CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208870Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Memorandum to Consult Request from Biopharmaceutics

FROM:	Satish Misra, Ph. D., Primary Statistical Reviewer, DB1
THROUGH:	Jyoti Zalkikar, Ph. D., Secondary Statistical Reviewer, DB1
THROUGH:	Peiling Yang, Ph. D., Tertiary Statistical Reviewer, DB1
APPLICATION #:	NDA 208870
REQUESTED BY:	Poonam R. Delvadia, Ph.D., Biopharmaceutics Reviewer, Branch 3\ONDP\OPQ\CDER\FDA
PRODUCT:	Tc99m Exametazime Injection
SPONSOR:	Jubilant Draximage, Inc.
DATE OF SUBMISSION:	July 19, 2016
PDUFA DATE:	May 19, 2017
EDR LOCATION:	\\CDSESUB1\evsprod\NDA208870\208870.enx

Jubilant DraxImage Kit for the Preparation of Technetium Tc 99m Exametazime Injection is diagnostic radiopharmaceutical for intravenous use. It is indicated for (b) (4) leukocytes labeled scintigraphy as an adjunct in the localization of (b) (4) intra-abdominal infection, inflammatory bowel disease, (b) (4)

According to the sponsor, the proposed drug product and the listed drug are chemically and pharmaceutically equivalent. They both have the same formulation, strength, dosage form, and route of administration. The reference listed drug for this application is Ceretec™ manufactured by GE Healthcare and approved under NDA 019829. Ceretec™ is a radiopharmaceutical product used as a radiodiagnostic agent in nuclear medicine, indicated for brain imaging and leukocytes labeled scintigraphy for almost 30 years. Therefore, the active pharmaceutical ingredient in the formulation is not a new chemical entity. No new clinical data were submitted for review.

Branch 3 of the Division of Biopharmaceutics\ONDP\OPQ\CDER\FDA interacted with the reviewer and requested a consult review. The sponsor had submitted analyses which were not considered standard for establishing bioequivalence (BE). An Information Request to the sponsor on 5 December 2015 resulted in the submission of proper data in xpt format and proper analyses. These datasets in requested xpt format and analyses are located in the submission no. 0008 dated 19 December 2016.

Biopharmaceutics Division requested to confirm analyses for % labeling efficiency ((i.e., comparing each test lot with each RLD lot) and % cell efflux radioactivity data by batch (i.e., comparing each test lot with each Reference lot) and by fasted/fed state; and perform two one sided

t-test using geometric mean ratio approach and computing 90% CI. The 90% CI should be within the acceptable range of 80-125%.

These analyses were performed using SAS version 9.4. Analyses for % labeling efficiency and % % cell efflux radioactivity by batch (i.e., comparing each test lot with each RLD/Reference lot) and by fasted/fed state were performed. The results are given in the appendix below. Statistical analyses show that the proposed product and the listed drug are sufficiently similar across batch and food Intake (fast/fed). The data can be pooled.

The data for labelling efficiency (LE) and % cell efflux radioactivity data were analyzed using the approach for the Bioequivalence (BE) data. The ratio of LE for Test Product and the RLD/Reference was compared. A 90% confidence interval was applied, with an acceptance criterion of 80-125%. The results were similar to the sponsor provided results for the 4 tested samples, Test Lot to each RLD/Reference lot. Minor differences in the confidence intervals were noted, however for each comparison, the 90% Confidence Interval is between the acceptance criterion of 80% and 125%. The same was repeated for % cell efflux radioactivity data (CMAX & AUS0t), and the results were similar. The Test Product and the Reference Listed Drug can be considered to be equivalent in terms of labeling efficiency and % cell efflux radioactivity.

The two products demonstrate sufficient similarity between the proposed product and the listed drug. The results support biowaiver.

Appendix

Analysis 1: %labeff -Effect of Product and Food Intake (fast/fed) and interaction RLD product

The GLM Procedure

Class	Levels	Values
LOTNO	2	12966581 13053380
FASTFED	2	fast fed

Number of observations = 54

Dependent Variable: nloglabeff

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	3	0.29997829	0.09999276	1.04	0.3830
Error	50	4.80669386	0.09613388		
Corrected Total	53	5.10667215			

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
LOTNO	1	0.13821243	0.13821243	1.44	0.2362
FASTFED	1	0.14664624	0.14664624	1.53	0.2226
LOTNO*FASTFED	1	0.01511963	0.01511963	0.16	0.6934

Analysis 2: %labeff -Effect of Product and Food Intake (fast/fed) with no interaction for RLD product

Number of observations = 54

Dependent Variable: nloglabeff

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	0.28485866	0.14242933	1.51	0.2314
Error	51	4.82181348	0.09454536		
Corrected Total	53	5.10667215			

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
LOTNO	1	0.13821243	0.13821243	1.46	0.2322
FASTFED	1	0.14664624	0.14664624	1.55	0.2187

Analysis 3: %labeff - Effect of Product and Food Intake (fast/fed) and interaction
Test product

The GLM Procedure
Number of observations = 54

Class Level Information

Class	Levels	Values
LOTNO	2	5B142 5F648
FASTFED	2	fast fed

Dependent Variable: nloglabeff

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	3	0.10451950	0.03483983	0.28	0.8371
Error	50	6.14579451	0.12291589		
Corrected Total	53	6.25031401			

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
LOTNO	1	0.02802900	0.02802900	0.23	0.6351
FASTFED	1	0.01447111	0.01447111	0.12	0.7329
LOTNO*FASTFED	1	0.06201939	0.06201939	0.50	0.4808

Analysis 4: %labeff - Effect of Product and Food Intake (fast/fed) with no interaction
Test product

Number of observations = 54
Dependent Variable: nloglabeff

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	0.04250011	0.02125005	0.17	0.8403
Error	51	6.20781390	0.12172184		
Corrected Total	53	6.25031401			

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
LOTNO	1	0.02802900	0.02802900	0.23	0.6334
FASTFED	1	0.01447111	0.01447111	0.12	0.7317

Analysis 5: Cmax -Effect of Product and Food Intake (fast/fed) and interaction Reference product

The GLM Procedure
Number of observations = 216

Class Level Information

Class	Levels	Values
LOTNO	2	12966581 13053380
FASTFED	2	fast fed

Dependent Variable: nlogcmax

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	3	0.77970545	0.25990182	6.29	0.0004
Error	212	8.75347033	0.04128995		
Corrected Total	215	9.53317577			

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
LOTNO	1	0.08156990	0.08156990	1.98	0.1613
FASTFED	1	0.68502006	0.68502006	16.59	<.0001
LOTNO*FASTFED	1	0.01311549	0.01311549	0.32	0.5736

Analysis 6: Cmax -Effect of Product and Food Intake (fast/fed) with no interaction for Reference product

Number of observations = 216

Dependent Variable: nlogcmax

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	0.76658996	0.38329498	9.31	0.0001
Error	213	8.76658581	0.04115768		
Corrected Total	215	9.53317577			

Analysis 7: Cmax -Effect of Product and Food Intake (fast/fed) and interaction

Reference product

The GLM Procedure - Number of observations = 216

Class Level Information

Class	Levels	Values
LOTNO	2	5B142 5F648
FASTFED	2	fast fed

Dependent Variable: nlogcmax

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	3	1.57613759	0.52537920	15.18	<.0001
Error	212	7.33819699	0.03461414		
Corrected Total	215	8.91433459			

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
LOTNO	1	0.00256188	0.00256188	0.07	0.7858
FASTFED	1	1.55794183	1.55794183	45.01	<.0001
LOTNO*FASTFED	1	0.01563388	0.01563388	0.45	0.5023

Analysis 8: Cmax - Effect of Product and Food Intake (fast/fed) -no interaction

Test product

The GLM Procedure - Number of observations = 216

Class Level Information

Source	DF	Sum of Squares
Model	2	1.56050371
Error	213	7.35383087
Corrected Total	215	8.91433459

Dependent Variable: nlogcmax

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	1.56050371	0.78025186	22.60	<.0001
Error	213	7.35383087	0.03452503		
Corrected Total	215	8.91433459			

Source	DF	Type I SS	Mean Square	F Value	Pr > F
LOTNO	1	0.00256188	0.00256188	0.07	0.7856
FASTFED	1	1.55794183	1.55794183	45.12	<.0001

Analysis 9: AUC -Effect of Product and Food Intake (fast/fed) and interaction Reference product

The GLM Procedure -- Number of observations = 216

Class Level Information

Class	Levels	Values
LOTNO	2	12966581 13053380
FASTFED	2	fast fed

Dependent Variable: nlogauc

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	3	0.73455495	0.24485165	5.76	0.0008
Error	212	9.01493486	0.04252328		
Corrected Total	215	9.74948981			

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
LOTNO	1	0.08153549	0.08153549	1.92	0.1676
FASTFED	1	0.64197183	0.64197183	15.10	0.0001
LOTNO*FASTFED	1	0.01104764	0.01104764	0.26	0.6108

Analysis 10: AUC -Effect of Product and Food Intake (fast/fed) with no interaction for Reference product

The GLM Procedure - Number of observations = 216

Dependent Variable: nlogauc

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	0.72350731	0.36175366	8.54	0.0003
Error	213	9.02598250	0.04237550		
Corrected Total	215	9.74948981			

Source	DF	Sum of Squares SS	Mean Square	F Value	Pr > F
LOTNO	1	0.08153549	0.08153549	1.92	0.1669
FASTFED	1	0.64197183	0.64197183	15.15	0.0001

Analysis 11: AUC -Effect of Product and Food Intake (fast/fed) and interaction Test product

The GLM Procedure
Number of observations = 216

Class Level Information

Class	Levels	Values
LOTNO	2	5B142 5F648
FASTFED	2	fast fed

Dependent Variable: nlogauc

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	3	1.23280956	0.41093652	14.42	<.0001
Error	212	6.04333769	0.02850631		
Corrected Total	215	7.27614725			

Source	DF	Type I SS	Mean Square	F Value	Pr > F
LOTNO	1	0.04598153	0.04598153	1.61	0.2055
FASTFED	1	1.09735735	1.09735735	38.50	<.0001
LOTNO*FASTFED	1	0.08947068	0.08947068	3.14	0.0779

Analysis 12: AUC -Effect of Product and Food Intake (fast/fed) with no interaction for Test product

The GLM Procedure Number of observations = 216

Class Level Information

Class	Levels	Values
LOTNO	2	5B142 5F648
FASTFED	2	fast fed

Dependent Variable: nlogauc

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	1.14333889	0.57166944	19.85	<.0001
Error	213	6.13280836	0.02879253		
Corrected Total	215	7.27614725			

Source	DF	Type I SS	Mean Square	F Value	Pr > F
LOTNO	1	0.04598153	0.04598153	1.60	0.2077
FASTFED	1	1.09735735	1.09735735	38.11	<.0001

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/s/

SATISH C MISRA
03/30/2017

JYOTI ZALKIKAR
03/31/2017

PEILING YANG
03/31/2017
Signed for Dr. Hsien-Ming J Hung

STATISTICAL REVIEW AND EVALUATION
FILING REVIEW OF AN NDA/BLA

NDA/BLA #:	NDA 208870
Supplement #:	1
Related IND #:	Pre-Investigational New Drug Application PIND 123604
Product Name:	Kit for the Preparation of Tc99m Exametazime Injection Dosage Form: Lyophilized (b) (4) (0.5 mg/vial) Dose Range; 0.259 - 0.925 GBq (7-25 mCi) Route of Administration – Intravenous
Indication(s):	Jubilant DraxImage Kit for the Preparation of Technetium Tc 99m Exametazime Injection is indicated (b) (4) for leukocytes labeled scintigraphy as an adjunct in the localization of WBCs [leukocytes] due to (b) (4) (proposed).
Applicant:	Jubilant DraxImage Inc.
Dates:	Date submitted – July 19, 2016, Stamp date - July 20, 2016
Review Priority:	Standard
Biometrics Division:	DB1/OB/OTS/CDER
Statistical Reviewer:	Satish Misra, Ph. D.
Concurring Reviewers:	Jyoti Zalkikar, Ph. D.
Medical Division:	DMIP/ODEIV/CDER
Clinical Team:	MO- Phillip Davis, MD Medical CDTL – Danae Christodoulou, MD Division Director - Libero Marzella, MD
Project Manager:	Alberta Davis-Warren

1. Summary of Efficacy/Safety Clinical Trials to be reviewed

Jubilant DraxImage Inc. JDI) submitted NDA208870 (PIND123604) for the development of Technetium Tc-99m Exametazime Injection under 505(b)(2). Exametazime ((b) (4) Hexamethylpropylene amine oxime or (b) (4)HMPAO) has been used previously in the nuclear community under the reference listed drug (RLD) name, Ceretec (99mTc-Exametazime). Ceretec was approved in 1988 under NDA 19-829 for brain imaging. In 1995, this NDA was approved for white blood cell imaging as an additional indication. According to the sponsor, the formulation of Tc-99m Exametazime Injection is identical to the RLD and contains the same active and inactive ingredients at the same concentrations and in the same dosage form.

According to the meeting package, the proposed product, Tc-99m Exametazime is not a new chemical entity and is not being submitted for a new indication. The sponsor considers that the clinical and nonclinical findings of previously approved application for Ceretec and related amendments could be used in support of sponsor's NDA 505(b)(2).

Table 1: Summary of Trials to be Assessed in the Statistical Review

Trial ID	Design	Treatment/ Sample Size	Endpoint/Analysis*	Preliminary Findings

N/A; No new Clinical data submitted for review

2. Assessment of Protocols and Study Reports

Jubilant DraxImage's drug product formulation is quantitatively and qualitatively equivalent to Ceretec™ (NDA 019829), the reference listed drug for this application. The applicant addressed the agency's comments in the NDA submission.

Table 2: Summary of Information Based Upon Review of the Protocol(s) and the Study Report(s)

Content Parameter	Response/Comments
Designs utilized are appropriate for the indications requested.	N/A; No new Clinical data submitted for review
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	N/A; No new Clinical data submitted for review
Interim analyses (if present) were pre-specified in the protocol with appropriate adjustments in significance level. DSMB meeting minutes and data are available.	N/A; No new Clinical data submitted for review
Appropriate details and/or references for novel statistical methodology (if present) are included (e.g., codes for simulations).	N/A; No new Clinical data submitted for review
Investigation of effect of missing data and discontinued follow-up on statistical analyses appears to be adequate.	N/A; No new Clinical data submitted for review

3. Electronic Data Assessment

Table 3: Information Regarding the Data

Content Parameter	Response/Comments
Dataset location	\\CDSESUB1\evsprod\NDA203684\203684.enx
Were analysis datasets provided?	N/A; No new Clinical data submitted for review
Dataset structure (e.g., SDTM or ADaM)	N/A; No new Clinical data submitted for review
Are the define files sufficiently detailed?	N/A; No new Clinical data submitted for review
List the dataset(s) that contains the primary endpoint(s)	N/A; No new Clinical data submitted for review
Are the *analysis datasets* sufficiently structured and defined to permit analysis of the primary endpoint(s) without excess data manipulation? *	N/A; No new Clinical data submitted for review
Are there any initial concerns about site(s) that could lead to inspection? If so, list the site(s) that you request to be inspected and the rationale.	N/A; No new Clinical data submitted for review
Safety data are organized to permit analyses across clinical trials in the NDA/BLA.	N/A; No new Clinical data submitted for review

4. Filing Issues

Table 4: Initial Overview of the NDA/BLA for Refuse-to-file (RTF):

Content Parameter	Yes	No	NA	Comments
Index is sufficient to locate necessary reports, tables, data, etc.			X	
ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)			X	Per Reference Drug Ceretec
Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.			X	Per Reference Drug Ceretec
Data sets are accessible, sufficiently documented, and of sufficient quality (e.g., no meaningful data errors).			X	No new Clinical data submitted for review
Application is free from any other deficiency that render the application unreviewable, administratively incomplete, or inconsistent with regulatory requirements			X	

IS THE APPLICATION FILEABLE FROM A STATISTICAL PERSPECTIVE? -- NA

The sponsor has followed guidance during PIND meeting

5. Comments to be Conveyed to the Applicant

5.1. Refuse-to-File Issues - None

5.2. Information Requests/Review Issues – None at this time

Satish C. Misra, Ph. D.	August 31, 2016
Primary Reviewing Statistician	Date

Jyoti Zalkikar, Ph. D.	August 31, 2016
Secondary Reviewing Statistician	Date

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/s/

SATISH C MISRA
09/02/2016

JYOTI ZALKIKAR
09/02/2016