, 2 of 2	
		80	<i>Morganella</i> , 1 of 5	<i>Escherichia/Shigella</i> ', 4 of 5
	liver	3	<i>L. reuteri</i> Genotype 1A, 3 of 3	
		1	<i>L. reuteri</i> Genotype 1A	
	blood *			
	* 1 plate available			
3867	mes In	4	<i>Ligilactobacillus</i> , 2 of 4	<i>Lactobacillus</i> , 2 of 4
		3	<i>L. reuteri</i> Genotype 1A, 3 of 3	
		3	<i>L. reuteri</i> genotype 1B, 3 of 3	
	liver *			
	* 1 plate available			
	blood			
3868	mes In *	~ 120	<i>Ligilactobacillus</i> , 5 of 5	

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estimated TNTC	~4300	<i>L. reuteri</i> genotype 2, 3 of 5	<i>Lactobacillus</i> , 2 of 5			
	~375	<i>L. reuteri</i> Genotype 1A, 5 of 5				
liver	5	<i>L. reuteri</i> Genotype 1A, 5 of 5				
	6	<i>Enterococcus</i> 1 of 5	<i>Ligilactobacillus</i> , 1 of 5	<i>L. reuteri</i> genotype 2, 1 of 5	<i>Escherichia/Shigella</i> , 2 of 5	
	136	<i>Lactobacillus</i>	<i>Lactobacillus</i>	<i>L. reuteri</i> genotype 2	<i>Lactobacillus</i>	<i>Lactobacillus</i>
3869	mes in	15 <i>Escherichia/Shigella</i> , 5 of 5				
	1	<i>Ligilactobacillus</i>				
	14	<i>Lactobacillus</i> , 5 of 5				
	1	<i>Lactococcus</i>				
	16	<i>L. reuteri</i> genotype 2, 4 of 5	<i>Lactobacillus</i> , 1 of 5			
liver						
3870	blood	1 <i>L. reuteri</i> Genotype 1A				
	mes in	5 <i>Ligilactobacillus</i> , 5 of 5	<i>Ligilactobacillus</i>	<i>Ligilactobacillus</i>	<i>Ligilactobacillus</i>	<i>Ligilactobacillus</i>
	120	<i>Streptococcus</i> , 1 of 5	<i>Lactococcus</i> , 1 of 5	<i>Escherichia/Shigella</i> , 3 of 5		
liver	2	<i>Ligilactobacillus</i> , 1 of 2	<i>Enterococcus</i> , 1 of 2			
	2	<i>Lactobacillus</i> 1 of 2	<i>Escherichia/Shigella</i> , 1 of 2			
	1	<i>Morganella</i>				
blood						
<b>Group 4 Male</b>						
3876	mes in	24 <i>Enterococcus</i> , 3 of 5	<i>Escherichia/Shigella</i> , 2 of 5			
	35	<i>Enterococcus</i> , 2 of 5	<i>Ligilactobacillus</i> , 2 of 5	<i>L. reuteri</i> genotype 1B, 1 of 5		
	5	<i>Ligilactobacillus</i> 3 of 5	<i>L. reuteri</i> genotype 1B, 1 of 5	<i>Lactobacillus</i> , 1 of 5		
liver	1	<i>Lactobacillus</i>				
	1	<i>Lactobacillus</i>				
	3	<i>L. reuteri</i> genotype 2, 1 of 3	<i>Streptococcus</i> , 2 of 3			
3877	blood					
	mes in	37 <i>Lactobacillus</i> , 4 of 5	<i>Escherichia/Shigella</i> , 1 of 5			
liver	1	<i>Bacteroides</i>				
	1	<i>Streptococcus</i>				
	1	<i>Bacteroides</i>				
3878	blood					
	mes in					
	liver					
	blood*					
	* 1 plate					
	available					
3879	mes in					
	liver	1 <i>Streptococcus</i>				
	blood					
3880	mes in	183 <i>Lactobacillus</i> 5 of 5				

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	36	<i>Escherichia/Shigella</i> , 5 of 5	
	168	<i>Enterococcus</i> , 4 of 5	<i>L. reuteri</i> genotype 2, 1 of 5
liver	1	<i>Streptococcus</i>	
blood			

Appendix part 3.

Enumeration by Taxa

Group 1		plate	Calculate/Gram or	Taxa	/Gram	Taxa	/Gram	Taxa	/Gram
Male		count	ML						
3806	mes In	11	367	<i>L. reuteri</i> genotype 1A	200	<i>Morganella</i>	33	<i>Staphylococcus</i>	67
				<i>L. reuteri</i> genotype 1B	33	<i>Escherichia/Shigella'</i>	33		
3806	liver	0							
3806	blood	0							
3807	mes In	6	200	<i>L. reuteri</i> genotype 2	133	<i>Lactobacillus</i>	67		
3807	liver	1	33	<i>Lactobacillus</i>	33				
3807	blood	0							
3808	mes In	4	133	<i>Corynebacterium</i>	67	<i>Lactobacillus</i>	33	<i>L. reuteri</i> genotype 2	33
3808	liver	0							
3808	blood	0							
3809	mes In	0							
3809	liver	1	33	<i>Laetococcus</i>	33				
3809	blood	0							
3810	mes In	15	500	<i>Ligilactobacillus</i>	133	<i>Lactococcus</i>	167	<i>L. reuteri</i> genotype 2	67
				<i>Lactobacillus</i>	67	<i>Streptococcus</i>	33	Mixed colony	33
3810	liver*	0							
3810	* Only 1 plate available for evaluation.								
3810	blood	0							
Group 1									
Female									
3816	mes In	0							
3816	liver	0							
3816	blood	0							
3817	mes In	4	133	<i>Laetococcus, 1 of 3</i>	33	<i>Streptococcus</i>	67	<i>Ligilactobacillus</i>	33

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3817	liver	3	100	<i>Lactobacillus</i>	33	<i>Enterococcus</i>	33	Mixed colony	33
3817	blood	0							
3818	mes In	90	3000	<i>Lactobacillus</i>	2420	<i>Staphylococcus</i>	187	<i>Escherichia/Shigella</i>	267
				<i>L. reuteri</i> genotype 2	93	<i>Streptococcus</i>	33		
3818	liver	0							
3818	blood	0							
3819	mes In	30	1000	<i>Lactobacillus</i>	833	<i>L. reuteri</i> genotype 2	133	<i>Streptococcus</i>	33
3819	liver*	3	150	<i>Streptococcus</i>	100	<i>Lactococcus</i>	50		
				* Only 2 plates available for evaluation					
3819	blood	16	53						
3820	mes In	9	300	<i>Bacteroides</i>	167	<i>Enterococcus</i>	33	<i>Staphylococcus</i>	33
				<i>Escherichia/Shigella</i>	67				
3820	liver	1	33	<i>Morganella</i>	33				
3820	blood	0							

Group 2  
Male

3825	mes In	0							
3825	liver	0							
3825	blood*	4	200	<i>L. reuteri</i> genotype 2	100	<i>Lactobacillus</i>	50	<i>L. reuteri</i> genotype 1B	50
				* Only 2 plates available for evaluation					
3826	mes In	19	633	<i>Lactococcus</i>	400	<i>Lactobacillus</i>	100	<i>L. reuteri</i> genotype 2	100
				<i>Proteus</i>	33				
3826	liver	2	67	<i>Lactobacillus</i>	33	<i>Lactococcus</i>	33		
3826	blood	0							
3827	mes In	0							
	liver	0							
	blood	0							
3828	mes In	4	133	<i>Streptococcus</i>	67	<i>Morganella</i>	33	<i>L. reuteri</i> genotype 1B	33
3826	liver	0							

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3826	blood	0				
3830	mes In	1	33	<i>Bacillus</i>	33	
3830	liver	0				
3830	blood	0				

Group 2  
Female

3836	mes In	10	333	<i>Streptococcus</i>	200	<i>Enterococcus</i>	100	<i>Lactococcus</i>	33
3836	liver	0							
3836	blood	0							
3837	mes In	0							
3837	liver	0							
3837	blood	0							
3838	mes In	0							
3838	liver	3	100	<i>Morganella</i>	67	<i>Streptococcus</i>	33		
3838	blood	0							
3839	mes In*	4	200	<i>Staphylococcus</i>	100	<i>Streptococcus</i>	100		
				* Only 2 plates available for evaluation					
3839	liver*	0							
				* Only 2 plates available for evaluation					
3839	blood	0							
3840	mes In	1	33	<i>L. reuteri</i> genotype 2	33				
3840	liver	1	33	<i>L. reuteri</i> genotype 2	33				
3840	blood	0							

Group 3  
Male

3846	mes In	775	25833	<i>Escherichia/Shigella</i>	24433	<i>Enterococcus</i>	1367	<i>L. reuteri</i> genotype 1A	33
3846	liver	9	300	<i>Escherichia/Shigella</i>	160	<i>L. reuteri</i> genotype 2	53	<i>L. reuteri</i> genotype 1B	53

				<i>Lactococcus</i>	33			
3846	blood	0						
3847	mes In	0						
3847	liver*	0						
				* Only 2 plates available for evaluation				
3847	blood	0						
3848	mes In	0						
3848	liver	1	33	<i>Streptococcus</i>	33			
3848	blood	0						
3849	mes In	2	67	<i>Lactobacillus</i>	33	<i>Escherichia/Shigella/</i>	33	
3849	liver	0						
3849	blood	0						
3850	mes In	8	267	<i>Ligilactobacillus</i>	167	<i>L. reuteri</i> genotype 1B	67	<i>Streptococcus</i> 33
3850	liver	3	100	<i>Corynebacterium</i>	67	<i>Proteus</i>	33	
3850	blood	0						

Group 3  
Female

3856	mes In	0						
3856	liver	0						
3856	blood	0						
3857	mes In	20	667	<i>Lactobacillus</i>	433	<i>Ligilactobacillus</i>	100	<i>L. reuteri</i> genotype 2 67
				<i>Lactococcus</i>	33	<i>Bacillus</i>	33	
3857	liver	7	233	<i>Streptococcus</i>	100	<i>Lactobacillus</i>	67	<i>Ligilactobacillus</i> 33
				Mixed sequences	33			
3857	blood	0						
3858	mes In	41	1367	<i>Lactobacillus</i>	433	<i>Escherichia/Shigella/</i>	573	<i>Enterococcus</i> 220
				<i>L. reuteri</i> genotype 2	140			
3858	liver*	0						
				* Only 1 plate available for evaluation				

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3858	blood	0							
3859	mes ln	0							
3859	liver	0							
3859	blood	0							
3860	mes ln	8	267	<i>Morganella</i>	153	<i>Enterococcus</i>	73	<i>Escherichia/Shigella</i>	40
3860	liver	1	33	<i>Lactobacillus</i>					
3860	blood	0							

Group 4  
Male

3866	mes ln	110	3667	<i>Enterococcus</i>	747	<i>Escherichia/Shigella/</i>	2133	<i>Morganella</i>	533
				<i>Streptococcus</i>	187	<i>L. reuteri</i> genotype 1A	67		
3866	liver	4	133	<i>L. reuteri</i> genotype 1A	133				
3866	blood								
3866	*	0							
				* Only 1 plate available for evaluation					
3867	mes ln	10	333	<i>Ligilactobacillus</i>	67	<i>Lactobacillus</i>	67		
				<i>L. reuteri</i> genotype 1A	100	<i>L. reuteri</i> genotype 1B	100		
	liver *	0							
				* Only 1 plate available for evaluation					
	blood	0							
3868	mes ln								
	*	-4800	160000	<i>L. reuteri</i> genotype 2	86000	<i>Lactobacillus</i>	57333	<i>L. reuteri</i> genotype 1A	12500
				<i>Ligilactobacillus</i>	4000				
				*Too numerous for accurate count					
3868	liver	147	4900	<i>Lactobacillus</i>	3627	<i>L. reuteri</i> genotype 2	947	<i>L. reuteri</i> genotype 1A	167
				<i>Enterococcus</i>	40	<i>Ligilactobacillus</i>	40	<i>Escherichia/Shigella</i>	80
3868	blood	0							
3869	mes ln	47	1567	<i>Escherichia/Shigella</i>	500	<i>Lactobacillus</i>	467	<i>L. reuteri</i> genotype 2	533
				<i>Ligilactobacillus</i>	33	<i>Lactococcus</i>	33		

3869	liver	0						
3869	blood	1	3	<i>L. reuteri</i> genotype 1A	3			
3870	mes In	125	4166	<i>Escherichia/Shigella</i>	2400	<i>Lactococcus</i>	800	<i>Streptococcus</i> 800
				<i>Ligilactobacillus</i>	167			
3870	liver	5	167	<i>Ligilactobacillus</i>	33	<i>Enterococcus</i>	33	<i>Lactobacillus</i> 33
				<i>Escherichia/Shigella</i>	33	<i>Morganella</i>	33	
3870	blood	0						

Group 4  
Female

3876	mes In	92	3067	<i>Enterococcus</i> ,	1507	<i>Escherichia/Shigella</i>	693	<i>Ligilactobacillus</i> 567
				<i>L. reuteri</i> genotype 1B	267	<i>Lactobacillus</i> ,	33	
3876	liver	5	167	<i>Streptococcus</i>	67	<i>Lactobacillus</i>	67	<i>L. reuteri</i> genotype 2 33
3876	blood	0						
3877	mes In	37	1233	<i>Lactobacillus</i>	987	<i>Escherichia/Shigella</i>	247	
3877	liver	3		<i>Bacteroides</i>	67	<i>Streptococcus</i>	33	
3877	blood	0						
3878	mes In	Not Analyzed - plates available for evaluation						
3878	liver	0						
3878	blood*	0						
		* Only 1 plate available for evaluation						
3879	mes In	0						
3879	liver	1	33					
3879	blood	0						
3880	mes In	387	12900	<i>Lactobacillus</i>	6100	<i>Enterococcus</i>	4480	<i>Escherichia/Shigella</i> 1200
				<i>L. reuteri</i> genotype 2	1120			
3880	liver	1	33	<i>Streptococcus</i>	33			
3880	blood	0						

