# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**22-294**

# SUMMARY REVIEW

# CROSS DISCIPLINE TEAM LEADER REVIEW

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|---|---|
| **Date** | July 21, 2009 |
| **From** | Kellie Schoolar Reynolds, Pharm.D. |
| **Subject** | Cross Discipline Team Leader Review |
| **NDA #** | 22-294 |
| **Applicant** | Aurobindo Pharma, Ltd. |
| **Date of Submission** | October 7, 2008 |
| **PDUFA Goal Date** | August 7, 2009 |
| | |
| **Proprietary Name / Established (USAN) names** | Zidovudine |
| **Dosage forms / Strength** | 60 mg scored tablet |
| **Proposed Indication(s)** | Treatment of HIV-1 infection |
| **Recommended:** | Approval |

## 1. Introduction

This review summarizes the multi-disciplinary evaluation of the information submitted by Aurobindo Pharma, Ltd. in NDA 22-294 to support approval of their 60-mg scored zidovudine tablet. Aurobindo submitted this 505(b)(2) application for zidovudine 60-mg scored tablets for twice daily and [redacted] daily administration in HIV-1 infected children who weigh 4 kg or greater. The tablets can be crushed and dispersed in water to allow dosing for the proposed population. The applicant did not conduct a bioequivalence study for this application; they requested a biowaiver because they have approval of a higher strength (300-mg) tablet. The Office of Generic Drugs granted tentative approval of the 300-mg tablets on August 25, 2005 and granted full approval on September 19, 2005, under ANDA 77-267. The 300-mg tablet was approved based on the results of fasted and fed bioequivalence studies that used Retrovir (zidovudine, GlaxoSmithKline) 300-mg tablets as the reference product. ONDQA biopharmaceutics group granted a biowaiver for the 60-mg tablet based on formulation proportionality and acceptable comparative dissolution data.

b(4)

This 505(b)(2) application does not include any new pharmacokinetic, efficacy, or safety data. The following information supports approval.

- A comparison of the proposed doses with the approved doses in the Retrovir label
- Knowledge of the exposure resulting from the proposed doses (from the Retrovir label and literature)
- Safety and efficacy information from published literature to support any deviations from the approved doses

This application is eligible for full approval because the US patent protection for zidovudine expired on September 17, 2005. However, Aurobindo does not plan to market this formulation in the US. The 60-mg scored tablet formulation was developed for procurement by the President's Emergency Plan for AIDS Relief (PEPFAR) program. A user fee waiver was granted for this application based on the commitment not to market in the US.

## 2. Background

Zidovudine is a thymidine analog that, after intracellular phosphorylation to zidovudine triphosphate metabolite, inhibits HIV-specific reverse transcriptase and terminates pro-viral DNA. The innovator zidovudine product, Retrovir, was the first antiretroviral drug approved for the treatment of HIV-1 infection. Although originally administered as monotherapy, zidovudine is now administered only in combination with other antiretroviral drugs when used for the treatment of HIV-1.

As outlined below, the dosing regimens approved for treatment of adult and pediatric HIV-1 infected individuals have changed since the original approvals. The current approved doses are lower than the doses originally approved.

Zidovudine dosing regimens in adult patients

- Original approval of capsules in 1987: the dosing regimen was 200 mg every 4 hours around the clock.
- 1989: the syrup formulation was approved for use in adults.
- 1990: dosing regimen was reduced to 100 mg every 4 hours (600 mg total daily dose) as monotherapy or 200 mg every 8 hours in combination with zalcitabine.
- 1995/1996: the dosing regimen for adults was changed from 100 mg every 4 hours to 600 mg per day in divided doses. The dosing regimen change was based on a study in 158 patients comparing 100 mg every 4 hours to 300 mg twice daily. Tablet formulation was approved.

Zidovudine dosing regimens in pediatric patients

- 1990: use in pediatric patients 3 months – 12 years of age was approved. The original dosing regimen for pediatric patients was 180 mg/m$^2$ every 6 hours (720 mg/m$^2$ day), not to exceed 200 mg every 6 hours.
- Dosing instructions for pediatric patients were extended to include patients 6 weeks – 12 years of age and the dose was reduced to 160 mg/m$^2$ every 8 hours (480 mg/m$^2$/day up to a maximum of 200 mg every 8 hours).
- 1994: approved indication for prevention of mother-to-child transmission of HIV-1. This indication was based on a three-part regimen that includes neonate dosing (2 mg/kg orally every 6 hours) which begins within 12 hours after birth and continues through 6 weeks of age.
- 2008: dosing recommendations were changed from a body surface area based dose three times per day to a weight based dose twice a day. This application led to an alignment of recommended pediatric dosing of zidovudine worldwide. The US approved label still includes instructions for body surface area based dosing and three times daily dosing, as options.

Zidovudine is marketed as Retrovir® in the US by the innovator applicant, GlaxoSmithKline, for use in adult and pediatric HIV-1 infected patients. Retrovir is available for oral use as 100-mg capsules, 300-mg tablets, and 10-mg/mL syrup. The efficacy and safety of zidovudine were evaluated in previous New Drug Applications, including:

- Retrovir® Capsule NDA 19-655 (approved March 19, 1987)
- Retrovir® Syrup NDA 19-910 (approved September 28, 1989)
- Retrovir® Infusion IV NDA 19-951 (approved March 19, 1987)
- Retrovir® Tablet NDA 20-518 (approved December 19, 1995)

Zidovudine patent protection has expired and generic formulations are available. Some of the generic formulations were developed under the PEPFAR program. In addition, the Division of Antiviral Products has granted tentative approval to fixed dose combination products that include zidovudine. Some of these fixed dose products are formulations intended for pediatric patients. The tentative approvals were granted as part of the PEPFAR program.

Aurobindo developed the 60-mg scored tablet in response to the WHO Pediatric Antiretroviral Working Group 2007 report entitled "Preferred antiretroviral medicines for treating and preventing HIV infection in younger children." Zidovudine 60-mg tablets were designated a high priority for development. Although many drugs for use in pediatric patients are available as liquid formulations, the liquid formulations have a number of disadvantages in the developing world. The disadvantages include: storage difficulties, volumes required for dosing, palatability, and cost. A scored tablet that can be dispersed in water allows dosing in small patients who are dosed on a mg/body size basis and who cannot take a tablet.

### 3. CMC/Device

There are no unresolved CMC issues. I agree with conclusions reached by the CMC reviewer, Dr. Ted Chang.

Drug substance and drug product summary

The drug product is manufactured using drug substance manufactured by Aurobindo Pharma Ltd under DMF 18714. The DMF was reviewed and found adequate. The NDA includes some drug substance information. However, acceptability of the drug substance is based on review of the DMF. Satisfactory drug substance specifications are supplied. All limits conform to ICH Q3C. The analytical methods are described at a satisfactory level of detail.

The tablets contain 60 mg zidovudine and inactive ingredients that are either compendial or are made of compendial materials. This product is a scaled-down formulation of the zidovudine 300-mg tablet that was approved in ANDA 77-267. The current application provides reasonable drug product specifications for appearance, identity, average weight, water dissolution, uniformity and assay. The analytical methods are the same as approved in ANDA 77-267. No novel impurities are identified. A justification for specifications is provided. The tablet does not have a residual solvent specification, but the applicant committed to complying with USP <467> and to submitting the supporting data within 6 months of approval.

Satisfactory analytical data are provided for 3 batches of [redacted] tablets manufactured in July 2007. b(4)
Tablets described in this application were made from the same blend as higher strength tablets that are bioequivalent to the Reference Listed Drug (Zidovudine tablets, 300-mg).

The container-closure systems are 40 cc [redacted] bottles that contain 60 tablets (Child Resistant closures and induction seals), 120 cc bottles that contain 1000 tablets (screw-cap closures and induction seals), [redacted] /aluminum foil blister packs of 10 tablets, [redacted]. The b(4)
components are covered by DMFs. Satisfactory container labels are supplied.

Satisfactory stability data are supplied for three batches stored at 30°C/75% RH and 40°C/75% RH for 6 months in each packaging configuration. In addition, satisfactory data are provided for one batch stored at 25°C/80% RH and at 50° for three months. The proposed expiration dating period of 24 months is acceptable. The storage conditions are: 20°C to 25°C (68°F to 77°F).

Data to support administration of half-tablets or tablet dispersion

An objective of this application was to support administration of drug product to children who are unable to swallow a tablet. In addition, doses for some weight groups require the administration of whole tablet(s) plus a half-tablet.

Dosing instructions are as follows:
Half or whole tablets can be swallowed with water. For children unable to swallow the tablets, the following procedure can be adopted:

1. Place the tablet(s) in container and add two teaspoonfuls (10 mL) of water per tablet.
2. Swirl the container until tablet(s) break up into pieces small enough for the child to swallow. A spoon can be used to crush pieces, if needed.
3. Drink the mixture within 1 hour.
4. Rinse the container with additional small amount of water and drink the contents to assure that the entire dosage is taken.

Do not mix zidovudine tablet with any liquid other than water.

In response to a request from the Agency, the applicant conducted a stability study for tablets dispersed in water. The submitted data also support use of half-tablets. The applicant broke ten tablets in half at the break-line (score), dissolved each half in 5-mL of water, and determined the amount of drug present in an aliquot. The assay results for the 20 half-tablets indicated the aliquots contained 94.7% to 104.2% of the anticipated amount (mean= 99.4%). To demonstrate solution stability, the solutions for both halves of the first tablet were evaluated after 30 and 120 minutes. The amount of drug in solution did not change by more than 0.5% over 120 minutes. The data indicate that 60-mg tablets split in half at the break-line provide a dose of 30 mg with acceptable accuracy. In addition, the dispersed tablet is stable over the time period specified in the dosing instructions.

Manufacturing facilities
The drug substance is manufactured at Aurobindo Pharma Ltd., Andhra Pradesh, India. The drug product is manufactured at Aurobindo Pharma Ltd (Unit-III), Andhra Pradesh, India. Release testing will be performed at both sites. Primary packaging materials and container-closure systems will be tested at APL Research Center (a division of Aurobindo Pharma, Ltd.) in Andhra Pradesh, India. The applicant provided a cGMP certification for each of the manufacturing and testing sites.

The Office of Compliance deemed the drug substance manufacturing site acceptable based on profile. The Office of Compliance deemed the drug product manufacturing site acceptable based on file review.

Environmental Assessment or Claim of Categorical Exclusion
The applicant claimed categorical exclusion. The request was deemed reasonable.

**4. Nonclinical Pharmacology/Toxicology**

Not applicable. No new information submitted.

**5a. Biopharmaceutics (Biowaiver)**

The applicant did not conduct a bioequivalence study for this application because they have approval of a higher strength (300-mg) tablet. The 300-mg tablet was approved under ANDA 77-267 based on the results of fasted (Study No. Zid-01/04) and fed (Study No. Zid-02/04) bioequivalence studies that used Retrovir (zidovudine, GlaxoSmithKline) 300-mg tablets as the reference product. The applicant requested a biowaiver based on formulation proportionality and dissolution data. The biowaiver request was reviewed by T.M. Chen, Ph.D. from the ONDQA Biopharmaceutics group.

ONDQA Biopharmaceutics granted the biowaiver based on the information summarized below. I agree with the assessment by the reviewer, Dr. T.M. Chen.

The 300-mg and 60-mg tablets use a common blend, so the 60-mg tablet contains exactly 20% of all ingredients in 300-mg tablet.

Dissolution profiles were compared between the 300-mg and 60-mg tablets in the following dissolution media: water, pH 1.2 buffer, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer. The f2 (similarity factor) was determined for 4 batches of tablets in water, using USP Type II apparatus (paddles) at 50 rpm. Sample times for f2 calculation were 5, 10, and 15 minutes, based on rapid dissolution. The resulting f2 values of 63.8 to 83.6 indicate similarity in dissolution.

The f2 values were not determined in the other media, because water is the accepted dissolution medium for this product. However, visual inspection of the profiles in other media indicate mean percent dissolved was at least 85% for 60-mg and 300-mg tablets in all media.

**5b. Clinical Pharmacology**

There are no unresolved clinical pharmacology issues. I agree with the assessment of the clinical pharmacology reviewer, Dr. Shirley Lu, that the available data support approval of the twice daily dosing regimen [redacted] b(4)

This 505(b)(2) application does not include any new pharmacokinetic, efficacy, or safety data. The following information supports approval.

- A comparison of the proposed doses with the approved doses in the Retrovir label
- Knowledge of the exposure resulting from the proposed doses (from the Retrovir label and literature)
- Safety and efficacy information from published literature to support any deviations from the approved doses.

The current US-approved dosing regimens for the reference listed drug (Retrovir, zidovudine) for treatment of HIV-1 infection in pediatric patients are listed below.

**Table 1. Approved Pediatric Dosing Regimens of RETROVIR (zidovudine)**

| Body Weight (kg) | Total Daily Dose | Dosage Regimen and Dose | |
|---|---|---|---|
| | | b.i.d. | t.i.d. |
| 4 to <9 | 24 mg/kg/day | 12 mg/kg | 8 mg/kg |
| ≥9 to <30 | 18 mg/kg/day | 9 mg/kg | 6 mg/kg |
| ≥30 | 600 mg/day | 300 mg | 200 mg |

Alternatively, dosing for Retrovir can be based on body surface area for each child. The recommended dose of RETROVIR is 480 mg/m$^2$/day in divided doses (240 mg/m$^2$ twice daily or 160 mg/m$^2$ three times daily).

Twice daily dosing

Aurobindo proposed the following twice daily dosing regimens using the 60-mg scored tablet. Doses for children who weigh 28.1 to 30 kg were added by to allow dosing across the entire relevant weight range.

**Table 2. Proposed twice daily dosing regimen for 60-mg scored zidovudine tablet**

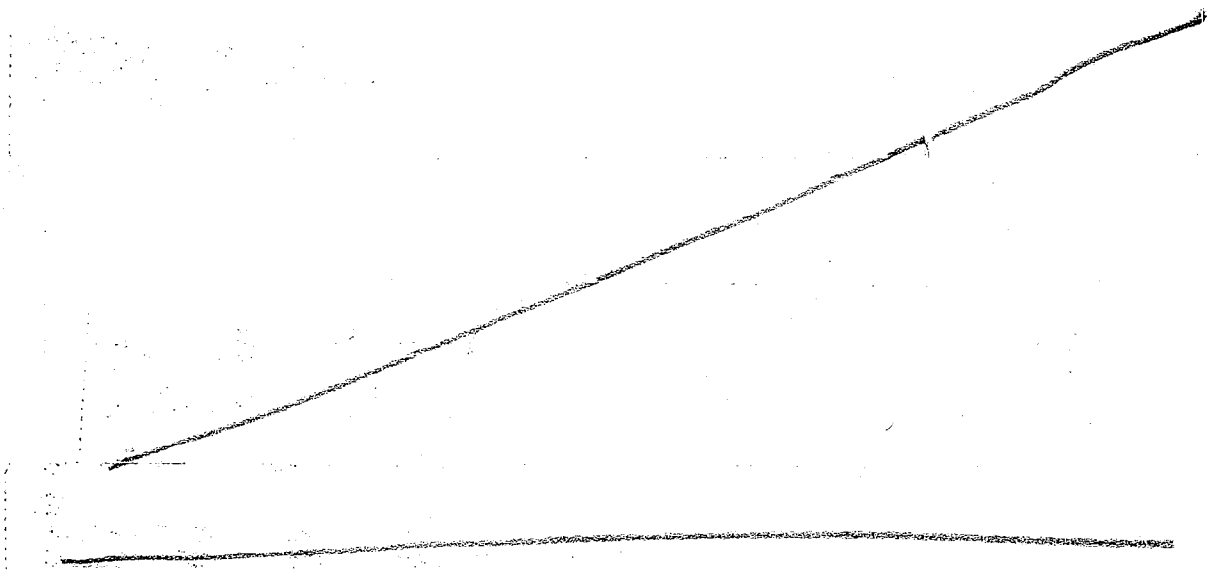
| Weight of Child (kg) | Twice daily regimen | Total daily dose |
|---|---|---|
| 4 to 6 | 1 tablet (60 mg ) bid | 120 mg |
| 6.1 to 11 | 1.5 tablets (90 mg) bid | 180 mg |
| 11.1 to 14 | 2 tablets (120 mg) bid | 240 mg |
| 14.1 to 18 | 2.5 tablets (150 mg) bid | 300 mg |
| 18.1 to 22 | 3 tablets (180 mg) bid | 360 mg |
| 22.1 to 25 | 3.5 tablets (210 mg) bid | 420 mg |
| 25.1 to 28 | 4 tablets (240 mg) bid | 480 mg |
| 28.1 to <30 | 4.5 tablets (270 mg) bid | 540 mg |
| 30 | 5 tablets (300 mg) bid | 600 mg |

Because the safety and efficacy of the innovator product (Retrovir) have been established, the applicant's proposed doses for each weight band were compared to the approved doses that are included in the Retrovir label. An example of the comparison is shown below, for patients who weigh 4 or 5 kg.

**Table 3. Difference between Aurobindo proposed dose and two approved regimens of Retrovir**

| Weight in kg | Dose proposed by Aurobindo | Retrovir weight based dose | % difference (proposed vs. Retrovir weight-based) | Retrovir BSA-based dose (based on 50th percentile for height and weight) | % difference (proposed vs Retrovir BSA based) |
|---|---|---|---|---|---|
| 4 | 60 mg bid | 48 mg bid | +25% | 54 mg bid | +10.1% |
| 5 | 60 mg bid | 60 mg bid | 0% | 64 mg bid | –6.4% |

The primary consideration was the comparison to the BSA-based dose, because the safety and efficacy of zidovudine was established based on that regimen. However, the comparison to the zidovudine weight based dose was also considered because it is an approved regimen. Zidovudine safety and efficacy data presented in the literature support doses that vary from approved doses (in Retrovir label) by up to 20%. There are only two instances where the proposed dose varies by more than 20% from the approved BSA-based dose. The differences occur at the 6.1 kg breakpoint (+23%) and the 11 kg breakpoint (–20.3%). Neither of these differences can be avoided when using the tablet formulation. The available safety and efficacy data support the proposed dosing regimens, as discussed in sections 7 and 8 below. The doses proposed in Table 2 above are acceptable.



b(4)

b(4)

## 6. Clinical Microbiology

No new clinical virology data were submitted with this application.

## 7. Clinical/Statistical- Efficacy

I agree with the assessments made by Dr. Regina Alivisatos in the medical officer review. The available data support approval of the twice daily dosing regimen

b(4)

As summarized in Dr. Alivisatos' review, adequate efficacy data exist to support the decreases in zidovudine dose and exposure that result from the proposed twice daily dosing regimen compared to the approved dosing regimens in the Retrovir label. The dose differences are described in section 5b, above.

[redacted] b(4)

**8. Safety**

I agree with the assessments made by Dr. Regina Alivisatos in the medical officer review. The available data support approval of the twice daily dosing regimen; [redacted] b(4)

As summarized in Dr. Alivisatos' review, adequate safety data exist to support the increases in zidovudine dose and exposure that result from the proposed twice daily dosing regimen compared to the approved dosing regimens in the Retrovir label. The dose differences are described in section 5b, above. Safety at the proposed twice daily doses is well-established based on clinical trials and postmarketing experience with the innovator product.

[redacted] tablets. For some weight bands the zidovudine total daily dose and predicted exposures with the 60-mg scored tablets are 47% higher compared to the approved dosing based on body surface area. The higher exposure is of potential concern. The most common adverse events with zidovudine are related to the GI-tract (nausea and vomiting). Laboratory abnormalities that occur frequently include anemia, granulocytopenia, thrombocytopenia, and increased ALT and AST. b(4)

**9. Advisory Committee Meeting**

Not applicable.

**10. Pediatrics**

The review team submitted the following documents for the PeRC subcommittee's review:

1) PREA partial waiver for children less than 6 weeks of age and less than 4 kg, including draft language to include in the label. The draft language indicated dosing in these children is not possible with this formulation and could result in children being underdosed by as much as 35%
2) Pediatric page; PREA triggered by new dosage form
3) PREA language for approval letter
4) Proposed PLR labeling with review team's preliminary revisions

During the June 3, 2009 PeRC meeting with the review team, a final determination regarding PREA was not reached. The decision was deferred pending further discussion with PeRC. After review of formulation information, the PeRC subcommittee determined the scored 60-mg tablet that disperses in water is not considered a new dosage form; therefore, the application does not trigger PREA. Zidovudine is already available in tablet form and a new strength tablet with a score is not considered a new dosage form. Please refer to the appropriate pediatric and regulatory documents amended accordingly by Monica Zeballos, Pharm.D.

### 11. Other Relevant Regulatory Issues

No regulatory issues are outstanding for this application.

### 12. Labeling

The label for this product is similar to the approved label for Retrovir. The applicant provided the label in PLR format, based on a request from the Agency. The label includes dosing instructions relevant to this formulation.

Section 2.0 of the label is presented below, because it is the label section that differs from the innovator label.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Treatment of HIV-1 Infection

Pediatric Patients (6 weeks to <18 years of age who weigh 4 kg or greater): Healthcare professionals should pay special attention to accurate calculation of the dose of zidovudine, transcription of the medication order, dispensing information, and dosing instructions to minimize risk for medication dosing errors.

Prescribers should calculate the appropriate dose of zidovudine for each child based on body weight (kg) and should not exceed the recommended adult dose.

Before prescribing zidovudine tablets, children should be assessed for the ability to swallow tablets. If a child is unable to reliably swallow a zidovudine tablet, the method of preparation procedure listed below should be followed or the zidovudine syrup formulation should be prescribed.

The recommended dosage in pediatric patients 6 weeks of age and older and weighing greater than or equal to 4 kg is provided in Table 1. Zidovudine syrup should be used to provide accurate dosage in pediatric patients who weigh less than 4 kg.

**Recommended Pediatric Dosage of Zidovudine Tablets**

| Body Weight (kg) | Dosage Regimen Using Scored 60 mg Tablets | | Total Daily Dose |
|---|---|---|---|
| | AM Dose | PM Dose | |
| 4 to 6 | 1 tablet (60 mg) | 1 tablet (60 mg) | 120 mg |
| 6.1 to 11 | 1.5 tablet (90 mg) | 1.5 tablet (90 mg) | 180 mg |
| 11.1 to 14 | 2 tablets (120 mg) | 2 tablets (120 mg) | 240 mg |
| 14.1 to 18 | 2.5 tablets (150 mg) | 2.5 tablets (150 mg) | 300 mg |
| 18.1 to 22 | 3 tablets (180 mg) | 3 tablets (180 mg) | 360 mg |
| 22.1 to 25 | 3.5 tablets (210 mg) | 3.5 tablets (210 mg) | 420 mg |
| 25.1 to 28 | 4 tablets (240 mg) | 4 tablets (240 mg) | 480 mg |
| 28.1 to < 30 | 4.5 tablets (270 mg) | 4.5 tablets (270 mg) | 540 mg |
| ≥30 | 5 tablets (300 mg)* | 5 tablets (300 mg)* | 600 mg |

* For recommended doses of 300 mg twice daily, the adult formulation (300 mg tablet) can be used. Safety and efficacy have not been established in patients weighing less than 4 kg.

Method of Preparation

For children unable to swallow the tablet(s), the following procedure can be used:

1. Place the tablet(s) in a container and add two teaspoonfuls (10 mL) of water per tablet.
2. Swirl the container until tablet(s) breaks up into pieces small enough for the child to swallow; a spoon can be used to crush the pieces, if needed.
3. Drink the mixture within 1 hour.
4. Rinse the container with additional small amount of water and drink the contents to assure that the entire dosage is taken.

DO NOT MIX ZIDOVUDINE TABLET(S) WITH ANY LIQUID OTHER THAN WATER.

**13 Recommendations/Risk Benefit Assessment**

- Recommended Regulatory Action

I concur with the assessments made by the review team and recommend approval of zidovudine 60-mg tablets for use in HIV-1 infected children. I recommend approval of the twice daily dosage regimen. b(4)

- Risk Benefit Assessment

The risk benefit assessment considered several factors.

- The twice daily dosing regimen provides a similar zidovudine dose as the approved regimens of the innovator product.
- b(4)
- b(4)

- Recommendation for Postmarketing Risk Management Activities

No postmarketing risk management activities are required for this application.

- Recommendation for other Postmarketing Study Commitments

No postmarketing study commitments are required for this application

- Recommended Comments to Applicant

No additional comments to convey to the applicant.

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/s/

Kellie Reynolds
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