CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

220934Orig1s000

Trade Name:	Foundayo
Generic or Proper Name:	orforglipron
Sponsor:	Eli Lilly and Company
Approval Date:	April 1st, 2026
Indication:	Foundayo (orforglipron) tablets in combination with a reduced calorie diet and increased physical activity to reduce excess body weight and maintain weight reduction long term in adults with obesity or adults with overweight in the presence of at least one weight-related comorbid condition

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APPLICATION NUMBER:

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APPROVAL LETTER

NDA 220934

NDA APPROVAL

Eli Lilly and Company
Attention: Ingrid Hensley, PhD
Executive Director, Global Regulatory Affairs – Americas Region
Lilly Corporate Center, Drop Code 2543
Indianapolis, IN 46285

Dear Dr. Hensley:

Please refer to your new drug application (NDA) received January 20, 2026, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Foundayo (orforglipron) tablets.

This NDA provides for the use of Foundayo (orforglipron) tablets in combination with a reduced calorie diet and increased physical activity to reduce excess body weight and maintain weight reduction long term in adults with obesity or adults with overweight in the presence of at least one weight-related comorbid condition.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, and Medication Guide) as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible via publicly available labeling repositories.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *SPL Standard for Content of Labeling Technical Qs & As.* For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 220934**." Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Foundayo (orforglipron) tablets shall be 24 months from the date of manufacture when stored at 20°C to 25°C.

Results of ongoing stability studies should be submitted throughout the dating period in your annual report , as they become available, including the results of stability studies from the first three production lots.

ADVISORY COMMITTEE

Your application for Foundayo was not referred to an FDA advisory committee because there were no controversial issues that would benefit from advisory committee discussion

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages birth to less than 6 years for orforglipron because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group and is not likely to be used in a substantial number of pediatric patients in this group. Because of growth and development requirements in children under the age of 2, weight loss is not recommended in the 0- to 2-year-old age group. In children 2 to 6 years of age, pharmacological treatment of obesity does not represent a meaningful therapeutic benefit over existing non-pharmacological therapies (such as diet and lifestyle) and is therefore not likely to be used in a substantial number of patients. This is in line with draft guidance for industry *Obesity and Overweight: Developing Drugs and Biological*

Products for Weight Reduction, which recommends that pediatric trials should include subjects aged 6 years and older.

We are deferring submission of your pediatric studies for ages 6 to 11 years inclusive and 12 to 17 years inclusive because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required under section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of the FDCA. These required studies are listed below.

4977-1 Complete the ongoing 72-week, randomized, double-blind, placebo-controlled, multicenter, parallel-arm study J4M-MC-PW01 (ADVANCE-ATTAIN-ADOLESCENTS) to evaluate the safety and efficacy of orforglipron as an adjunct to lifestyle intervention to reduce excess body weight and maintain weight reduction long term in a cohort of pediatric patients aged 12 to less than 18 years with obesity.

Study Completion:	March 2028
Final Report Submission:	December 2028

4977-2 Conduct an 84-week, randomized, double-blind, placebo-controlled, multicenter, parallel-arm study J4M-MC-PW03 to evaluate the pharmacokinetics, safety, and efficacy of orforglipron as an adjunct to lifestyle intervention to reduce excess body weight and maintain weight reduction long term in a cohort of pediatric patients aged 6 to less than 12 years with obesity.

Draft Protocol Submission:	October 2027
Final Protocol Submission:	January 2028
Study Completion:	March 2031
Final Report Submission:	February 2032

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit the protocol(s) to your IND 156143, with a cross-reference letter to this NDA. Reports of these required pediatric postmarketing studies must be submitted as an NDA or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the signal of the serious risk of medullary thyroid cancer, and to identify unexpected serious risks of long-term use in pediatric patients with obesity, and exposure to orforglipron in pregnancy.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

4977-3 Establish a disease-based registry for pediatric obesity focused on safety in pediatric patients who receive pharmacological treatment for weight reduction beginning at ages less than 12 years old. The registry will enroll pediatric patients aged 6 years and older receiving non-pharmacological or pharmacological treatment for weight reduction during childhood and adolescence. Conduct a registry-based cohort study of at least 10 years duration to describe growth and development (height, weight, and pubertal development by Tanner staging), adverse events (including fractures and malnutrition), and development of obesity-related comorbid conditions. The registry must provide an option to enroll some patients who have participated in clinical trials of weight reduction medications for obesity, including orforglipron.

The timetable you submitted on March 2025, 2026, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: April 2027
Final Protocol Submission: April 2028
Interim Report Submission: April 2029
April 2030
April 2031
April 2032
April 2033

	April 2034
	April 2035
	April 2036
	April 2037
Study Completion:	April 2038
Final Report Submission:	April 2039

4977-4 Collect global data from a prospective pregnancy exposure registry, preferably a disease-based multi-product pregnancy registry, using a registry-based cohort study to compare the maternal, fetal, and infant outcomes of women exposed to orforglipron for weight reduction during pregnancy with unexposed comparator population(s). Align the study protocol with protocol(s) outside the United States to reach the target sample size. The registry will identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

The timetable you submitted on March 25, 2026, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	October 2026
Final Protocol Submission:	October 2027
Interim Report Submission:	June 2028
	June 2030
	June 2032
	June 2034
	June 2036
Study Completion:	June 2037
Final Report Submission:	June 2038

4977-5 Conduct an additional pregnancy study that uses a different design from the pregnancy exposure registry (for example a cohort study using claims or electronic medical record data) to compare the risks and prevalence of pregnancy and infant outcomes (including but not limited to major congenital malformations, spontaneous abortions, stillbirths, small-for-gestational-age births, preterm births, and postnatal growth and

development) between women exposed to orforglipron for weight reduction during pregnancy and unexposed comparator population(s).

The timetable you submitted on March 25, 2026, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	February 2027
Final Protocol Submission:	February 2028
Interim Report Submission:	September 2030
	September 2032
Study Completion:	September 2034
Final Report Submission:	September 2035

4977-6 Conduct a medullary thyroid carcinoma registry-based case series of at least 15 years duration to systematically monitor the annual incidence of medullary thyroid carcinoma in the United States and to identify any increase related to the introduction of orforglipron for the treatment of overweight and obesity into the marketplace. This study will also establish a registry of incident cases of medullary thyroid carcinoma and characterize their medical histories related to the use of orforglipron for the treatment of obesity/overweight.

The timetable you submitted on March 25, 2026, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	October 2026
Final Protocol Submission:	April 2027
Interim Report Submission:	May 2028
	May 2029
	May 2030
	May 2031
	May 2032
	May 2033
	May 2034
	May 2035
	May 2036
	May 2037
	May 2038
	May 2039
	May 2040
	May 2041
	May 2042
Study Completion:	August 2042
Final Report Submission:	August 2043

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[4]

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of retained gastric contents and to identify an unexpected serious risk for major adverse cardiovascular events (MACE), drug-induced liver injury (DILI), and exposure to orforglipron during lactation.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trials:

4977-7 Complete the ongoing randomized, open-label, active-controlled trial J2A-MC-GZGS (ACHIEVE-4) and provide additional safety data on orforglipron related to major adverse cardiovascular events (MACE) and the potential for drug-induced liver injury (DILI). Submit a clinical study report with adjudicated MACE (cardiovascular death, nonfatal myocardial infarction, hospitalization for unstable angina, and nonfatal stroke) and an assessment of potential DILI, including Hy's Law plots, shift tables for liver enzymes and bilirubin, and case reports in FDA-preferred DILI format for all cases meeting potential Hy's Law, having transaminase elevations >10x upper limit of normal (ULN), or having study drug discontinued due to DILI concerns.

The timetable you submitted on March 25, 2026, states that you will conduct this trial according to the following schedule:

Trial Completion:	April 2026
Final Report Submission:	July 2026

4977-8 Conduct a clinical pharmacology trial that uses ultrasound to measure the effect of both temporary withholding of orforglipron and fasting duration on retained gastric contents to evaluate delayed gastric emptying associated with glucagon-like peptide-1 receptor agonist (GLP-1 RA) use and inform

[4] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

potential recommendations to mitigate the serious risk of pulmonary aspiration.

The timetable you submitted on March 25, 2026, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission: March 2027
Final Protocol Submission: September 2027
Trial Completion: December 2028
Final Report Submission: March 2029

4977-9 Conduct a milk-only lactation study in lactating women who have received a dose of orforglipron to assess concentrations of orforglipron in breast milk using a validated assay.

The timetable you submitted on March 25, 2026, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission: December 2026
Final Protocol Submission: June 2027
Study Completion: June 2028
Final Report Submission: June 2029

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[5]

Submit clinical protocol(s) to your IND 156143 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o) ,REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o), REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o).**

Submission of the protocol(s) for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to

[5] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B(a)(1) of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B(a)(1) and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[6]

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[7] Information and Instructions for completing the form can be found at FDA.gov.[8]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

REQUESTED ENHANCED PHARMACOVIGILANCE (EPV)

We request that for Foundayo, for a period of 5 years following initial U.S. approval date,

1) you submit all serious unexpected domestic and foreign postmarketing cases of DILI attributable to orforglipron, resulting in jaundice, liver failure, liver transplant, or death as 15-day “Alert reports” (as described under 21 CFR 314.80(c)(1)), and

[6] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[7] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[8] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

2) you provide detailed analyses of potential events of DILI, defined as all cases meeting potential Hy's Law (alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥3x ULN with total bilirubin (TB) ≥2x ULN) or having transaminase elevations >10x ULN, in addition to the aforementioned expedited reports, reported from clinical study and postmarketing reports in your periodic safety report (i.e., the Periodic Adverse Drug Experience Report (PADER) required under 21 CFR 314.80(c)(2) or the ICH E2C Periodic Benefit-Risk Evaluation Report (PBRER) format).

These analyses should show cumulative data relative to the date of approval of orforglipron as well as relative to prior periodic safety reports. Your analyses should provide an assessment of causality, with documentation of indication, temporal association, duration of therapy, associated signs and symptoms, relevant laboratory values (especially baseline and peak ALT, AST, and TB) and diagnostic tests, concomitant therapies, confounders, underlying risk factors, treatment given for the event, drug disposition (e.g., dechallenge/rechallenge), and outcome at the time of the report (including whether the patient was hospitalized, experienced liver failure, liver transplant, or death). For each report with evidence to suggest a causal relationship between orforglipron and liver toxicity, we request a graph displaying sequential ALT, AST, and TB on the y-axis and time (in days) on the x-axis, if this information is available. Medical literature reviews for case reports/case series of DILI reported with orforglipron should also be provided in the periodic safety report.

POST APPROVAL FEEDBACK MEETING

New molecular entities qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

COMPENDIAL STANDARDS

A drug with a name recognized in the official United States Pharmacopeia or official National Formulary (USP-NF) generally must comply with the compendial standards for strength, quality, and purity, unless the difference in strength, quality, or purity is plainly stated on its label (see FD&C Act § 501(b), 21 USC 351(b)). FDA typically cannot share application-specific information contained in submitted regulatory filings with third parties, which includes USP-NF. To help ensure that a drug continues to comply with compendial standards, application holders may work directly with USP-NF to revise official USP monographs. More information on the USP-NF is available on USP's website[9].

[9] https://www.uspnf.com/

If you have any questions, contact Arati B. Kamath, PhD, Regulatory Project Manager, at (301) 796-3159 or Arati.Kamath@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Lisa B. Yanoff, MD
Deputy Director
Office of Cardiology, Hematology,
Endocrinology, and Nephrology
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide
- Carton and Container Labeling

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/

LISA B YANOFF
04/01/2026 09:10:30 AM