CLINICAL PHARMACOLOGY REVIEW

NDA	216774
Submission Type	505(b)(2)
Brand Name	ALVAIZ
Drug Name	Eltrombopag Choline
Submission Date	12/03/2021
PDUFA Goal Date	10/03/2022
Priority	Standard
Proposed Indication	- For the treatment of thrombocytopenia in adult and pediatric patients (b) (4) and older with persistent or chronic immune thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. - For the treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy. - For the treatment of patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy.
Proposed Strengths	9, 18, 36, and 54 mg that are equivalent to 12.5, 25, 50, and 75 mg strengths of PROMACTA®
Proposed Dosing Regimen	The dosing regimen is consistent with PROMACTA®, but with different (equivalent) strengths
Route of Administration	Oral
Applicant	Teva Pharmaceuticals Inc.
Clinical Pharmacology Reviewer	Hebing Liu, Ph.D.
Clinical Pharmacology Team Leader	Sudharshan Hariharan, Ph.D.
OCP Division	Division of Cardiometabolic and Endocrine Pharmacology (DCEP)
OND Division	Division of Non-malignant Hematology (DNH)

Contents

1. EXECUTIVE SUMMARY

Teva Pharmaceuticals, Inc has submitted a New Drug Application (NDA 216774) for ALVAIZ (eltrombopag choline) tablets of strengths 9 mg, 18 mg, 36 mg, and 54 mg under Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act. The application relies on Agency's safety and efficacy findings for the listed drug PROMACTA® (eltrombopag olamine) tablets approved under NDA 022291 in 2008. The Applicant is seeking approval for the following indications at different, however equivalent doses as approved for PROMACTA®:

- thrombocytopenia in adult and pediatric patients (b) (4) and older with persistent or chronic immune thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.
- thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy.
- patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy.

The proposed dosing regimen of ALVAIZ is consistent with that approved for PROMACTA®.

No additional clinical efficacy data is presented in this application and no new claims are being sought with this application.

The Applicant has conducted two clinical pharmacology studies: 1) A relative bioavailability (BA) study (ACT-19024) to bridge ALVAIZ (eltrombopag choline) tablet to PROMACTA® (eltrombopag olamine) tablets: open label, randomized, 4-way crossover study to assess the relative BA of single dose of 25 mg and 50 mg eltrombopag choline tablet compared to a single dose of PROMACTA® 50 mg under fasted conditions in healthy subjects. Food-effect for single oral dose of 50 mg eltrombopag choline tablet was also assessed in the same study; 2) A pivotal relative BA study (ACT-21003): open label, randomized, 2-way crossover study to evaluate the relative BA of single dose of 54 mg eltrombopag choline tablet compared to a single dose of PROMACTA® (eltrombopag olamine) tablet 75 mg in healthy subjects under fasted conditions.

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Cardiometabolic and Endocrine Pharmacology (OCP/DCEP) has reviewed the NDA submission. The results of the relative BA study support approval of eltrombopag choline tablets for the proposed indication at the doses equivalent to those approved for the listed drug PROMACTA®. The clinical pharmacology section of the proposed label was updated to reflect the current Guidance on Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products. OSIS determined that inspection of the clinical and bioanalytical sites for the pivotal relative BA study (ACT-21003) were not warranted at this time, as the sites were recently inspected and were classified as No Action Indicated (NAI).

1.2 Post-marketing requirements and commitments

None.

1.3 Summary of clinical pharmacology findings

- The results of the relative BA study (ACT-19024) demonstrate that eltrombopag choline tablets, 25 mg or 50 mg and the listed drug, PROMACTA® (50 mg tablet), are not bioequivalent. ALVAIZ 25 mg has 29% lower C_{max} and AUC_{0-t} compared to PROMACTA® 50 mg. ALVAIZ 50 mg has 32% higher C_{max} and 34% higher AUC_{0-t} compared to PROMACTA® 50 mg. The results of the relative BA study are summarized in *Table 4*. These results indicated that ALVAIZ has a higher bioavailability compared to PROMACTA® and only a strength that is approximately 30% lower will likely be equivalent to the corresponding strength of PROMACTA®.
- The results of the pivotal relative BA study (ACT-21003) demonstrate that eltrombopag choline tablets 54 mg and the listed drug, PROMACTA® (75 mg tablet), are bioequivalent under fasted conditions. The results of the relative BA study are summarized in *Table 5*.
- Administration of eltrombopag choline after a high fat, high calorie meal decreased AUC_{inf} by approximately 36% and C_{max} by approximately 39% as compared to fasted conditions in Study ACT-19024. The food effect results are summarized in *Table 6*.
- The bioanalytical method used to measure eltrombopag choline is validated and the performance of the method in the clinical studies is acceptable as per the specifications outlined in the Bioanalytical Method Validation Guidance (see *Table 3*).

2. QUESTION BASED REVIEW

This is an abridged version of the question-based review. For review of clinical and clinical pharmacology studies supporting the approval of PROMACTA®, refer to the reviews associated with original NDA 022291.

2.1 General attributes of the drug product

2.1.1 What are the general features of the drug product?

The applicant has developed 9, 18, 36 and 54 mg strengths of ALVAIZ tablets for oral administration. The 9 mg strength is available as round, biconvex, film-coated blue tablets debossed with “TV” on one side and “Z9” on the other side; the 18 mg strength is available as round, biconvex, film-coated off-white tablets debossed with “TV” on one side and “Z18” on the other side; 36 mg strength is available as round, biconvex, film-coated red tablets debossed with “TV” on one side and “Z36” on the other side; and the 54 mg strength is available as round, biconvex, film-coated orange tablets debossed with “TV” on one side and “Z54” on the other side. The ALVAIZ tablet contains anhydrous lactose, copovidone (b) (4) (b) (4) croscarmellose sodium, edetate disodium dihydrate, magnesium stearate, poloxamer 188, polyethylene glycol 4000, povidone K12, silicified microcrystalline cellulose, and silicon dioxide, as excipients.

2.1.2 What is the applicant’s rationale in developing this product?

The Applicant developed formulations of eltrombopag tablets containing eltrombopag choline salt, which has the active moiety ‘eltrombopag’. Choline is found in regular diet and is produced endogenously. The amounts of choline salt that are intended for inclusion in Teva’s eltrombopag choline products is well below the recommended maximum tolerable levels in children and adults. Furthermore, choline has been used in other drug products (fenofibrate choline) without posing any safety or efficacy concerns.

2.1.3 What are the proposed mechanism(s) of action of eltrombopag?

Eltrombopag is an orally bioavailable, small-molecule thrombopoietin (TPO)-receptor agonist that interacts with the transmembrane domain of the human TPO-receptor and initiates signaling cascades that induce proliferation and differentiation from bone marrow progenitor cells.

2.1.4 What are the proposed therapeutic indication(s)?

The proposed therapeutic indications for ALVAIZ are:

- **for the treatment of thrombocytopenia in adult and pediatric patients (b) (4) and older with persistent or chronic ITP who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy (see *Note* under 2.1.5).**
- **for the treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy.**
- **for the treatment of patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy.**

The Applicant is not seeking approval for the first-line treatment of adult and pediatric patients 2 years and older with severe aplastic anemia in combination with standard immunosuppressive therapy due to patent and/or exclusivity reasons.

2.1.5 What are the proposed dose(s)?

The proposed dosing instructions for ALVAIZ are listed in *Table 1*.

Table 1. Indication and dosing instructions for ALVAIZ and the listed drug PROMACTA®.

Indication	Proposed dosing regimen for ALVAIZ	Approved dosing regimen for PROMACTA
General	Take ALVAIZ without a meal or with a meal low in calcium (≤ 50 mg). Take ALVAIZ at least 2 hours before or 4 hours after any medications or products containing polyvalent cations, such as antacids, calcium-rich foods, and mineral supplements.	Take PROMACTA without a meal or with a meal low in calcium (≤ 50 mg). Take PROMACTA at least 2 hours before or 4 hours after any medications or products containing polyvalent cations, such as antacids, calcium-rich foods, and mineral supplements.
Persistent or chronic immune thrombocytopenia	Initiate ALVAIZ at 36 mg once daily for most adult and pediatric patients 6 years and older, (b) (4) (b) (4) (b) (4) Dose reductions are needed for patients with hepatic impairment and some patients of Asian ancestry. Adjust to maintain platelet count greater than or equal to	Initiate PROMACTA at 50 mg once daily for most adult and pediatric patients 6 years and older, and at 25 mg once daily for pediatric patients aged 1 to 5 years. Dose reductions are needed for patients with hepatic impairment and some patients of Asian ancestry. Adjust to maintain platelet count greater than or equal to

	50 x 10^9/L. Do not exceed 54 mg per day.	50 x 10^9/L. Do not exceed 75 mg per day.
Chronic hepatitis C-associated thrombocytopenia	Initiate ALVAIZ at 18 mg once daily for all patients. Adjust to achieve target platelet count required to initiate antiviral therapy. Do not exceed a daily dose of 72 mg.	Initiate PROMACTA at 25 mg once daily for all patients. Adjust to achieve target platelet count required to initiate antiviral therapy. Do not exceed a daily dose of 100 mg.
Refractory severe aplastic anemia	Initiate ALVAIZ at 36 mg once daily. Reduce initial dose in patients with hepatic impairment or patients of Asian ancestry. Adjust to maintain platelet count greater than 50 x 10^9/L. Do not exceed 108 mg per day.	Initiate PROMACTA at 50 mg once daily. Reduce initial dose in patients with hepatic impairment or patients of Asian ancestry. Adjust to maintain platelet count greater than 50 x 10^9/L. Do not exceed 150 mg per day.

Note: (b) (4) the use of ALVAIZ for the treatment of persistent or chronic ITP will be restricted to patients 6 years and older.

2.2 Review of clinical studies supporting the submission

2.2.1 What are the design features of clinical pharmacology studies used to support dosing or label claims?

The Applicant submitted two clinical pharmacology studies in this NDA (***Table 2***). 1) The pilot relative BA study (ACT-19024) compared the bioavailability of 25 mg and 50 mg eltrombopag choline tablet to 50 mg PROMACTA® (eltrombopag olamine) tablet following single oral dose administration in 24 healthy subjects under fasted conditions. Food-effect for single oral dose of 50 mg eltrombopag choline tablet was also assessed in the same study. 2) The pivotal relative bioavailability study (ACT-21003) compared the bioavailability of 54 mg eltrombopag choline tablet to 75 mg PROMACTA® (eltrombopag olamine) tablet following single oral dose administration in 80 healthy subjects under fasted conditions.

The studies have been summarized in ***Table 2***. Please refer *Appendix* for the individual study reviews.

Table 2. Summary of clinical pharmacology studies.

Study number Study type	Design	Study participants
ACT-19024 Relative bioavailability study	Open label, randomized, single dose, four-way crossover study to assess the relative bioavailability of a test formulation of a single 25 mg (Treatment A) and 50 mg	Enrolled: 24 (20 men and 4 women) Completed: 23 (19 men and 4 women) Age Range: 27-55 years

	(Treatment B) dose of eltrombopag choline tablet, under fasted and fed conditions (Treatment C, 50 mg) versus PROMACTA® (Treatment D) 50 mg tablets under fasted conditions in healthy adults	
ACT-21003 Relative bioavailability study	Open label, randomized, single dose, two-way crossover study to assess the relative bioavailability of a test formulation of a single 54 mg dose of eltrombopag choline tablet (Treatment A) versus PROMACTA® (Treatment B) 75 mg tablets under fasted conditions in healthy adults	Enrolled: 80 (54 men and 26 women) Completed: 77 (51 men and 26 women) Age Range: 21-60 years

2.2.2 Is the active moiety in the plasma appropriately identified and measured to assess pharmacokinetic parameters?

A validated LC-MS/MS analytical method for quantifying eltrombopag in human plasma treated with K2EDTA was used for the bioanalysis of this study. Eltrombopag $^{13}C_4$ was used as the internal standard (IS) for eltrombopag. Human plasma containing eltrombopag, and the internal standard, eltrombopag $^{13}C_4$, was extracted using liquid-liquid extraction.

The bioanalytical validation summary for study ACT-19024 and study ACT-21003 is provided in *Table 3*.

Table 3. Bioanalytical method validation summary for eltrombopag plasma concentration analysis.

Parameter	Study	
	ACT-19024	ACT-21003
Method	LC-MS/MS	LC-MS/MS
LLOQ (ng/mL)	50.9	50
CS concentration (ng/mL)	50, 100, 500, 1500, 3000, 7500, 15000, 25000, 30000	50, 100, 500, 1500, 3000, 7500, 15000, 25000, 30000
QCs (ng/mL)	LQC – 151.8 MQC – 15175 HQC – 23067	LQC – 148.1 MQC – 14407 HQC – 23523
CS accuracy (bias) (%)	-2.1 to 2.3	-2.1 to 5.0
CS precision (%)	≤2.75	≤2.67
QC accuracy (bias) (%)	-1.0 to 0.8	-9.3 to 0.02
QC precision (%)	≤2.74	≤3.11
Average recovery of drug (%) IS (%)	74.9 82.1	58.5 60.1

CS: Calibration curve standard, QC: Quality control samples, LLOQ: Lower Limit of Quantification

Source: Bioanalytical study validation report (Study ACT-19024 and Study ACT-21003).

2.2.3 What is the relative bioavailability of ALVAIZ tablet compared to PROMACTA® tablet?

2.2.3.1 Relative bioavailability from study ACT-19024

The results of the relative bioavailability study ACT-19024 show that eltrombopag choline (25 mg or 50 mg tablet) and the listed drug, PROMACTA® (50 mg tablet), are not bioequivalent. The mean systemic exposure (AUC_{0-72}) of eltrombopag following administration of 25 mg eltrombopag choline is 29% lower than PROMACTA® (50 mg), while AUC_{0-72} of eltrombopag following administration of 50 mg eltrombopag choline is 34% higher (*Table 4*). Peak plasma concentration for 25 mg ALVIAZ is 29% lower, while the peak plasma concentration for 50 mg ALVAIZ is 32% higher compared to that for 50 mg PROMACTA®. These results indicated that ALVAIZ has a higher bioavailability compared to PROMACTA® and only a strength that is approximately 30% lower will likely be equivalent to the corresponding strength of PROMACTA®.

Table 4. PK results from relative bioavailability study for ALVAIZ 25 mg and 50 mg tablets (ACT-19024).

Parameter	Test 1(A)/ Reference (D) Ratio %	90% CI (%)	Test 2(B)/ Reference (D) Ratio %	90% CI (%)
AUC_{0-72}	71.4	(61.1, 83.3)	134.2	(106.7, 168.8)
AUC_{0-inf}	70.9	(60.6, 83.0)	136.9	(109.9, 170.6)
C_{max}	71.4	(58.5, 87.3)	131.5	(99.0, 174.8)

Test product 1 (A): Eltrombopag Choline Tablets, Eq. 25 mg Eltrombopag (fasting), Test product 2 (B): Eltrombopag Choline Tablets, Eq. 50 mg Eltrombopag (fasting), Reference product (D): PROMACTA® (eltrombopag) Tablets, 50 mg (fasting)

Source: Applicant's ACT-19024 report. Table 7 on page 78.

2.2.3.2 Relative bioavailability from study ACT-21003

The geometric mean ratios along with its 90% confidence interval (CI) for C_{max}, AUC_{0-72} and AUC_{0-inf} for 54 mg ALVAIZ tablets compared to 75 mg PROMACTA® tablets from pivotal study ACT-21003 are summarized in *Table 5*.

Table 5. PK results from relative bioavailability study for ALVAIZ 54 mg (ACT-21003).

Parameter	Test (T)/ Reference (R) Ratio %	90% C.I (%)
AUC_{0-72}	94.5	(89.3, 99.9)
AUC_{0-inf}	94.7	(89.5, 100.3)
C_{max}	95.4	(89.8, 101.3)

Test product: Eltrombopag Choline Tablets, Eq. 54 mg Eltrombopag (fasting), Reference product: PROMACTA® (eltrombopag) Tablets, 75 mg (fasting)

Source: Applicant's ACT-21003 report. Table on page 60.

The test formulation of 54 mg eltrombopag choline tablets is bioequivalent to the PROMACTA® 75 mg tablets, under fasted conditions.

Note: Office of Study Integrity and Surveillance (OSIS) inspection of the clinical and bioanalytical sites for Study ACT-21003 was requested. However, OSIS determined that inspection of the sites were not warranted at this time as the sites were recently inspected and were classified as No Action Indicated (NAI).

2.2.4 What is the effect of food on the bioavailability of the drug from the drug product?

The effect of food is evaluated in Study ACT-19024. Taking ALVAIZ tablet with a high-fat, high-calorie meal decreases AUC_{inf} by approximately 36% and C_{max} by approximately 39% as compared to fasted conditions (*Table 6*). T_{max} is delayed by 30 minutes (median T_{max}: 3.0 h vs 3.5 h) in fed state.

Table 6. PK results from food effect study for ALVAIZ 50 mg tablets.

Parameter	Test 2(C)/ Test 2(B) Ratio %	90% C.I (%)
AUC_{0-72}	65.1	(50.7, 83.6)
AUC_{0-inf}	64.0	(50.6, 81.0)
C_{max}	60.9	(45.0, 82.4)

Test product 2 (B): Eltrombopag Choline Tablets, Eq. 50 mg Eltrombopag (fasting), Test product 2 (C): Eltrombopag Choline Tablets, Eq. 50 mg Eltrombopag (fed)

Source: Applicant's ACT-19024 report. Table 7 on page 79.

Although the Applicant did not conduct food effect studies with varying levels of calcium, the interaction of PROMACTA® with calcium is specific for eltrombopag regardless of the salt form. Therefore, information about the lack of interaction with diet low in calcium can be borrowed from PROMACTA® to support administration of ALVAIZ with meals low in calcium. Therefore, ALVAIZ should be taken without a meal or with a meal low in calcium (≤50 mg).

3. APPENDICES

3.1 Relative bioavailability study report – ACT-19024

Study No: ACT-19024	EDR: \\CDSESUB1\evsprod\nda216774\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\act-19024\report-body.pdf
Clinical Study Start Date: 28-Apr-2020 Clinical Study Completion Date: 01-Jun-2020	
Title of Study: An open label, randomized, single dose, four-way crossover comparative bioavailability study of Eltrombopag tablets, 25 mg and 50 mg in healthy human, adult males and females of non-childbearing potential under fasting and fed conditions.	
Investigational Product: Test Product: ALVAIZ (eltrombopag choline) 25 mg, 50 mg tablet Reference: PROMACTA® (eltrombopag olamine) 50 mg tablet	
Study: Study Design: An open label, randomized, balanced, four-treatment, four-period, four-sequence, single dose crossover comparative bioavailability study under fasting and fed conditions. o Test Product 1 (A): Eltrombopag Choline Tablets, Eq. 25 mg Eltrombopag (under fasting conditions) o Test Product 2 (B): Eltrombopag Choline Tablets, Eq. 50 mg Eltrombopag (under fasting conditions)	

- Test Product 2 (C): Eltrombopag Choline Tablets, Eq. 50 mg Eltrombopag (under fed conditions)
- Reference Product (D): Promacta® (eltrombopag) Tablets, 50 mg (under fasting conditions)

- Washout: At least 10 days between doses
- Study participants: 23 healthy adults (19 men and 4 women), 27-55 years of age
- Treatment administration
  - 1 × 25 mg tablet of test product 1 (A) given as a single oral dose with approximately 240 mL (8 fluid ounces) of water at ambient temperature after an overnight fast of at least 10 hours.
  - 1 × 50 mg tablet of test product 2 (B) given as a single oral dose with approximately 240 mL (8 fluid ounces) of water at ambient temperature after an overnight fast of at least 10 hours.
  - 1 × 50 mg tablet of test product 2 (C) given as a single oral dose with approximately 240 mL (8 fluid ounces) of water at ambient temperature 30 minutes after the start of standardized high calorie, high fat breakfast administered after an overnight fast of at least 10 hours.
  - 1 × 50 mg tablet of Reference product (D) given as a single oral dose with approximately 240 mL (8 fluid ounces) of water at ambient temperature after an overnight fast of at least 10 hours.
- Sampling times (h): pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 10, 12, 16, 24, 36, 48, and 72 h post-dose

Pharmacokinetic parameters calculated: AUC_{0-72}, AUC_{0-inf}, C_{max}, T_{max}, K_{el} and $t_{1/2}$

Analytical Methods:

- A validated LC-MS method, as described in *section 2.2.2*, was used for the estimation of eltrombopag in human K2EDTA plasma using eltrombopag $^{13}C_4$ as internal standard.
- The analytical range for eltrombopag in plasma was 50 ng/mL - 30000 ng/mL

Reviewer comment: The performance of the analytical method is acceptable per the specifications in Bioanalytical Method Validation Guidance.

Statistical Methods:

- These pharmacokinetic parameters were calculated by non-compartmental analysis. The log-transformed pharmacokinetic parameters (C_{max}, AUC_{0-72} and AUC_{0-inf}) were analyzed using sum of squares with the main effects of treatment, period and sequence as fixed effects, and subjects nested within sequence as random effect.
- ANOVA was used to analyze each of the parameters. The main effects were tested at the 5% level of significance against the residual error (mean square error/MSE) from the ANOVA as the error term.

Results:

23 subjects completed the study. A total of 23 blood samples were collected in each study period for pharmacokinetic analysis of eltrombopag concentrations.

Table 7. Demographics

Age range	27 – 55 years
Males Females	19 (82.6%) 4 (17.4%)
Weight	69.7 – 97.0 kg

Table 8. Subject disposition

	All subjects N (%)
Randomized	24 (100)
Completed	23 (95.8)
Not completed	1 (4.2)
Protocol deviation	1 (4.2)
Lost to follow-up	1 (4.2)

One subject did not complete the study as the subject was no-show to Period 3 admission but was considered for pharmacokinetic and statistical analysis as this subject had completed two periods of the study and received the reference product in at least one of the completed periods.

For statistical summary of relative BA data, refer to *Table 4* in section 2.2.3.1 and comparison of fed and fasted state, refer to *Table 6* in *section 2.2.4*.

Table 9. Summary of PK parameters

Parameter	Test Product 1 (A) Mean(SD) (N = 23)	Test Product 2 (B) Mean(SD) (N = 23)	Test Product 3 (C) Mean(SD) (N = 24)	Reference Product (D) Mean (SD) (N = 24)
AUC_{0-72} (h.ng/mL)	36569 (9627)	76686 (25618)	45839 (13283)	55066 (21911)
AUC_{0-inf} (h.ng/mL)	38953 (11038)	83311 (29151)	49359 (15047)	59258 (24546)
C_{max} (ng/mL)	3942 (816)	8142 (2279)	4692 (1794)	6012 (2106)
T_{max} (h)	3.0 (1.5 – 5.0)	3.0 (1.5 – 4.5)	3.5 (1.0 – 8.0)	3.0 (2.0 – 6.0)
$t_{1/2}$ (h)	21.4 (7.3)	25.6 (7.5)	23.0 (8.2)	23.0 (7.4)
K_{el} (h-1)	0.04 (0.02)	0.03 (0.01)	0.04 (0.02)	0.03 (0.02)

Test Product 1 (A): Eltrombopag Choline Tablets, Eq. 25 mg Eltrombopag (Under fasting conditions)
Test Product 2 (B): Eltrombopag Choline Tablets, Eq. 50 mg Eltrombopag (Under fasting conditions)
Test Product 2 (C): Eltrombopag Choline Tablets, Eq. 50 mg Eltrombopag (Under fed conditions)
Reference Product (D): Promacta® (eltrombopag) Tablets, 50 mg (Under fasting conditions)
Source: Applicant's ACT-19024 report. Table on page 59.

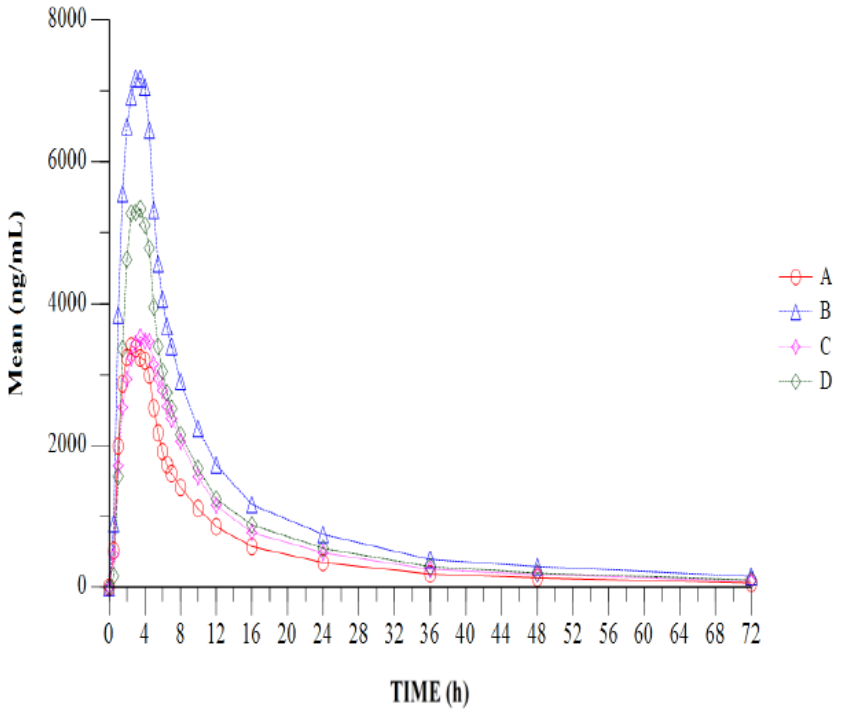

Figure 1. Plot of mean plasma eltrombopag concentration vs time profiles.

(A: Eltrombopag Choline Tablets, Eq. 25 mg Eltrombopag – Fasted, B: Eltrombopag Choline Tablets, Eq. 50 mg Eltrombopag – Fasted, C: Eltrombopag Choline Tablets, Eq. 50 mg Eltrombopag – Fed, D: Promacta® (eltrombopag) Tablets, 50 mg – Fasted)
Source: Applicant's ACT-19024 report. Figure 1 on page 65.

Conclusion:
The study results demonstrate that eltrombopag choline tablets, 25 mg or 50 mg and the listed drug, PROMACTA® (50 mg tablet), are not bioequivalent. The relative bioavailability of eltrombopag choline tablets is approximately 30% higher than PROMACTA®.
Following administration of eltrombopag choline tablets, 50 mg after a high fat high calorie meal decreased $AUC_{0\text{-}inf}$ by approximately 36% and Cmax by approximately 39%.

3.2 Relative bioavailability study report – ACT-21003

Study No: ACT-21003	EDR: \\CDSESUB1\evsprod\nda216774\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\act-21003\report-body.pdf
Clinical Study Start Date: 05-May-2021 Clinical Study Completion Date: 23-May-2021	
Title of Study: An open label, randomized, single dose, two-way crossover bioequivalence study of Eltrombopag Choline Tablets, Eq. 54 mg Eltrombopag in healthy human, adult males and females of non-childbearing potential under fasting conditions.	
Investigational Product: Test Product:	

ALVAIZ (eltrombopag choline) 54 mg tablet
Reference:
PROMACTA® (eltrombopag olamine) 75 mg tablet

Study:
Study Design: An open label, randomized, balanced, two-treatment, two-period, two-sequence, single dose crossover bioequivalence study under fasting conditions.

- Test Product (T): Eltrombopag Choline Tablets, Eq. 54 mg Eltrombopag (under fasting conditions)
- Reference Product (R): Promacta® (eltrombopag) Tablets, 75 mg (under fasting conditions)

- Washout: At least 14 days between doses
- Study participants: 77 healthy adults (51 men and 26 women), 21-60 years of age
- Treatment administration
  - Following an overnight fast of at least 10 hours, a single oral dose of investigational product [1 x 54 mg tablet of Test product or 1 x 75 mg tablet of Reference product] was administered with 240 mL of water at ambient temperature.
- Sampling times (h): pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 10, 12, 16, 24, 36, 48, and 72 h post-dose

Pharmacokinetic parameters calculated: AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, K_{el} and $t_{1/2}$
Analytical Methods:

- A validated LC-MS method, as described in *section 2.2.2*, was used for the estimation of eltrombopag in human K2EDTA plasma using eltrombopag $^{13}C_4$ as internal standard.
- The analytical range for eltrombopag in plasma was 50 ng/mL - 30000 ng/mL

Reviewer comment: The performance of the analytical method is acceptable per the specifications in Bioanalytical Method Validation Guidance.
Statistical Methods:

- These pharmacokinetic parameters were calculated by non-compartmental analysis. The log-transformed pharmacokinetic parameters (C_{max}, AUC_{0-72} and AUC_{0-inf}) were analyzed using sum of squares with sequence, subjects nested within sequence, period and treatment as the fixed effects.
- ANOVA was used to analyze each of the parameters. All the fixed effects were tested at 5 % level of significance, using the residual error (mean square error or MSE) from the ANOVA as the error term. The sequence effect was also tested at the 10 % level of significance using the mean sum of square of subjects nested within sequence, from the ANOVA as the error term.

Results:
77 subjects completed the study. A total of 23 blood samples were collected in each study period for pharmacokinetic analysis of eltrombopag concentrations.

Table 10. Demographics

Age range	21 – 60 years
Males Females	51 (66.2%) 26 (33.8%)
Weight	59.0 – 106.4 kg

Table 11. Subject disposition

	All subjects N (%)
Randomized	80 (100)

Completed	77 (96.3)
Not completed	3 (3.7)
Protocol deviation	0 (0)
Lost to follow-up	3 (100)

One subject did not complete the study as the subject was no-show to Period 2 admission, the other two subjects withdrew consent due to personal reasons.

For statistical summary of relative BA data, refer to *Table 5* in *section 2.2.3.2*.

Table 12. Summary of PK parameters

Parameter	Test Product (T) Mean (SD) (N = 77)	Reference Product (R) Mean (SD) (N = 77)
AUC_{0-t} (h.ng/mL)	92203 (32755)	84668 (23539)
AUC_{0-inf} (h.ng/mL)	100953 (37424)	93078 (28131)
C_{max} (ng/mL)	10115 (3358)	9310 (2190)
T_{max} (h)	3.0 (1.5 – 5.0)	2.5 (1.5 – 5.5)
$t_{1/2}$ (h)	27.3 (8.2)	28.2 (8.5)
K_{el} (h-1)	0.03 (0.01)	0.03 (0.01)

Test Product (T): Eltrombopag Choline Tablets, Eq. 54 mg Eltrombopag (Under fasting conditions)
Reference Product (R): Promacta® (eltrombopag) Tablets, 75 mg (Under fasting conditions)
Source: Applicant's ACT-21003 report. Table on page 60.

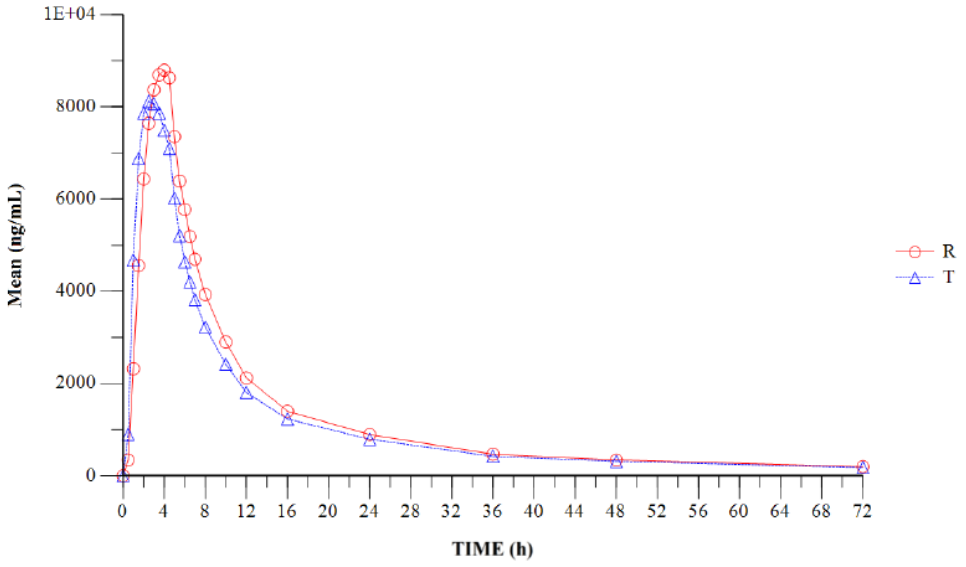

Figure 2. Plot of mean plasma eltrombopag concentration vs time profiles.

(T: Eltrombopag Choline Tablets, Eq. 54 mg Eltrombopag – Fasted, R: Promacta® (eltrombopag) Tablets, 75 mg – Fasted)
Source: Applicant's ACT-21003 report. Figure 1 on page 61.

Conclusion:
The study results demonstrate that eltrombopag choline tablets, equivalent to 54 mg eltrombopag and the listed drug, PROMACTA® (75 mg tablet), are bioequivalent.

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/s/

HEBING LIU
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SUDHARSHAN HARIHARAN
09/02/2022 01:37:11 PM