

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207620Orig1s000

CHEMISTRY REVIEW(S)



Product Quality Recommendation: APPROVAL

**NDA 207620
Review # 01 Addendum
Review Date: June 30, 2015**

Drug Name/Dosage Form	Entresto (sacubitril and valsartan) Tablets
Strength	24 mg sacubitril and 26 mg valsartan 49 mg sacubitril and 51 mg valsartan 97 mg sacubitril and 103 mg valsartan
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Novartis Pharmaceuticals Corporation
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Amendment	25-JUN-2015
Amendment	26-JUN-2015
Amendment	15-JUN-2015
Amendment	11-JUN-2015
Amendment	04-JUN-2015
Amendment	02-JUN-2015
Amendment	26-MAY-2015
Amendment	15-MAY-2015
Amendment	15-MAY-2015

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Anamitro Banerjee	ONDP Branch III/Division I
Drug Product	Sherita McLamore-Hines	ONDP Branch I/Division I
Process	Bogdan Kurtyka	OPF Branch 1/Division of Process Assessment I
Microbiology	Robert Mello	OPF Branch /Division of Microbiology Assessment
Facility	Zhong Li	OPF Branch /Division of Inspectional Assessment
Biopharmaceutics	Salaheldin Hamed	ONDP Branch III/Division of Biopharmaceutics
Project/Business Process Manager	Maryam Kord Bacheh Changi	OPRO Branch I/Division I
Application Technical Lead	Wendy Wilson-Lee	ONDP Branch I /Division I
Laboratory (OTR)	-	-
ORA Lead	Karen D'Orzio	ORA
Environmental Assessment (EA)	Raanan Bloom	ONDP EA Team

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Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

2. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS ¹	REVIEW DATE	COMMENTS
23902	Type II	Novartis Pharmaceutical Corporation	Valsartan	1	25-NOV-2014	

¹ Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	104628	LCZ696 (sacubitril/valsartan) for heart failure and chronic heart failure
IND		

(b) (4)

3. CONSULTS:

No consults requested.

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

We recommend **approval of NDA 207620 from a product quality perspective** for Entresto™ (sacubitril/valsartan) Tablets, 97/103, 49/51, and 24/26 mg when stored in the intended packaging and stored at USP Controlled Room Temperature.

Additional OPO Language for Action Letter

The comparability protocols supporting post-approval changes to 1) the drug product manufacturing site, control, batch size, and process and 2) the (b) (4) intermediate manufacturing site, control, batch size, and process are acceptable.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Post-Marketing Commitment Subject to 506B: None

Post-Marketing Agreements Not Subject to 506B: Development of a new dissolution method for all strengths with demonstrated discriminating ability, (b) (4)

Using the new dissolution method and data from the overall multipoint dissolution profile from a minimum of 12 commercial batches per strength, manufactured under the same conditions as those used for the manufacture of the batches used in pivotal clinical trials, set the final dissolution acceptance criterion for Entresto™ (sacubitril/valsartan) Tablets, 97/103, 49/51, and 24/26 mg.

II. Summary of Quality Assessments

A. Drug Substance [Sacubitril (b) (4) and Valsartan] Quality Summary

1. Chemical Name or IUPAC Name/Structure

Sacubitril: 4-[[[(1S,3R)-1-([1,1'-Biphenyl]-4-ylmethyl)-4-ethoxy-3-methyl-4-oxobutyl]amino]-4-oxobutanoic acid

Valsartan: N-Pentanoyl-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-L-valine

2. Properties/CQAs Relevant to Drug Product Quality

The CQAs relevant to drug product quality are physical form, bulk density, and (b) (4) (b) (4).

3. List of starting materials

(b) (4)

4. Suppliers of starting materials (site)

The quality of starting materials is controlled via the starting material specifications. These specifications are based on the expected, common routes of synthesis for the starting materials and provide for sourcing from multiple suppliers.

5. Summary of Synthesis

Sacubitril (b)(4) drug substance is synthesized (b)(4) using the (u)(4) starting material.

(b)(4) is synthesized in (b)(4) synthetic steps, starting from the (b)(4) (b)(4)

6. Process

The critical process steps are the (b)(4) (b)(4) These process steps are considered critical due to their potential to impact the (b)(4) Critical process parameters such as (b)(4) . The process also includes in-process controls for (b)(4) Sacubitril (b)(4) and valsartan are designated as the regulatory drug substances (b)(4) (b)(4) under Novartis' quality system. However, the specifications for sacubitril (u)(4) and valsartan include tests and acceptance criteria to control the identity, purity, strength, and quality of these compounds (b)(4)

7. Container Closure

The commercial container closure is (b)(4) .

8. Retest Period & Storage Conditions

(b)(4) Based on the stability data provided in the submission, (b)(4) is granted for sacubitril (b)(4) drug substance. Based on the data and in accordance with ICH Q1E, a (b)(4) month re-test period is granted for the (b)(4) drug product in-process material. The recommended storage condition for both drug substances and the in-process material is (b)(4) .

B. Drug Product [Sacubitril and Valsartan] Quality Summary

1. Strength

The drug product is available as a fixed dose combination of 24 mg sacubitril and 26 mg valsartan; 49 mg sacubitril and 51 mg valsartan; and 97 mg sacubitril and 103 mg valsartan

2. Description/Commercial Image

24 mg sacubitril and 26 mg valsartan: violet white ovaloid biconvex film-coated tablet with beveled edges, unscored, debossed with “NVR” on one side and “LZ” on the other side; approximately 13.1 mm length and 5.2 mm width

49 mg sacubitril and 51 mg valsartan: pale yellow ovaloid biconvex film-coated tablet with beveled edges, unscored, debossed with “NVR” on one side and “L1” on the other side; approximately 13.1 mm length and 5.2 mm width

97 mg sacubitril and 103 mg valsartan: light pink ovaloid biconvex film-coated tablet with beveled edges, unscored, debossed with “NVR” on one side and “(b) (4)” on the other side; approximately 15.1 mm length and 6.0 mm width

3. Summary of Product Design

The target product was an oral, immediate-release dosage form. Initial clinical studies used (b) (4)

4. List of Excipients:

Microcrystalline cellulose, low substituted hydroxypropylcellulose, crospovidone, magnesium stearate, talc, colloidal silicon dioxide

5. Process Selection (Unit Operations Summary)

The manufacturing process consists of (b) (4) major unit operations – (b) (4)

6. Container Closure

Commercial (24 mg sacubitril and 26 mg valsartan; 49 mg sacubitril and 51 mg valsartan) – 60-ct and 180-ct, 90 cc square, white, HDPE bottles with 38 mm, (b) (4) induction sealed, (b) (4) closures

Commercial (97 mg sacubitril and 103 mg valsartan) – 60-ct, 90 cc and 180-ct, 175 cc square, white, HDPE bottles with 38 mm, (b) (4) induction sealed, (b) (4) closures

Physician’s Sample (all strengths) – 14 ct, 45 cc round, white, HDPE bottle with 28 mm, (b) (4) induction-sealed, (b) (4) closures

(b) (4) Packs (all strengths) – clear, (b) (4), formed, blister pack with a

push through, aluminum foil blister lidding

7. Expiration Date & Storage Conditions

Based on the drug product stability information provided and in accordance with ICH Q1E, we grant a 24 month drug product expiration date when stored at USP controlled room temperature, protected from moisture, in the intended container closure.

8. List of co-packaged components

There are no co-packaged components.

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Entresto
Non Proprietary Name of the Drug Product	Sacubitril and Valsartan
Non Proprietary Name of the Drug Substances	Sacubitril (b)(4) and Valsartan
Proposed Indication(s) including Intended Patient Population	Treatment of Heart Failure
Duration of Treatment	Chronic
Maximum Daily Dose	97 mg sacubitril and 103 mg valsartan, administered twice daily
Alternative Methods of Administration	None identified

D. Biopharmaceutics Considerations

1. BCS Classification:

- Drug Substance: No BCS Classification proposed by the Applicant. The solubility is pH dependent. In 0.1 N HCL, solubility is 0.05 mg/mL and >50 mg/mL at pH 6.8. Absolute bioavailability of valsartan is 25%, but it is known to undergo significant first-pass metabolism. Most likely the permeability is high. The absolute bioavailability 60% for sacubitril. The BCS classification is BCS IV.
- Drug Product: Not Applicable

2. Biowaivers/Biostudies

- Biowaiver Requests: Not Applicable
- PK studies: Bridging study for the 24/26 mg formulation
- IVIVC: Not Applicable

E. Novel Approaches

The drug product contains (b)(4) two active ingredients – sacubitril and valsartan. Sacubitril is a new molecular entity. Valsartan is an approved drug substance. (b)(4) quickly hydrolyzes *in vivo* to release sacubitril and valsartan. (b)(4)

The drug substance control strategy relies on control of [redacted] (b) (4)
[redacted] to ensure the identity, purity, strength, quality, and bioavailability of sacubitril and valsartan. As agreed upon by the Agency, [redacted] (b) (4)
[redacted] the applicant's quality systems and standards control [redacted] (b) (4)
[redacted] specifications for sacubitril [redacted] (b) (4) and valsartan [redacted] (b) (4)
[redacted] include appropriate tests and acceptance criteria to ensure the identity, purity, strength, quality, and bioavailability of these compounds. [redacted] (b) (4)
[redacted] is granted to control the shelf-life of sacubitril [redacted] (b) (4)

F. Any Special Product Quality Labeling Recommendations

There are no special labeling recommendations from a product quality perspective.

G. Process/Facility Quality Summary (see Attachment A)

H. Life Cycle Knowledge Information (see Attachment B)

Wendy I.
Wilson -S

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For the OPQ Quality Review Team

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Product Quality Recommendation: Pending

NDA 207620
Review # 01
Review Date: May 15, 2015

Drug Name/Dosage Form	Entresto (sacubitril and valsartan) Tablets
Strength	24 mg sacubitril and 26 mg valsartan 49 mg sacubitril and 51 mg valsartan 97 mg sacubitril and 103 mg valsartan
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Novartis Pharmaceuticals Corporation
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Amendment	13-MAY-2015
Amendment	15-APR-2015
Amendment	24-FEB-2015
Amendment	16-JAN-2015
Amendment	16-JAN-2015
Original	30-SEP-2014

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Anamitro Banerjee	ONDP Branch III/Division I
Drug Product	Sherita McLamore-Hines	ONDP Branch I/Division I
Process	Bogdan Kurtyka	OPF Branch 1/Division
Microbiology	Robert Mello	OPF Branch /Division of
Facility	Zhong Li	OPF Branch /Division of
Biopharmaceutics	Salaheldin Hamed	ONDP Branch III/Division of Biopharmaceutics
Project/Business Process Manager	Olga Simakova	OPRO Branch I/Division I
Application Technical Lead	Wendy Wilson-Lee	ONDP Branch I /Division I
Laboratory (OTR)	-	-
ORA Lead	Karen D'Orzio	
Environmental Assessment (EA)	Raanan Bloom	ONDP EA Team

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Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

2. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS ¹	DATE REVIEW COMPLETED	COMMENTS
23902	Type II	Novartis Pharmaceutical Corporation	Valsartan	1	25-NOV-2014	

¹ Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	104628	LCZ696 (sacubitril/valsartan) for heart failure and chronic heart failure
IND		(b) (4)

3. CONSULTS:

No consults requested.

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The overall product quality recommendation is pending due to the following outstanding items:

1. Completion of facilities inspections and evaluations
2. Submission of revised carton and container labels
3. Submission of confirmatory stability data for the drug product and (b) (4)
4. Submission of a revised dissolution specification

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

The comparability protocols supporting post-approval changes to 1) the drug product manufacturing site, control, batch size, and process and 2) the (b) (4) intermediate manufacturing site, control, batch size, and process are acceptable.

II. Summary of Quality Assessments

A. Drug Substance [Sacubitril (b) (4) and Valsartan] Quality Summary

1. Chemical Name or IUPAC Name/Structure

Sacubitril: 4-{{[(1*S*,3*R*)-1-([1,1'-Biphenyl]-4-ylmethyl)-4-ethoxy-3-methyl-4-oxobutyl]amino}-4-oxobutanoic acid

Valsartan: *N*-Pentanoyl-*N*-{[2'-(1*H*tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl}-*L*-valine

2. Properties/CQAs Relevant to Drug Product Quality

The CQAs relevant to drug product quality are physical form, bulk density, and (b) (4).

3. List of starting materials

(b) (4)

4. Suppliers of starting materials (site)

The quality of starting materials is controlled via the starting material specifications. These specifications are based on the expected, common routes of synthesis for the starting materials and provide for sourcing from multiple suppliers.

5. Summary of Synthesis

Sacubitril (b)(4) drug substance is synthesized (b)(4) using the (u)(4) starting material.

(b)(4) is synthesized in (b)(4) synthetic steps, starting from the (b)(4)

6. Process

The critical process steps are the (b)(4)

These process steps are considered critical due to their potential to impact the (b)(4). Critical process parameters such as (b)(4)

. The process also includes in-process controls (b)(4) Sacubitril (u)(4) and valsartan are designated as the regulatory drug substances (b)(4) under Novartis' quality system. However, the specifications for sacubitril (u)(4) and valsartan include tests and acceptance criteria to control the identity, purity, strength, and quality of these compounds (b)(4).

7. Container Closure

The commercial drug substance container closure is (b)(4)

8. Retest Period & Storage Conditions

(b)(4) Based on the stability data provided in the submission, (b)(4) is granted for sacubitril (b)(4) drug substance. Based on the data and in accordance with ICH Q1E, a (b)(4) month re-test period is granted for the (b)(4) drug product in-process material. The recommended storage condition for both drug substances and the in-process material is (b)(4)

B. Drug Product [Sacubitril and Valsartan] Quality Summary

1. Strength

The drug product is available as a fixed dose combination of 24 mg sacubitril and 26 mg valsartan; 49 mg sacubitril and 51 mg valsartan; and 97 mg sacubitril and 103 mg valsartan

2. Description/Commercial Image

24 mg sacubitril and 26 mg valsartan: violet white ovaloid biconvex film-coated tablet with beveled edges, unscored, debossed with “NVR” on one side and “LZ” on the other side; approximately 13.1 mm length and 5.2 mm width

49 mg sacubitril and 51 mg valsartan: pale yellow ovaloid biconvex film-coated tablet with beveled edges, unscored, debossed with “NVR” on one side and “L1” on the other side; approximately 13.1 mm length and 5.2 mm width

97 mg sacubitril and 103 mg valsartan: light pink ovaloid biconvex film-coated tablet with beveled edges, unscored, debossed with “NVR” on one side and “(b) (4)” on the other side; approximately 15.1 mm length and 6.0 mm width

3. Summary of Product Design

The target product was an oral, immediate-release dosage form. Initial clinical studies used (b) (4)

4. List of Excipients:

Microcrystalline cellulose, low substituted hydroxypropylcellulose, crospovidone, magnesium stearate, talc, colloidal silicon dioxide

5. Process Selection (Unit Operations Summary)

The manufacturing process consists of (b) (4) major unit operations – (b) (4)

6. Container Closure

Commercial (24 mg sacubitril and 26 mg valsartan; 49 mg sacubitril and 51 mg valsartan) – 60-ct and 180-ct, 90 cc square, white, HDPE bottles with 38 mm, (b) (4), induction sealed, (b) (4) closures

Commercial (97 mg sacubitril and 103 mg valsartan) – 60-ct, 90 cc and 180-ct, 175 cc square, white, HDPE bottles with 38 mm, (b) (4) induction sealed, (b) (4) closures

Physician’s Sample (all strengths) – 14 ct, 45 cc round, white, HDPE bottle with 28 mm, (b) (4) induction-sealed, (b) (4) closures

(b) (4) Packs (all strengths) – clear, (b) (4), formed, blister pack with a push through, aluminum foil blister lidding

7. Expiration Date & Storage Conditions

Based on the drug product stability information provided in the submission and in accordance with ICH Q1E, we grant a 24 month drug product expiration date when stored at controlled room temperature, protected from moisture, in the intended container closure.

8. List of co-packaged components

There are no co-packaged components.

C. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	Entresto
Non Proprietary Name of the Drug Product	Sacubitril and Valsartan
Non Proprietary Name of the Drug Substance	Sacubitril (b) (4) Valsartan
Proposed Indication(s) including Intended Patient Population	Treatment of Heart Failure
Duration of Treatment	Chronic
Maximum Daily Dose	97 mg sacubitril and 103 mg valsartan, administered twice daily
Alternative Methods of Administration	None identified

D. Biopharmaceutics Considerations

1. BCS Classification:

- Drug Substance: No BCS Classification proposed by the Applicant. The solubility is pH dependent. In 0.1 N HCL, solubility is 0.05 mg/mL and >50 mg/mL at pH 6.8. Absolute bioavailability of valsartan is 25%, but it is known to undergo significant first-pass metabolism. Most likely the permeability is high. The absolute bioavailability 60% for sacubitril. The BCS classification is BCS IV.
- Drug Product: Not Applicable

2. Biowaivers/Biostudies

- Biowaiver Requests: Not Applicable
- PK studies: Bridging study for the 50 mg formulation
- IVIVC: Not Applicable

E. Novel Approaches

The drug product contains (b) (4) two active ingredients – sacubitril and valsartan. Sacubitril is a new molecular entity. Valsartan is an approved drug substance. (b) (4) quickly hydrolyzes *in vivo* to release sacubitril and valsartan. (b) (4)

The drug substance control strategy relies on control of (b) (4) to ensure the identity, purity, strength, quality, and bioavailability of sacubitril and valsartan. As agreed upon by the Agency, (b) (4) the applicant's quality systems and standards control (b) (4) specifications for sacubitril (b) (4) and valsartan (b) (4) include appropriate tests and acceptance criteria to ensure the identity, purity, strength, quality, and bioavailability of these compounds. (b) (4) is granted to control the shelf-life of sacubitril (b) (4).

F. Any Special Product Quality Labeling Recommendations

There are no special labeling recommendations from a product quality perspective.

G. Process/Facility Quality Summary (see Attachment A)

H. Life Cycle Knowledge Information (see Attachment B)

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ASSESSMENT OF THE BIOPHARMACUETICS

27. Are the in-vitro dissolution test and acceptance criteria adequate for assuring consistent bioavailability of the drug product?

LCZ696 film-coated tablets (FCT) are designed as a combination of sacubitril (AHU377, a new molecular entity) and valsartan (b) (4). (b) (4) (the drug substance) is a salt complex comprising LCZ696 (Sacubitril/Valsartan anionic moieties), sodium cations, and water molecules. LCZ696 has been formulated as 50 mg (24.3 mg/24.7 mg), 100 mg (48.6 mg/51.4 mg), 200 mg (97.2 mg/102.8 mg) immediate release film-coated tablets for oral administration. Following oral administration, LCZ696 dissociates into two components, valsartan and the pro-drug sacubitril (AHU377); the latter is further metabolized to the neprilysin inhibitor LBQ657. The 200 mg and the 100 mg tablets are (b) (4).

DISSOLUTION METHOD

The proposed dissolution method is summarized in table 1:

Table 1. Proposed Dissolution Method and Acceptance Criterion.

Apparatus	Speed	Volume	Medium	Detection	Acceptance Criterion
USP II	50 rpm	900 mL	Phosphate Buffer, pH 6.8	HPLC/UV $\lambda=255$ nm	Q = (b) (4)

The Applicant proposed the use of apparatus II with paddles for dissolution testing because it is considered a standard apparatus. The Applicant provided data to justify the selection of the dissolution medium pH. The proposed pH is based on the solubility profile of valsartan and sacubitril, both of which exhibit high solubility at pH higher than 5.0 and low solubility at acidic pH (figure 1). Therefore, the Applicant chose pH 6.8 for physiological relevance.

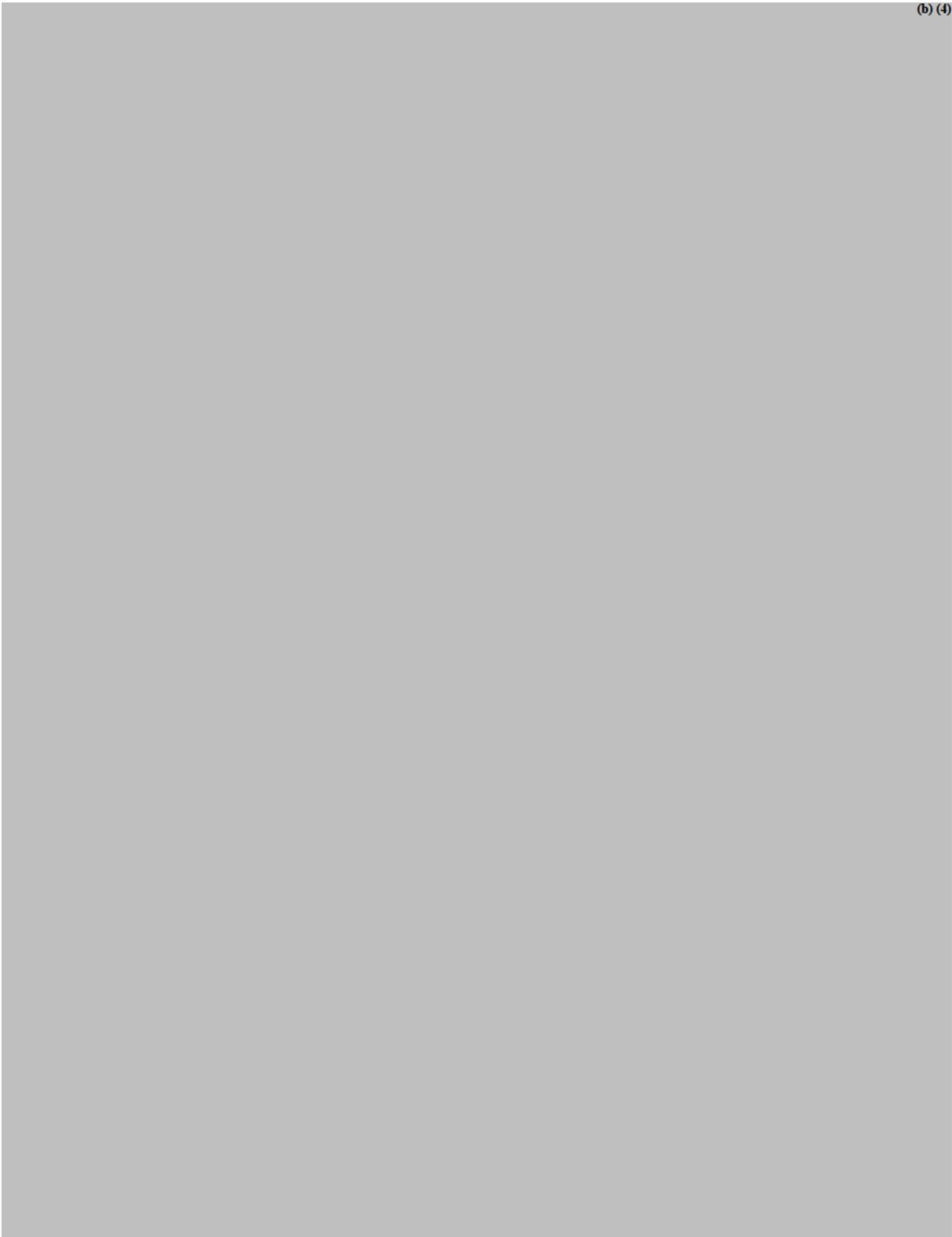
(b) (4)

METHOD DISCRIMINATING ABILITY

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ACCEPTANCE CRITERION

The applicant proposes $Q = \frac{(b)}{(4)}\%$ for both sacubitril and valsartan at $\frac{(b)}{(4)}$ minutes for the three dosage strengths. The dissolution data for the registration batches are provided tables 2-4. The dissolution data do not support the proposed acceptance criteria. $Q = \frac{(b)}{(4)}\%$ at $\frac{(b)}{(4)}$ minutes is likely to result in an under-discriminating method, $\frac{(b)}{(4)}$



(b) (4)

Reviewer's Assessment:

Dissolution Method: ACCEPTABLE

The applicant investigated the effect of medium pH on dissolution and provided data to support the selection of pH 6.8. The selection of the remaining method parameters (i.e., apparatus, paddle speed, buffer type, etc.) were not supported. The selected method, however, is mild (i.e. 50 rpm and no surfactant), which provides more discriminating ability.

Discriminating Ability of the Dissolution Method: ACCEPTABLE

The applicant investigated the effect of critical material attributes of drug substance (particle size distribution) and the effect of tablet hardness, a critical quality attribute, on dissolution. The proposed dissolution method and acceptance criterion were not able to discriminate batches with parameters outside the target ranges. However, the discriminating ability of the method can be enhanced with tighter dissolution acceptance criteria.

Acceptance Criterion: NOT ACCEPTABLE

The applicant proposes $Q = \frac{(b)}{(4)}\%$ at $\frac{(b)}{(4)}$ minutes as the acceptance criterion for all dosage strengths. The provided data for the registration batches do not support the proposed acceptance criterion, with $\frac{(b)}{(4)}\%$ dissolved at $\frac{(b)}{(4)}$ minutes $\frac{(b)}{(4)}$. The proposed acceptance criterion compromises the discriminating ability of the method, $\frac{(b)}{(4)}$. The applicant will be requested to change the acceptance criteria to $Q = \frac{(b)}{(4)}\%$ at 25 instead of the proposed $Q = \frac{(b)}{(4)}$.

28. Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?

$\frac{(b)}{(4)}$

The coated 100 mg and 200 mg tablets used in the Phase 3 clinical trials were of the same component and composition as the To-be-marketed formulation. Therefore, no bioequivalence studies were performed. The 50 mg formulation, however, was further developed during commercial scale up to the To-be-marketed formulation and a bioequivalence study (study LCZ696B2114) was conducted to ensure therapeutic equivalence.

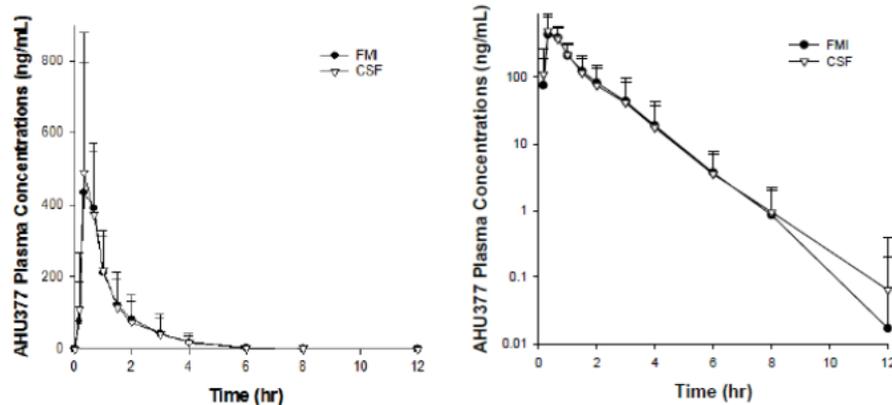
Study Title	Bioequivalence of 50 mg LCZ696 final market image (FMI) and the 50 mg LCZ696 clinical service form (CSF) in healthy volunteers
Design	A randomized, open-label, single-dose, two-treatment, two sequence, three-period, replicate cross-over
Methodology	Subjects were randomized into one of two sequences in a 1:1 ratio. In the first sequence (TRT), subjects received FMI in period 1, CSF in period 2, and FMI in period 3. In the second sequence (RTR), subjects received CSF in period 1, FMI in period 2, and CSF in period 3.

	<p><u>Test product</u>: LCZ696 50 mg FMI (Batch No. AEUS/2010-0432) <u>Reference product</u>: LCZ696 50 mg CSF (Batch No. H941CI)</p> <p>The study consisted of a screening period up to 28 days, a baseline evaluation prior to each treatment period, three single-dose treatment periods, and 2 washout periods that lasted from 7 to 14 days.</p> <p>Log-transformed PK parameters (AUC_{last}, AUC_{inf}, and C_{max}) were analyzed for AHU377, LBQ657, and valsartan by linear-fixed effects model, with formulation, sequence, period, and subject as fixed factors. The analysis was carried out on the set of subjects with evaluable PK parameters for at least one test and one reference period.</p>																																																																											
<p>Subjects/ Demographics</p>	<p>A total of 85 subjects (63 males and 22 females) were enrolled and randomized in the study. Four subjects were discontinued early from the study, one subject was withdrawn due to a protocol deviation, two subjects were lost to follow-up, and one subject was withdrawn as per the physician’s decision. Demographic summary of the patients recruited for the study is summarized in the following table :</p> <table border="1" data-bbox="479 903 1380 1491"> <thead> <tr> <th colspan="2"></th> <th>Sequence 1 N=42</th> <th>Sequence 2 N=43</th> <th>All subjects N=85</th> </tr> </thead> <tbody> <tr> <td rowspan="3">Age (years)</td> <td>Mean (SD)</td> <td>39.5 (10.4)</td> <td>41.0 (8.9)</td> <td>40.3 (9.6)</td> </tr> <tr> <td>Median</td> <td>41.0</td> <td>44.0</td> <td>43.0</td> </tr> <tr> <td>Range</td> <td>21 - 55</td> <td>19 - 54</td> <td>19-55</td> </tr> <tr> <td rowspan="2">Sex- n(%)</td> <td>Female</td> <td>10 (24%)</td> <td>12 (28%)</td> <td>22 (26%)</td> </tr> <tr> <td>Male</td> <td>32 (76%)</td> <td>31 (72%)</td> <td>63 (74%)</td> </tr> <tr> <td rowspan="2">Race - n(%)</td> <td>Black</td> <td>9 (21%)</td> <td>7 (16%)</td> <td>16 (19%)</td> </tr> <tr> <td>Caucasian</td> <td>33 (79%)</td> <td>36 (84%)</td> <td>69 (81%)</td> </tr> <tr> <td rowspan="3">Ethnicity - n(%)</td> <td>Hispanic or Latino</td> <td>40 (95%)</td> <td>38 (88%)</td> <td>78 (92%)</td> </tr> <tr> <td>Other</td> <td>2 (5%)</td> <td>5 (12%)</td> <td>7 (8%)</td> </tr> <tr> <td>Weight (kg)</td> <td>75.5 (10.3)</td> <td>77.4 (11.3)</td> <td>76.5 (10.82)</td> </tr> <tr> <td rowspan="3">Height (cm)</td> <td>Mean (SD)</td> <td>170.4 (8.2)</td> <td>170.2 (9.3)</td> <td>170.3 (8.7)</td> </tr> <tr> <td>Median</td> <td>172.3</td> <td>170.0</td> <td>170.0</td> </tr> <tr> <td>Range</td> <td>149.5 - 181.5</td> <td>153.5 - 190.5</td> <td>149.5 – 190.5</td> </tr> <tr> <td rowspan="3">BMI (kg/m²)</td> <td>Mean (SD)</td> <td>26.0 (2.8)</td> <td>26.7 (2.6)</td> <td>26.3 (2.7)</td> </tr> <tr> <td>Median</td> <td>26.5</td> <td>26.7</td> <td>26.6</td> </tr> <tr> <td>Range</td> <td>19.7 - 29.9</td> <td>21.8 - 29.8</td> <td>19.7 – 29.9</td> </tr> </tbody> </table> <p>Sequence 1: LCZ696 50mg FMI // LCZ696 50mg CSF // LCZ696 50mg FMI Sequence 2: LCZ696 50mg CSF // LCZ696 50mg FMI // LCZ696 50mg CSF</p>			Sequence 1 N=42	Sequence 2 N=43	All subjects N=85	Age (years)	Mean (SD)	39.5 (10.4)	41.0 (8.9)	40.3 (9.6)	Median	41.0	44.0	43.0	Range	21 - 55	19 - 54	19-55	Sex- n(%)	Female	10 (24%)	12 (28%)	22 (26%)	Male	32 (76%)	31 (72%)	63 (74%)	Race - n(%)	Black	9 (21%)	7 (16%)	16 (19%)	Caucasian	33 (79%)	36 (84%)	69 (81%)	Ethnicity - n(%)	Hispanic or Latino	40 (95%)	38 (88%)	78 (92%)	Other	2 (5%)	5 (12%)	7 (8%)	Weight (kg)	75.5 (10.3)	77.4 (11.3)	76.5 (10.82)	Height (cm)	Mean (SD)	170.4 (8.2)	170.2 (9.3)	170.3 (8.7)	Median	172.3	170.0	170.0	Range	149.5 - 181.5	153.5 - 190.5	149.5 – 190.5	BMI (kg/m ²)	Mean (SD)	26.0 (2.8)	26.7 (2.6)	26.3 (2.7)	Median	26.5	26.7	26.6	Range	19.7 - 29.9	21.8 - 29.8	19.7 – 29.9
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<p>Summary of Results</p>	<p>Out of the recruited 85 subjects, Subject #1001002 did not meet the inclusion criteria; Subject #1001067 and Subject #1001074 completed only period 1; and Subject #1001069 completed period 1 and period 2 of the study. In the study, the observed pre-dose valsartan concentrations were >5% of C_{max} for subject #1001113 at all three treatment periods and for Subject #1001055 at period 1. Therefore, data from these subjects were excluded from the PK/statistics analysis according to the analysis plan.</p> <p>The PK parameters for AHU377 are summarized in the following</p>																																																																											

table:

Formulations		AUCinf (ng*hr/mL)	AUClast (ng*hr/mL)	Cmax (ng/mL)	T1/2 (hr)	Tmax (hr)
CSF	N	123	123	123	123	123
	Mean	547	544	580	0.990	-
	SD	161	161	333	0.277	-
	Min	170	168	116	0.552	0.333
	Median	516	514	499	0.943	0.333
	Max	1020	1010	1650	2.09	3.00
	CV%	29.5	29.6	57.4	28.0	-
FMI	N	122	124	124	122	124
	Mean	547	541	561	0.994	-
	SD	159	159	287	0.239	-
	Min	120	117	92.0	0.534	0.333
	Median	528	525	511	0.948	0.533
	Max	993	989	1850	2.10	4.00
	CV%	29.1	29.4	51.1	24.0	-

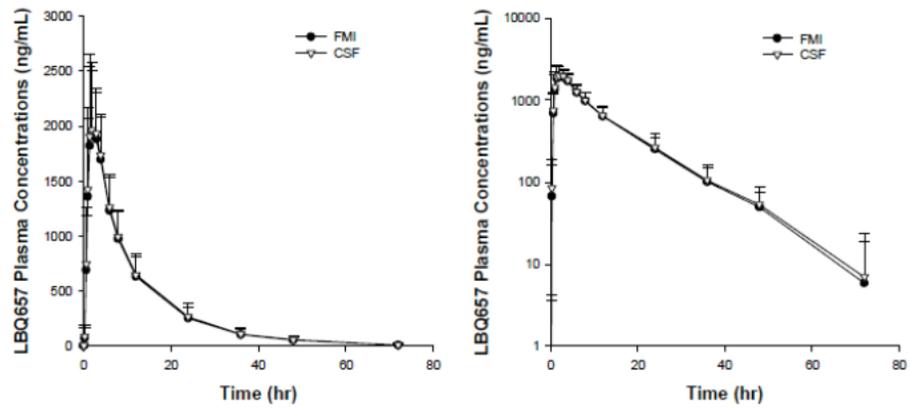
The AHU377 Mean PK profiles are shown in the following figure:



The PK parameters for LBQ657 are summarized in the following table:

Tablets		AUCinf (ng*hr/mL)	AUClast (ng*hr/mL)	Cmax (ng/mL)	T1/2 (hr)	Tmax (hr)
CSF	N	123	123	123	123	123
	Mean	24200	23600	2220	10.2	-
	SD	7140	6910	505	2.59	-
	Min	8960	8590	822	6.56	1.00
	Median	23400	22700	2140	9.43	2.00
	Max	59400	57300	4130	18.5	4.00
	CV%	29.5	29.3	22.8	25.3	-
FMI	N	124	124	124	124	124
	Mean	23300	22800	2180	10.1	-
	SD	6210	6080	482	2.28	-
	Min	6450	5980	497	6.68	1.00
	Median	22600	22000	2180	9.53	2.00
	Max	57400	56100	4240	19.6	6.00
	CV%	26.6	26.7	22.1	22.7	-

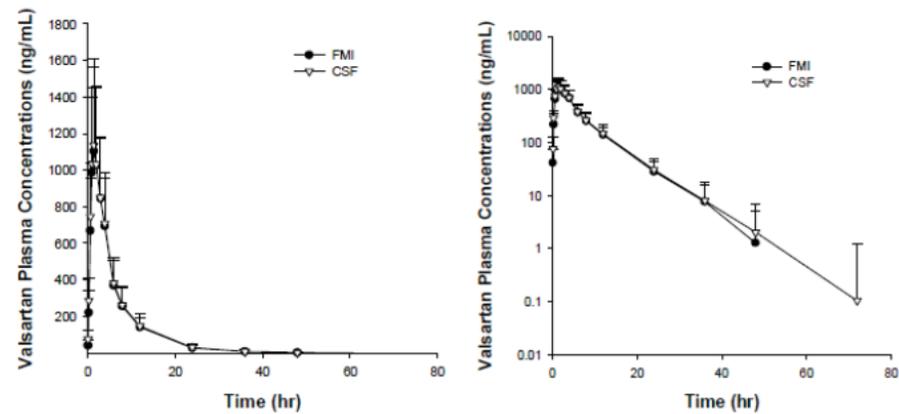
The mean LBQ657 PK profiles are shown in the following figure:



The PK parameters for valsartan are summarized in the following table:

Tablets		AUCinf (ng*hr/mL)	AUClast (ng*hr/mL)	Cmax (ng/mL)	T1/2 (hr)	Tmax (hr)
CSF	N	118	120	120	118	120
	Mean	7300	7130	1190	6.11	-
	SD	2740	2720	463	4.27	-
	Min	2010	1890	288	3.34	0.667
	Median	6890	6760	1120	5.43	1.50
	Max	18000	17700	3680	48.6	4.00
	CV%	37.6	38.2	39.0	69.9	-
FMI	N	123	123	123	123	123
	Mean	7030	6890	1160	5.76	-
	SD	2480	2480	455	1.83	-
	Min	2210	1830	315	3.68	0.667
	Median	6840	6700	1080	5.38	1.50
	Max	15400	15300	2680	20.4	4.00
	CV%	35.3	36.0	39.1	31.7	-

The mean valsartan PK profiles are shown in the following figure



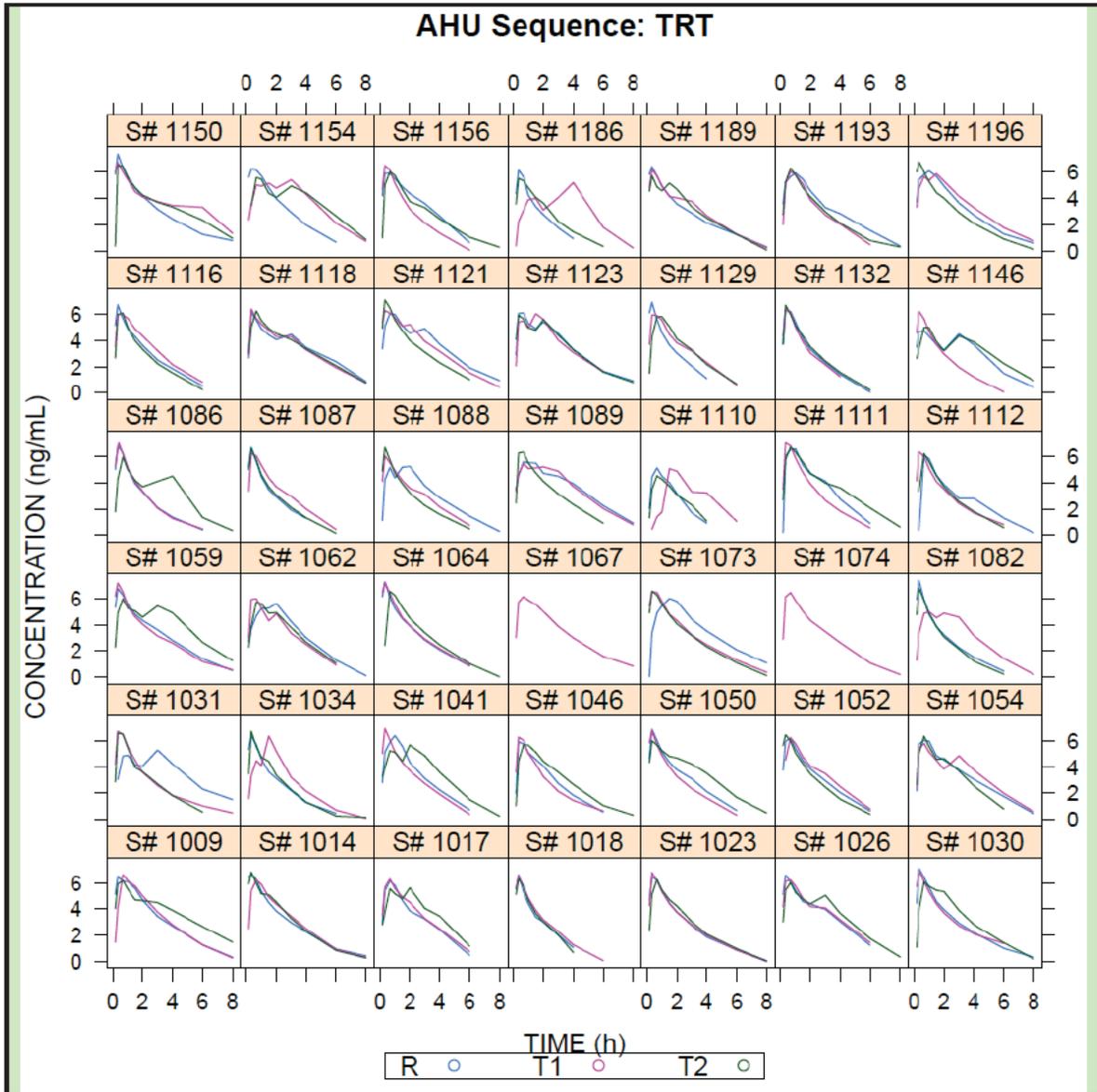
The statistical analysis of the PK parameters is summarized in the following table:

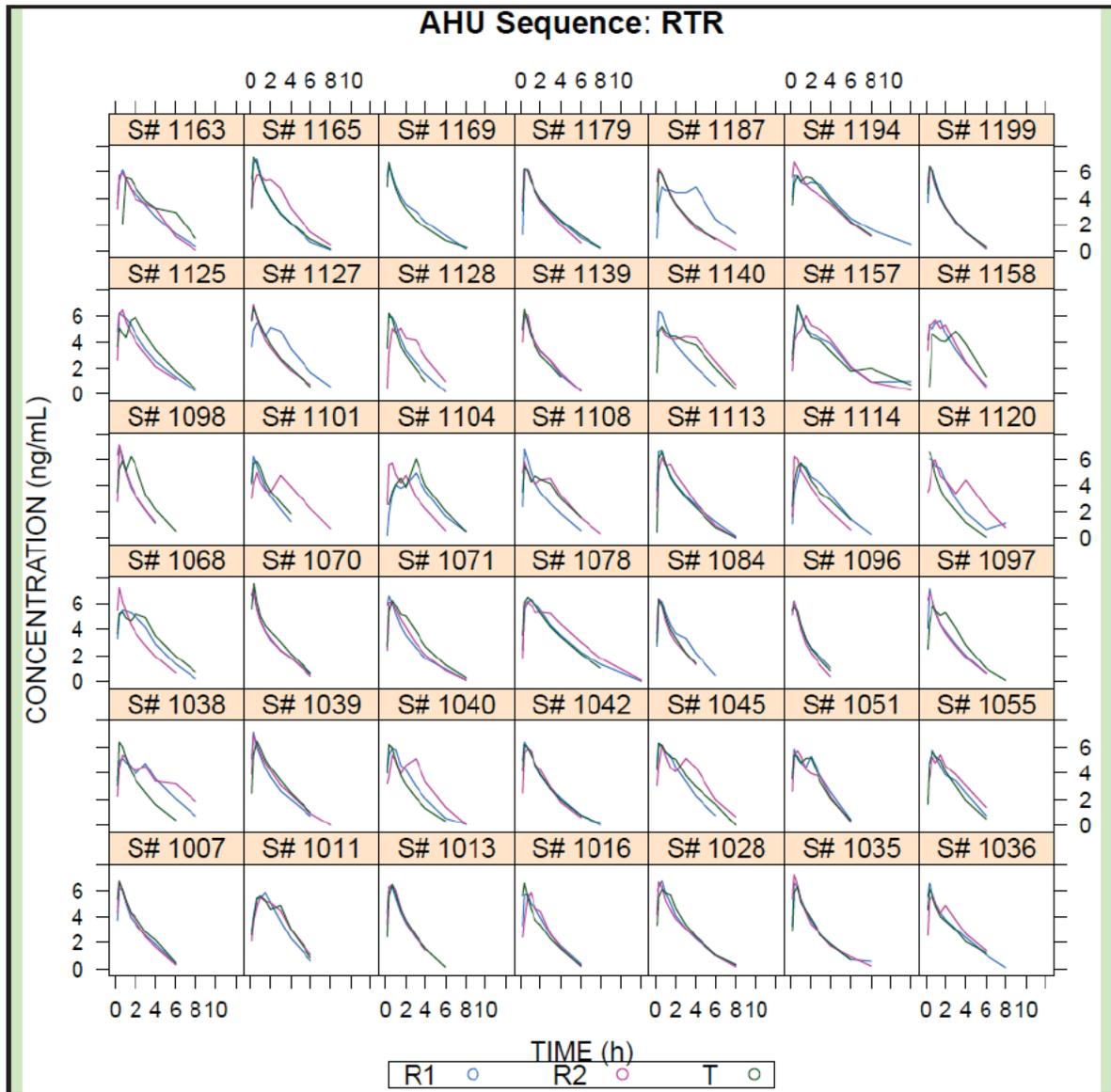
Analyte	Parameter [Unit]	Treatment	N	Adjusted geometric mean *	Ratio (Test/Reference, %)*	90% CI for ratio (%)*
AHU377	AUCinf (ng*hr/mL)	Test	120	514.23	97.65	[94.97 , 100.41]
		Reference	123	526.62		
	AUClast (ng*hr/mL)	Test	122	510.70	97.30	[94.62 , 100.23]
		Reference	123	524.50		
	Cmax (ng/mL)	Test	122	485.52	96.18	[86.61 , 106.80]
		Reference	123	504.82		
LBQ657	AUCinf (ng*hr/mL)	Test	122	22774.02	98.79	[97.61 , 99.99]
		Reference	123	23053.01		
	AUClast (ng*hr/mL)	Test	122	22212.25	98.85	[97.63 , 100.08]
		Reference	123	22470.74		
	Cmax (ng/mL)	Test	122	2134.68	99.71	[97.35 , 102.14]
		Reference	123	2140.84		
Valsartan	AUCinf (ng*hr/mL)	Test	121	6551.66	95.62	[90.13 , 101.45]
		Reference	118	6851.74		
	AUClast (ng*hr/mL)	Test	121	6396.96	95.70	[90.05 , 101.70]
		Reference	120	6684.38		
	Cmax (ng/mL)	Test	121	1070.45	95.76	[89.46 , 102.50]
		Reference	120	1117.86		
Summary of Safety	<p>The safety evaluation included all subjects who received at least one dose of the study drug. A total of 18 adverse events were reported in 15 subjects (17.6%) during the study. No deaths or severe adverse events occurred after randomization. Most AEs were not suspected to be related to the study medication. Only three AEs (Subject #1001064; headache, and Subjects #100116 and #1001156; dizziness) were suspected to be related to the study drug by the study investigator. All AEs were mild in intensity, and most often resolved within the duration of the study without any treatment. None of the AEs led to the discontinuation of any of the subjects.</p>					

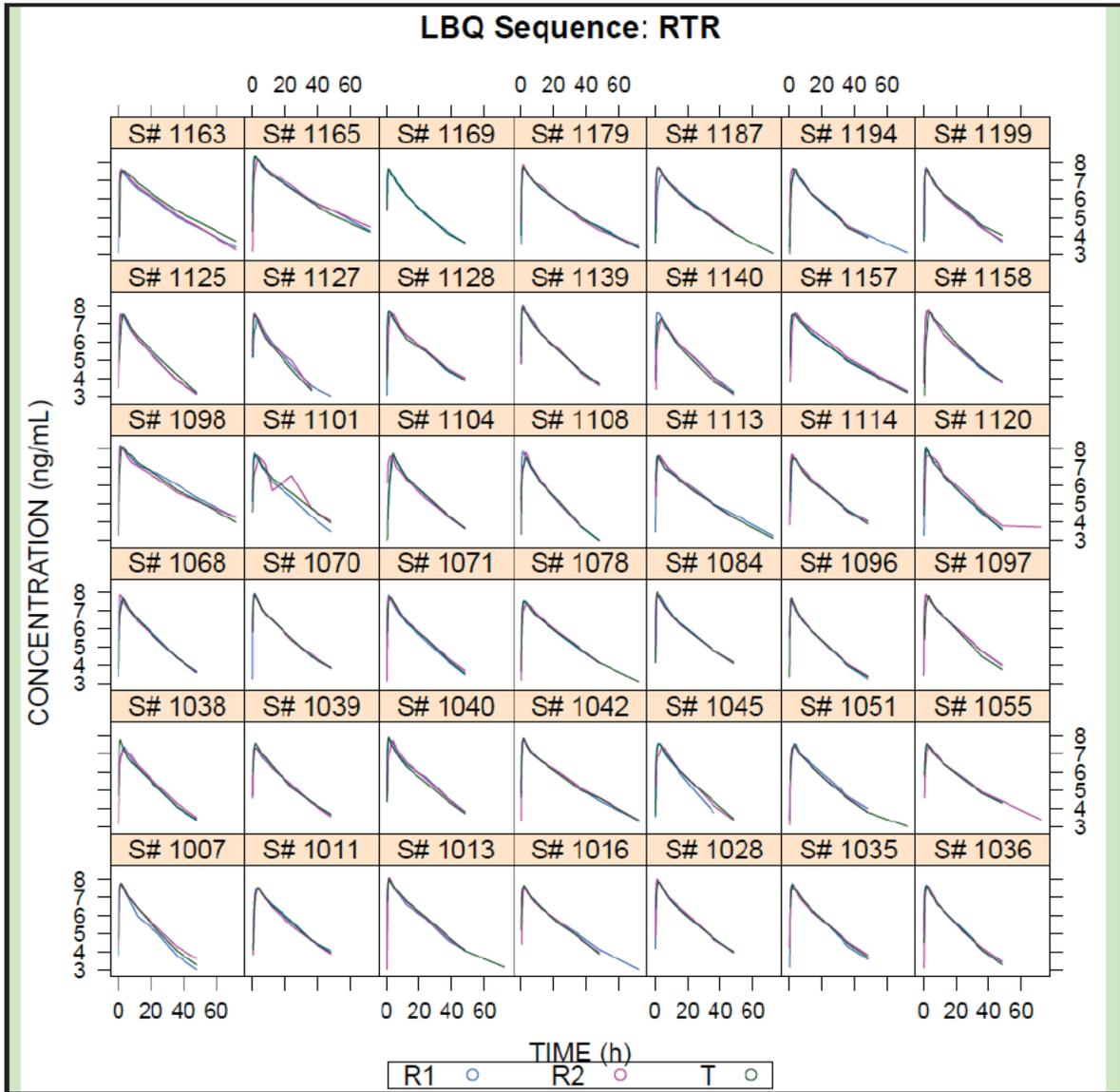
The applicant provides a detailed method validation report of the bioanalytical method for the sacubitril pro-drug (AHU377), active metabolite (BLQ657), and valsartan. The validation report investigated the specificity, absolute recovery and matrix effects, carryover, calibration, intra- and inter-day accuracy and precision, linearity, and stability. The reported results met the acceptance criteria outlined by the bioanalytical method validation guidance.

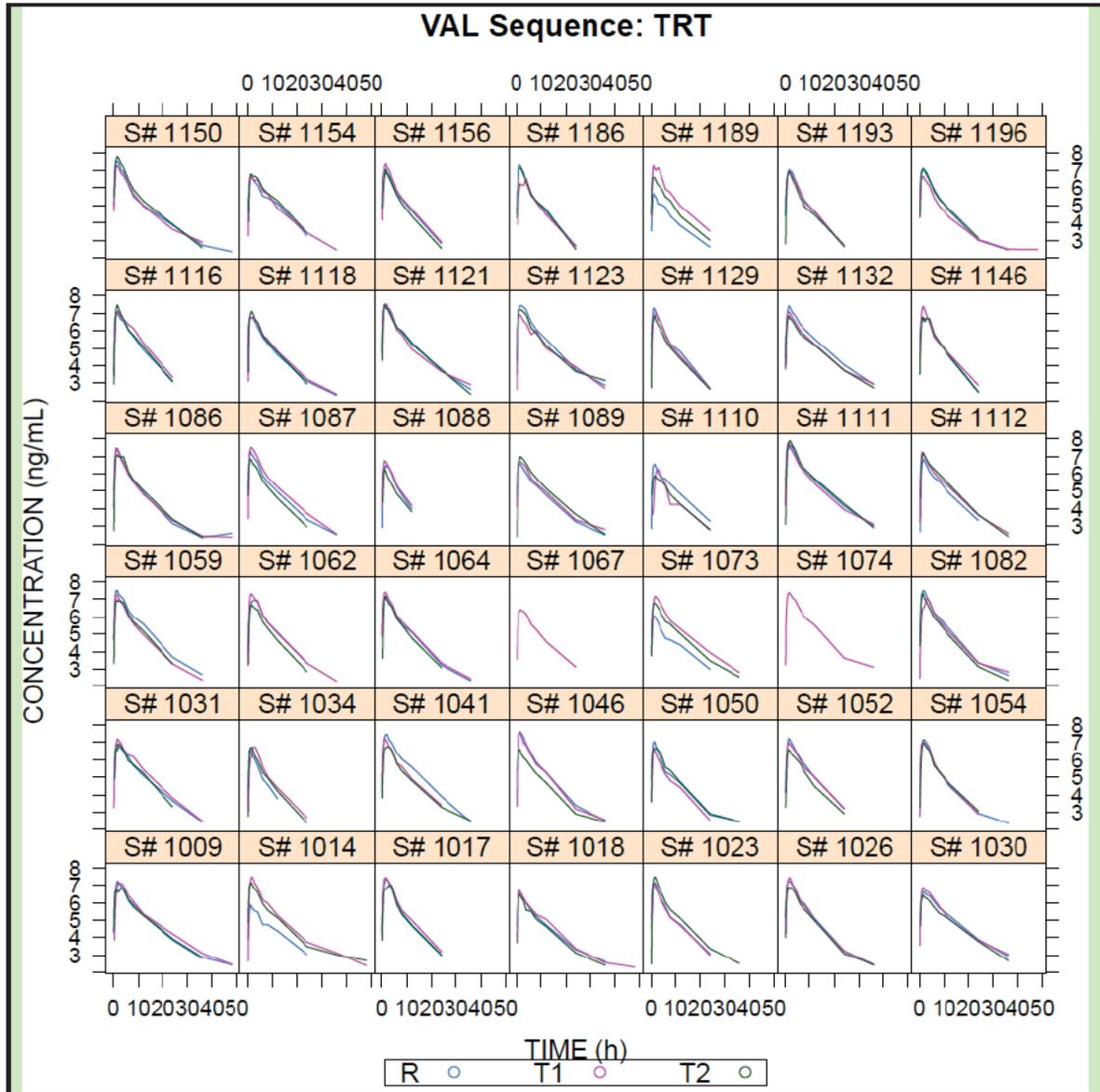
Reviewer’s Assessment: 50 mg Formulation Bridging BE Study ACCEPTABLE

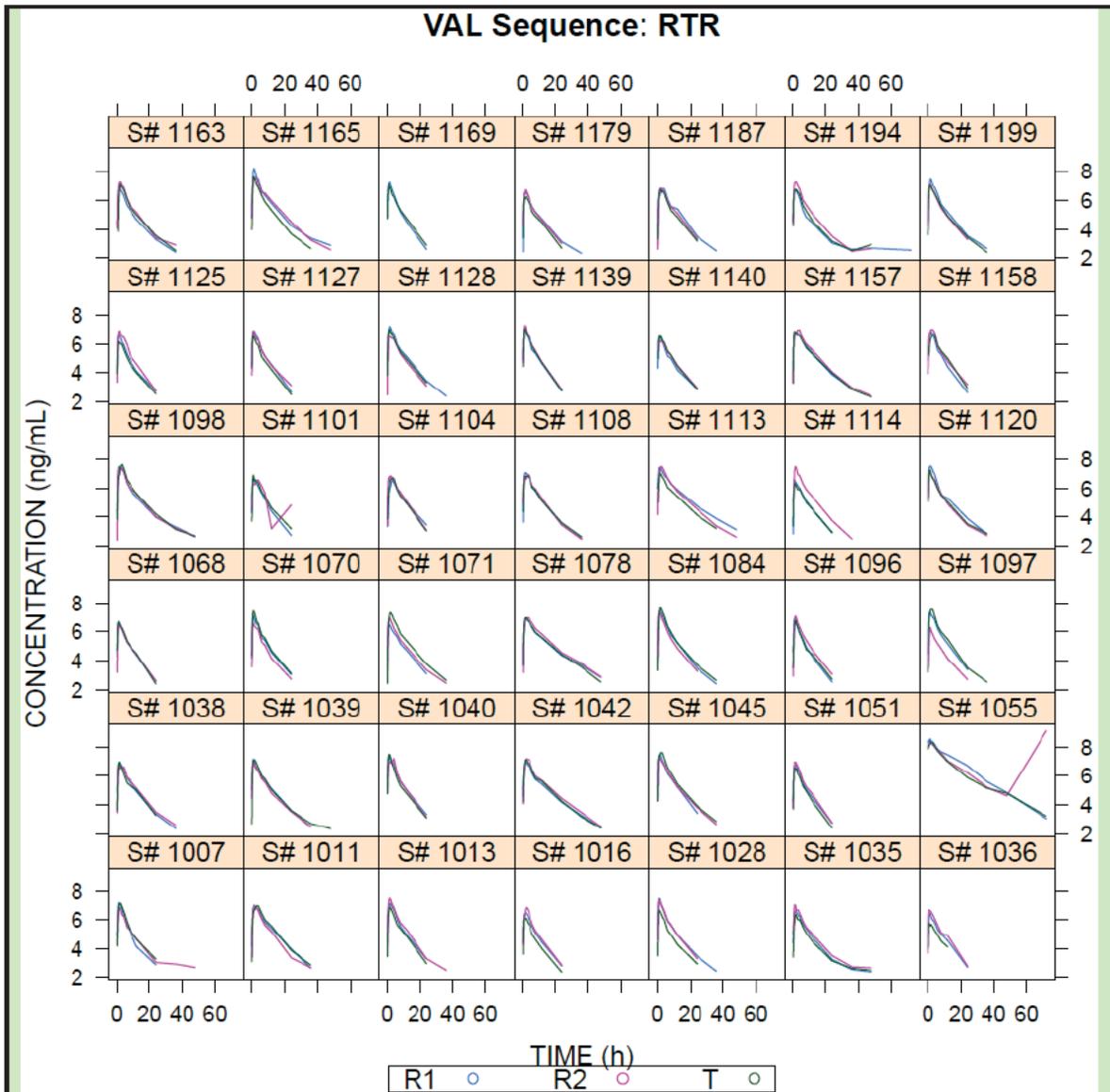
The BE study was executed using an acceptable protocol for demonstrating BE (e.g., sample size, dosing schedule, washout period). The PK profiles of AHU377, LBQ657, and valsartan in each individual subject were analyzed by the reviewer using time-concentration data provided by the applicant. The PK profiles for the CSF formulation and the final market image formulation are similar in individual subjects as shown in the following figure:











The applicant used a linear fixed effect model with formulation, period, treatment, sequence, and subjects as fixed effect variables. The statistical analysis should be conducted with a linear mixed-effects model with formulation, period, and sequence as fixed effects whereas subjects within a given sequence are to be treated as random effects. The statistical analysis conducted by this reviewer yielded the following results:

Analyte	Parameter	T/R (%)	Lower 90% CI	Upper 90% CI
AHU377	C _{max}	96.5	86.9	107.2
	AUC _{last}	97.4	94.7	100.3
	AUC _{inf}	97.5	94.7	100.3
LBQ657	C _{max}	99.8	97.4	102.2

	AUC _{last}	98.8	97.6	100.1
	AUC _{inf}	98.8	97.6	100.0
VAL	C _{max}	95.1	88.5	102.2
	AUC _{last}	94.7	88.4	101.4
	AUC _{inf}	94.2	88.0	100.9

The results indicate that the two products are bioequivalent because the T/R geometric mean ratio for each parameter along with the 90% confidence interval fall within 80-125%.

BIOPHARMACEUTICS INFORMATION REQUEST (dated 02/13/15)

- 1. The dissolution method development report contains dissolution profiles only but does not contain dissolution data (individual, mean, and standard deviation). Provide complete dissolution data (individual, mean, standard deviation) for all the profiles reported in the NDA.*
- 2. Provide the PK profiles and PK parameters for pivotal bioequivalence study (CLCZ696B2114) for the 50 mg final market image and clinical service form in SAS export file format.*

The responses provided by the applicant (dated 02/24/15) are summarized in the biopharmaceutics assessment above.

**OVERALL ASSESSMENT AND SIGNATURES:
BIOPHARMACEUTICS**

Reviewer's Assessment and Signature: PENDING

The recommendation for NDA 207620 is PENDING from a Biopharmaceutics perspective until the dissolution acceptance criterion (a) has/ have been finalized.

The proposed dissolution method is ACCEPTABLE; however, the applicant is requested to change the acceptance criteria to Q = $\frac{(b)}{(4)}$ % at 25 minutes instead of the proposed Q = $\frac{(b)}{(4)}$ % at $\frac{(b)}{(4)}$ minutes.

The dissolution method and acceptance criteria should be the following:

Apparatus	Speed	Volume	Medium	Detection	Acceptance Criterion
USP II	50 rpm	900 mL	Phosphate Buffer, pH 6.8	HPLC/UV $\lambda=255$ nm	Q = $\frac{(b)}{(4)}$ % at 25 min

Salaheldin S. Hamed, Ph.D.
Biopharmaceutics Reviewer
Division of Biopharmaceutics/ONDP
Office of Pharmaceutical Quality

Salaheldin S. Hamed
Digitally signed by Salaheldin S. Hamed
DN: cn=Salaheldin S. Hamed, o=US FDA, ou=CDER, email=salaheldin.hamed@fda.hhs.gov, c=US
Date: 2015.05.15 11:24:47 -04'00'

Supervisor Comments and Concurrence:

Elsbeth Chikhale, Ph.D.
Acting Biopharmaceutics Lead
Division of Biopharmaceutics/ONDP
Office of Pharmaceutical Quality

Elsbeth G. Chikhale - S
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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300136142, cn=Elsbeth G. Chikhale - S
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Note: additional reviewers can be added, as appropriate

ASSESSMENT OF MICROBIOLOGY

29. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Applicant's Response:

Reviewer's Assessment: Acceptable

7 Pages Have Been Withheld In Full As b4 (CCI/TS)
Immediately Following This Page