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APPLICATION NUMBER:

219293Orig1s000

CLINICAL REVIEW(S)

Clinical Review of 505b2 Application of Nilotinib
Division of Hematologic Malignancies I

NDA Number:	219293
Date:	October 1, 2024
From:	Joseph Wynne, MD, PhD
Subject:	Clinical Review
Applicant:	Azurity Pharmaceuticals, Inc
Date of Submission:	January 30, 2024
PDUFA Goal Date:	November 30, 2024
Proprietary Name/ Non-Proprietary name:	Danziten/ nilotinib
Dosage Form/ Strengths:	Oral tablets: • 71 mg tablet (taken as two tablets BID for newly-diagnosed Ph+ CP-CML) • 95 mg tablet (taken as two tablets BID for resistant or intolerant Ph+ CML-CP and CML-AP)
Applicant Proposed Indication(s)/Populations (s):	• Adult patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase. • Adult patients with chronic phase (CP) and accelerated phase (AP) Ph+ CML resistant to or intolerant to prior therapy that included imatinib.
Recommendation on Regulatory Action:	Approval
Recommended Indication(s)/Population(s) (if applicable):	As above per Applicant proposed indications

Regulatory History:

1. January 22, 2024: Agreed iPSP letter for nilotinib tartrate (Danziten) tablets issued to PIND 144071.
2. January 30, 2024: New NDA 505 (b) (2) submitted by Azurity

Background and Summary:

Nilotinib is a second generation, oral tyrosine kinase inhibitor and binds to and stabilizes the inactive confirmation of the kinase domain of the ABL protein. Nilotinib (Tasigna) is currently approved for:

a) Adult patients with newly-diagnosed, Philadelphia positive (Ph+) chronic myeloid leukemia in chronic phase (CML-CP).
b) Adult patients with Ph+ CML-CP or Ph+ CML-AP (accelerated phase) that are resistant or intolerant to prior TKI, including imatinib.
c) Pediatric patients greater than or equal to 1 year of age with Ph+ CML-CP and CML-AP resistant or intolerant to prior tyrosine-kinase inhibitor (TKI) therapy.

Nilotinib tablets (Danziten), by Azurity Pharmaceuticals, is another oral formulation of nilotinib developed from alternative salt. The listed drug, Tasigna, is produced from the chloride salt of nilotinib while Danziten is made from the tartrate salt of nilotinib. Due to improved bioavailability of the Applicant's formulation, the proposed tablet strengths of 71 mg and 95 mg of Danziten are bioequivalent with similar exposure to current corresponding strengths of Tasigna (listed drug, LD) of 150 mg and 200 mg, respectively. Please see the clinical pharmacology review for additional details. No significant safety signals were identified from the healthy volunteer trials.

The Applicant is seeking the following indications:

a) Adult patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase.
b) Adult patients with chronic phase (CP) and accelerated phase (AP) Ph+ CML resistant to or intolerant to prior therapy that included imatinib.

The Applicant is not seeking a pediatric indication due to remaining patents and exclusivities that Tasigna holds for these indications.

The Applicant conducted 6 pivotal studies to demonstrate the bioequivalence and food effects of their nilotinib tartrate formulation that are summarized below:

1. Pivotal Study #1: 010-22: Phase 1, An open-label, balanced, randomized, single-dose, two-treatment, two-period, two-sequence, crossover, oral relative bioavailability of nilotinib tablets 95 mg (2 x 95 mg) in normal, healthy, adult, human subjects under fasting conditions.
    a. The primary objective was to evaluate the oral relative bioavailability of Nilotinib Tablets 95 mg (2 x 95 mg) of Slayback Pharma with Tasigna® (nilotinib) Capsules 200 mg (2 x 200 mg), in normal, healthy, adult, human subjects under fasting condition.
    b. Volunteers received standard meal (check-in night dinner) provided on day 01 (i.e., check-in day) after check-in activity was completed, on day 02 (breakfast, lunch, snacks and dinner) at -24.00, -20.00, -16.00 and -12.00 pre-dose, on day 03 (lunch, snacks and dinner) at 4.00, 8.00 and 12.00 hours post dose and on day 04 (breakfast, lunch, snacks and dinner) at 24.00, 28.00, 32.00 and 36.00 hours post dose. All the subjects had fasted overnight for at least 10.00 hours prior to dosing and till 4.00 hours post dose.
    c. Enrolled 96 healthy adult volunteers, 92 completed the study.
    d. N=2 volunteers withdrew, one for positive drug screen for prior to second period, one for personal reasons. N= 2 volunteers were dropouts as they did not return for period two of the study.
    e. No reported AEs
    f. No new safety signals were identified and there were no deaths or serious adverse events.

2. Pivotal Study #2: 011-22: Phase 1, An open-label, balanced, randomized, single-dose, three-treatment, three-period, three-sequence, three-way crossover oral relative bioavailability and food effect study of Nilotinib tablets 95 mg (2 x 95 mg) in normal, healthy, adult, human subjects under modified fasting and fed conditions.

a. The primary objective was to evaluate the oral relative bioavailability and food effect study of Nilotinib tablets 95 mg (2 x 95 mg) of Slayback Pharma with Tasigna® (nilotinib) capsules 200 mg (2 x 200 mg) in normal, healthy, adult, human subjects under modified fasting and fed conditions.
b. Volunteers received standard meal (check-in night dinner) provided on day 01 (i.e., check-in day) after check-in activity was completed, on day 02 (breakfast, lunch, snacks and dinner).
    i. Under fed conditions: In each study period, the respective subjects had fasted overnight for at least 10.00 hours prior to start of consumption of a high-fat high-calories non-vegetarian breakfast 30 minutes before dosing and till 4.00 hours post dose.
    ii. Under modified Fasting: In each study period, the respective subjects had fasted overnight for at least 10.00 hours prior to start of consumption of a high-fat high-calories non-vegetarian breakfast with dosing occurring 2 hours after dosing.
c. Enrolled 36 + 1 standby healthy volunteers and 32 completing the study.
d. N=3 volunteers withdrew, one voluntarily, one for non-consumption of high fat meal, and one prior to period 3 check in. N= 2 volunteers were dropouts as they did not return for period two of the study.
e. 3 healthy volunteers experienced at least 1 TEAE:
    i. TEAEs experienced by >1 HV was headache (N=2)
f. No new safety signals were identified and there were no deaths or serious adverse events.

3. Pivotal Study #3: 128-22: Phase 1, open-label, balanced, randomized, single-dose, two-treatment, two-period, two-sequence, crossover, oral relative bioavailability study of Nilotinib Tablets 71 mg (2X71 mg) in normal, healthy, adult, human subjects under fasting condition
    a. Primary endpoint was to evaluate the oral relative bioavailability study of Nilotinib Tablets 71 mg (2 x 71 mg) of Slayback Pharma with that Tasigna® (nilotinib) Capsules 150 mg (2 x 150 mg) in normal, healthy, adult, human subjects under fasting condition.
    b. Volunteers received standard meal (check-in night dinner) provided on day 01 (i.e., check-in day) after check-in activity was completed, on day 02 (breakfast, lunch, snacks and dinner) at -24.00, -20.00, -16.00 and -12.00 pre-dose, on day 03 (lunch, snacks and dinner) at 4.00, 8.00 and 12.00 hours post dose and on day 04 (breakfast, lunch, snacks and dinner) at 24.00, 28.00, 32.00 and 36.00 hours post dose. All the subjects had fasted overnight for at least 10.00 hours prior to dosing and till 4.00 hours post dose.
    c. Enrolled 90 healthy volunteers with 87 completing the study.
    d. N=3 volunteers dropped out at the time of period 2 for personal reasons.
    e. 10 healthy volunteers experienced at 1 TEAE
        i. TEAEs experienced by >1 HV was chest pain (N=2), itching rash (N=2), and eosinophilia (N=2) (occurred in post-study assessments).
    f. No new safety signals were identified and there were no deaths or serious adverse events.

4. Pivotal Study #4: 006-23: Phase 1, open-label, balanced, randomized, single-dose, single-treatment, three period, three-sequence, three-way crossover oral relative bioavailability and food effect study of Nilotinib Tablets 95 mg (2 x 95 mg) in normal, healthy, adult, human subjects under fasting, fed and modified fasting conditions
    a. The primary objective was to evaluate oral relative bioavailability and food effect of Nilotinib Tablets 95 mg (2 x 95 mg) Test product (T) of Slayback Pharma India LLP, Hyderabad, India in normal, healthy, adult, human subjects under fasting, fed and modified fasting conditions.
    b. Volunteers received standard meal (check-in night dinner) provided on day 01 (i.e., check-in day) after check-in activity was completed, on day 02 (breakfast, lunch, snacks and dinner).
        i. Under fed conditions: In each study period, the respective subjects had fasted overnight for at least 10.00 hours prior to start of consumption of a high-fat high-calories non-vegetarian breakfast 30 minutes before dosing and till 4.00 hours post dose.
        ii. Under modified Fasting: In each study period, the respective subjects had fasted overnight for at least 10.00 hours prior to start of consumption of a high-fat high-calories non-vegetarian breakfast with dosing occurring 2 hours after dosing.
        iii. Under fasting: All the subjects had fasted overnight for at least 10.00 hours prior to dosing and till 4.00 hours post dose.
    c. Enrolled 36 + 2 standby healthy volunteers and 30 subjects completed all three study periods.
    d. N=3 volunteers withdrew: one for non-consumption of high fat meal, and one for AE of fever and chills, and one for AE vomiting. N= 5 volunteers were dropouts, 4 as they did not return for period two or three and 1 volunteer for personal reasons.
    e. 8 healthy volunteers experienced at least 1 TEAE
        i. The TEAEs reported in >1 HV vomiting in 2.
    f. No new safety signals were identified and there were no deaths or serious adverse events.

5. Pivotal Study #5: 007-23: Phase 1, open-label, balanced, randomized, single-dose, single-treatment, three-period, three-sequence, three-way crossover oral relative bioavailability and food effect study of Nilotinib Tablets 71 mg (2 x 71 mg) in normal, healthy, adult, human subjects under fasting, fed and modified fasting conditions
    a. The primary objective was to evaluate oral relative bioavailability and food effect of Nilotinib Tablets 71 mg (2 x 71 mg) Test product (T) of Slayback Pharma healthy, adult, human subjects under fasting, fed and modified fasting conditions.
    b. Volunteers received standard meal (check-in night dinner) provided on day 01 (i.e., check-in day) after check-in activity was completed, on day 02 (breakfast, lunch, snacks and dinner).
        i. Under fed conditions: In each study period, the respective subjects had fasted overnight for at least 10.00 hours prior to start of consumption of a high-fat

high-calories non-vegetarian breakfast 30 minutes before dosing and till 4.00 hours post dose.

ii. Under modified Fasting: In each study period, the respective subjects had fasted overnight for at least 10.00 hours prior to start of consumption of a high-fat high-calories non-vegetarian breakfast with dosing occurring 2 hours after dosing.

iii. Under fasting: All the subjects had fasted overnight for at least 10.00 hours prior to dosing and till 4.00 hours post dose

c. Enrolled 36 + 2 standby healthy volunteers with 32 completing the study.
d. N = 3 volunteers withdrew one for non-consumption of high fat meal, and two for personal reasons. N = 2 volunteers were dropouts as they did not return for period two or three.
e. 4 healthy volunteers experienced at least 1 TEAE
    i. No TEAEs reported in >1 HV.
f. No new safety signals were identified and there were no deaths or serious adverse events.

6. Pivotal Study #6: 052-23: Phase 1, open-label, balanced, randomized, single-dose, two-treatment, two-period, two-sequence, crossover, oral relative bioavailability study of Nilotinib Tablets 95 mg (2 x 95 mg) in normal, healthy, adult, human subjects under modified fasting condition
    a. Primary objective was to evaluate the oral relative bioavailability study of Nilotinib Tablets 95 mg (2 X 95 mg) of Slayback Pharma with that of TASIGNA® (Nilotinib) Capsules 200 mg (2 x 200mg) of in normal, healthy, adult, human subjects under modified fasting condition.
    b. Volunteers received standard meal (check-in night dinner) provided on day 01 (i.e., check-in day) after check-in activity was completed, on day 02 (breakfast, lunch, snacks and dinner). Under modified Fasting: In each study period, the respective subjects had fasted overnight for at least 10.00 hours prior to start of consumption of a high-fat high-calories non-vegetarian breakfast with dosing occurring 2 hours after dosing.
    c. Enrolled 90 + 4 standby healthy volunteers with 86 completing the study.
    d. N = 2 volunteers withdrew both due to AEs of vomiting. N = 6 volunteers were dropouts, 4 voluntarily and 2 as they did not return for period two.
    e. 22 healthy volunteers experienced at least 1 TEAE
        i. The TEAEs reported in >1 HV were headache (N=7), nausea (N=2), vomiting (N=2), backache (N=2), mild fever or fever (N=2), and dizziness (N=2).
    f. No new safety signals were identified and there were no deaths or serious adverse events.

In addition, the applicant completed 8 pilot studies comparing Danziten tablets to Tasigna capsule.

1. Pilot Study Number 033-18: An open-label, balanced, randomized, single-dose, two-treatment, three-period, three-sequence, three-way crossover oral relative bioavailability study of Nilotinib (Nilotinib Tartarate) tablets 50 mg of Slayback Pharma India LLP, Hyderabad, India and Tasigna®

(nilotinib) capsules 50 mg of Novartis Pharmaceuticals Corporation, East Hanover, New Jersey 07936 in normal, healthy, adult, human subjects under fasting and fed conditions. Sample Size: 18. Treatment Arms: 1

a. Two adverse events were reported in the same healthy volunteer (loose motions (diarrhea), Sinus tachycardia)

2. Pilot Study Number 075-20: An open-label, balanced, randomized, single-dose, two-treatment, three-period, six-sequence, three-way crossover oral relative bioavailability study of Nilotinib (Nilotinib Tartarate) tablets 300 mg (2 X 150 mg) of Slayback Pharma India LLP, Hyderabad, India and Tasigna® (nilotinib) capsules 400 mg (2 X 200 mg) of Novartis Pharmaceuticals Corporation, East Hanover, New Jersey 07936 in normal, healthy, adult, human subjects under fasting and fed conditions. Sample Size: 30. Treatment Arms: 1

a. A total of eighteen adverse events were reported for eleven subjects during the course of study. They included headache (N= 5), nausea (N=3), vomiting (N=3), itching over body (N=2), not feeling good (N=1), changes in ECG (N=1), aphthous ulcer (N=1), and increase in QTc interval (N=1).

3. Pilot Study 108-21: An open-label, balanced, randomized, single-dose, two-treatment, two-period, two-sequence, crossover, oral relative bioavailability study of Nilotinib (Nilotinib Tartrate) Tablets 240 mg (2 x 120 mg) of Slayback Pharma India LLP, Hyderabad, India with that Tasigna® (nilotinib HCl) Capsules 400 mg (2 x 200 mg) of Novartis Pharmaceuticals Corporation, East Hanover, New Jersey 07936, in normal, healthy, adult, human subjects under fasting condition. Sample Size: 16. Treatment Arms: 1

a. No in-house adverse events were reported during the course of study and six post study safety assessment AEs were reported for three subjects. They included abnormal bilirubin, abnormal uric acid, and abnormal blood urea in one healthy volunteer each and abnormal SGPT in 3 healthy volunteers.

4. Pilot Study 109-21: An open-label, balanced, randomized, single-dose, two-treatment, two-period, two-sequence, crossover, oral relative bioavailability study of Nilotinib (Nilotinib Tartrate) Tablets 120 mg of Slayback Pharma India LLP, Hyderabad, India with that Tasigna® (nilotinib HCl) Capsules 200 mg of Novartis Pharmaceuticals Corporation, East Hanover, New Jersey 07936, in normal, healthy, adult, human subjects under fasting condition. Sample Size: 16. Treatment Arms: 1

a. A total of two adverse events were reported for two subjects. One adverse event of vomiting and one of fever.

5. Pilot Study 032-21: An open-label, balanced, randomized, single-dose, two-treatment, three-period, six-sequence, three-way crossover oral relative bioavailability study of Nilotinib (Nilotinib Tartrate) Tablets 240 mg (2 X 120 mg) of Slayback Pharma India LLP, Hyderabad, India and Tasigna® (nilotinib) capsules 400 mg (2 X 200 mg) of Novartis Pharmaceuticals Corporation, East Hanover, New Jersey 07936 in normal, healthy, adult, human subjects under fasting and fed conditions. Sample Size: 30. Treatment Arms: 1

a. A total of six adverse events were reported for three subjects during the course of study. They included headache (N=2), loose stools (N=1), itching (N=1), vomiting (N=1), and abnormal ECG (N=1).

6. Pilot Study 135-21: An open-label, balanced, randomized, single-dose, two-treatment, two-period, two-sequence, crossover, oral relative bioavailability study of Nilotinib (Nilotinib Tartrate) Tablets 180 mg (2 x 90 mg) of Slayback Pharma India LLP, Hyderabad, India with that Tasigna® (nilotinib HCl) Capsules 300 mg (2 x 150 mg) of Novartis Pharmaceuticals Corporation, East Hanover, New Jersey 07936, in normal, healthy, adult, human subjects under fasting condition. Sample Size: 16. Treatment Arms: 1
    a. No in-house adverse events were reported during the course of study and only one post study safety assessment AE was reported in one subject, which was abnormal ECG.

7. Pilot Study 136-21: Study Title: An open-label, balanced, randomized, single-dose, two-treatment, two-period, two-sequence, crossover, oral relative bioavailability study of Nilotinib (Nilotinib Tartrate) Tablets 105 mg (2 x 105 mg) of Slayback Pharma India LLP, Hyderabad, India with that Tasigna® (nilotinib HCl) Capsules 400 mg (2 x 200 mg) of Novartis Pharmaceuticals Corporation, East Hanover, New Jersey 07936, in normal, healthy, adult, human subjects under fasting condition. Sample Size: 16. Treatment Arms: 1
    a. A total of two adverse events were reported for two subjects during in-house stay and no post study safety assessment AEs were reported. One adverse event was fever and the other vomiting.

8. Pilot Study 148-21: An open-label, balanced, randomized, single-dose, two-treatment, two-period, two-sequence, crossover, oral relative bioavailability study of Nilotinib (Nilotinib Tartrate) Tablets 100 mg (2 x 100 mg) of Slayback Pharma India LLP, Hyderabad, India with that Tasigna® (nilotinib HCl) Capsules 200 mg (2 x 200 mg) of Novartis Pharmaceuticals Corporation, East Hanover, New Jersey 07936, in normal, healthy, adult, human subjects under fasting condition. Sample Size: 16. Treatment Arms: 1
    a. No in-house adverse events were reported, and three post-study adverse events were reported in two subjects. The post-study adverse events were random blood sugar (RBS) increased, neutrophils decreased, and eosinophils increased.

<u>Labeling comments (Elizabeth Everhart):</u>
The applicant submitted a proposed proprietary, DANZITEN, which was found conditionally acceptable.

The following substantive changes were made to the USPI as a result of this review:

- Throughout the USPI, pediatric disclaimer statements were added to note that exclusivity-protected pediatric data from the listed drug (LD), Tasigna's, USPI (b) (4)
- A new subsection 2.1 Important Use and Administration Instructions was added to note that nilotinib may be available in different formulations, dosage forms, and strengths approved with different indications and dosages. Instructions were added to note that prescribers should ensure the recommended dosage of DANZITEN is prescribed and a dosage conversion table to assist in switching between DANZITEN and the listed drug (LD) Tasigna was added in subsection

2.2 Recommended Dosage. Other changes to improve sentence flow and clarity were made by FDA.

- A new subsection 2.8 Recommended DANZITEN Dosage in Patients with Hepatic Impairment was added to align with recommendations in the FDA guidance titled *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format.*
- A new subsection 5.1 Warning and Precaution (W&P) 5.1 titled "Substitution with Other Nilotinib Products and Risk of Medication Errors" was added to highlight the different strengths and dosages between DANZITEN and the LD, as well as potentially between DANZITEN and other nilotinib products.
- In the beginnings of subsection 6.1 Clinical Trials Experience and section 14 Clinical Studies, a "linkage" statement was added to clarify that the data presented in these sections was from the adequate and well-controlled clinical studies for the LD, Tasigna, which has different recommended dosages than DANZITEN.
- In sections 5 Warnings and Precautions and 6.1 Clinical Trials Experience, to avoid confusion with differing dosing between DANZITEN and the LD, in places where the dosing from the LD is used, FDA modified the language to include "the equivalent recommended dosage of DANZITEN xx mg".
- In subsection 12.2 Pharmacodynamics, FDA added the statement that the time course of pharmacodynamic response is unknown as per 21 CFR 201.57(c)(13)(i)(B) which requires that this information must be included if known or a statement added about the lack of information.
- In subsection 12.3 Pharmacokinetics, changes were made to indicate dosage equivalence to DANZITEN xx mg similar to the approach taken in subsections 5, 6, and 14. Additionally, pharmacokinetic data for DANZITEN added and (b) (4) proposed by the applicant was removed.
- Additional edits throughout the USPI were made to align with current labeling guidances, to replace symbols with their intended meaning, to add missing cross references, to correct cross references, and to correct other formatting issues.

Labeling Conclusion:

The labeling for NDA 219293 DANZITEN (nilotinib) tablets is acceptable for approval from the ADL standpoint.

See the USPI and Medication Guide attached to the approval letter for agreed upon labeling for the (b) (4) approval.

Pediatrics

To fulfill the pediatric requirements described in Section 505B(a)(1)(B) of the FD&C Act regarding pediatric investigations of certain molecularly targeted oncology drugs using appropriate pediatric formulations for each age group for which the study is required, the Applicant will be issued the following PMR:

1. Conduct a molecularly targeted pediatric cancer investigation, which includes developing an age-appropriate formulation.

(b) (4)

This pediatric plan developed during iPSP negotiations, and the Applicant agreed to the PREA PMR.

Recommended Regulatory Action:

This application was originally submitted on January 30, 2024. There are no clinical issues that preclude approval of this 505 (b) (2) application. Please see the clinical pharmacology review for establishment of BE/BA and discussion of the results of food effects of Danziten.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JOSEPH P WYNNE
10/04/2024 02:16:55 PM

CARA A RABIK
10/04/2024 02:18:00 PM