# Office of Clinical Pharmacology Review

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| **NDA or BLA Number** | NDA 214962 |
| **Link to EDR** | \\CDSESUB1\evsprod\nda214962 |
| **Submission Date** | 12/18/2020 |
| **Submission Type** | Original NDA – 505(b)(2) |
| **Brand Name** | (b) (4) |
| **Generic Name** | Fingolimod |
| **Dosage Form and Strength** | Orally disintegrating tablets (ODT), 0.25 mg (b) (4) |
| **Route of Administration** | Oral |
| **Proposed Indication** | Treatment of Relapsing forms of Multiple Sclerosis (MS) to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease (b) (4) |
| **Applicant** | Handa Neuroscience, LLC |
| **Associated IND** | IND 130544 |
| **OCP Review Team** | Xiaohan Cai, Ph.D.,<br>Gopichand Gottipati, Ph.D. |

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## 1. Executive Summary

Handa Neuroscience, LLC submitted an original New Drug Application (NDA 214962), seeking approval for [redacted] (b) (4) (fingolimod orally disintegrating tablets, ODT) via 505(b)(2) regulatory pathway for the treatment of relapsing forms of multiple sclerosis (MS) to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease [redacted] (b) (4) The proposed product, fingolimod ODT, is an alternative dosage form of fingolimod, which reportedly eases dosing, especially in MS patients with swallowing problems. The listed drug (LD) used in this application, *Gilenya* oral capsules[1] (NDA 022527), was approved in the US in 2010.

This application relies on two single-dose pivotal comparative bioavailability (BA) studies (Study FGL-01 and FGL-02) in healthy subjects to enable the reliance on FDA's previous findings for the LD, Gilenya capsules. The results from Study FGL-P01 showed that the 90% confidence interval (CI) for the geometric mean ratios (GMR) for $AUC_{0\text{-}144h}$ and $C_{max}$ of fingolimod between fingolimod ODT and the LD were within 80-125% under fasting condition. The results from Study FGL-P02 showed that the 90% CI for the GMR for $AUC_{0\text{-}144}$ and $C_{max}$ of fingolimod between fingolimod ODT and the LD were within 80-125% under fed condition (after taking a standard high-fat, high-calorie meal). In conclusion, these results demonstrate that an adequate PK bridge between fingolimod ODT and LD has been established under fasted and fed conditions, allowing the applicant to rely upon FDA's findings of LD for efficacy and safety, and other relevant information from respective label.

The applicant also evaluated the effect of dosing with or without water for fingolimod ODT in study FGL-01 in healthy subjects under fasting conditions. The exposure metrics, $C_{max}$, $AUC_{0\text{-}144h}$, as well as $T_{max}$ were unaffected when fingolimod was administered with/without water. Therefore, fingolimod ODT can be taken with or without water.

The Office of Study Integrity and Surveillance (OSIS) was consulted for clinical and analytical site for the pivotal comparative bioavailability studies FGL-01 and FGL-02. OSIS noted that inspection was not warranted for neither sites because they were inspected previously (DARRTS dated 2/18/2021).

## 2. Recommendations

The Office of Clinical Pharmacology (OCP) has reviewed the information submitted in the NDA and recommends approval based an adequate PK bridge demonstrated between fingolimod ODT and the listed drug *Gilenya* oral capsules for the treatment of relapsing

[1] USPI of Gilenya oral capsules:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022527s008lbl.pdf

forms of MS, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in patients 10 years of age and older.

## 3. Background and Regulatory History

The applicant is seeking approval of (b) (4) via 505(b)(2) pathway and intends to rely on FDA's findings of safety and efficacy of fingolimod based on results from the pivotal comparative bioavailability studies using *Gilenya* oral capsules as the LD.

In 2016, the FDA provided Written Responses to the Type B Meeting with the applicant's questions on the clinical development program. In this Type B meeting (dated July, 2016), the applicant discussed with the agency about the proposed 505(b)(2) regulatory drug development program, including the comparative BA studies and appropriateness of PK bridging strategy for fingolimod ODT. In addition, the Agency provided additional feedback (dated December, 2016) in response to applicant's questions related to the comparative BA studies.

Fingolimod is metabolized by sphingosine kinase to the active metabolite, fingolimod-phosphate (fingolimod-P), and therefore, the applicant conducted relative BA/BE assessments for fingolimod-P exposures, in addition to fingolimod PK following administration of ODT and LD.

## 4. Summary of Pivotal Relative Bioavailability Studies

### 4.1 Study FGL-01

**Title:** Single-dose, parallel, comparative bioavailability study of fingolimod 0.5 mg orally disintegrating tablets versus fingolimod 0.5 mg capsules following the administration of a 1 mg dose in healthy adult subjects under fasting conditions

**Primary Objectives:**

- To compare the relative BA between fingolimod ODT and Gilenya capsule under fasting conditions
- To compare the relative BA between fingolimod ODT administered with and without water under fasting conditions.

**Study Design and Methodology:**

The study was an open-label, randomized, single-dose, single-period, three-treatment, three-arm, parallel study in healthy male and female subjects. Subjects were fasted overnight for at least 10 hours prior to study treatment administration in the morning. A total of 75 subjects were randomized to 1:1:1 to receive one of the following treatments:

| | Treatment 1 | Treatment 2 | Treatment 3 |
|---|---|---|---|
| Product Administered | Fingolimod ODT | Fingolimod ODT | Fingolimod Capsule (Gilenya) |
| Dose/Strength | 1 mg [0.5 mg] | 1 mg [0.5 mg] | 1 mg [0.5 mg] |
| Route of Administration | Oral | Oral | Oral |
| Other Characteristics | Administered with 240 mL of water | Administered without water | Administered with 240 mL of water |

**Number of Subjects (Planned and Analyzed)**

A total of 75 subjects enrolled in the study, and all subjects completed the study and were included in the PK population and statistical analysis.

**PK Sampling:**

Blood samples for PK determination were collected at pre-dose and post-dose at 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 24, 28, 32, 36, 48, 60, 72, 96, 120, and 144 hours. Whole blood concentrations of fingolimod and fingolimod-P were quantified using a validated LC-MS/MS assay (please refer to section 5).

**Criteria for Evaluation**

Statistical inference of fingolimod and fingolimod-P was based on a comparative BA/BE approach using the following standards:

- The ratio of geometric least square (LS) means with corresponding 90% CI calculated from the exponential of the difference between the Treatment-1 and Treatment-2 product for the ln-transformed parameters $C_{max}$, $AUC_{0-144}$ should all be within the 80.00 to 125.00%.
- The ratio of geometric LS means with corresponding 90% CI calculated from the exponential of the difference between the Treatment-2 and Treatment-3 for the ln-transformed parameters $C_{max}$ and $AUC_{0-144}$ should all be within the 80.00 to 125.00%.

**Pharmacokinetics Results:**

**Fingolimod**

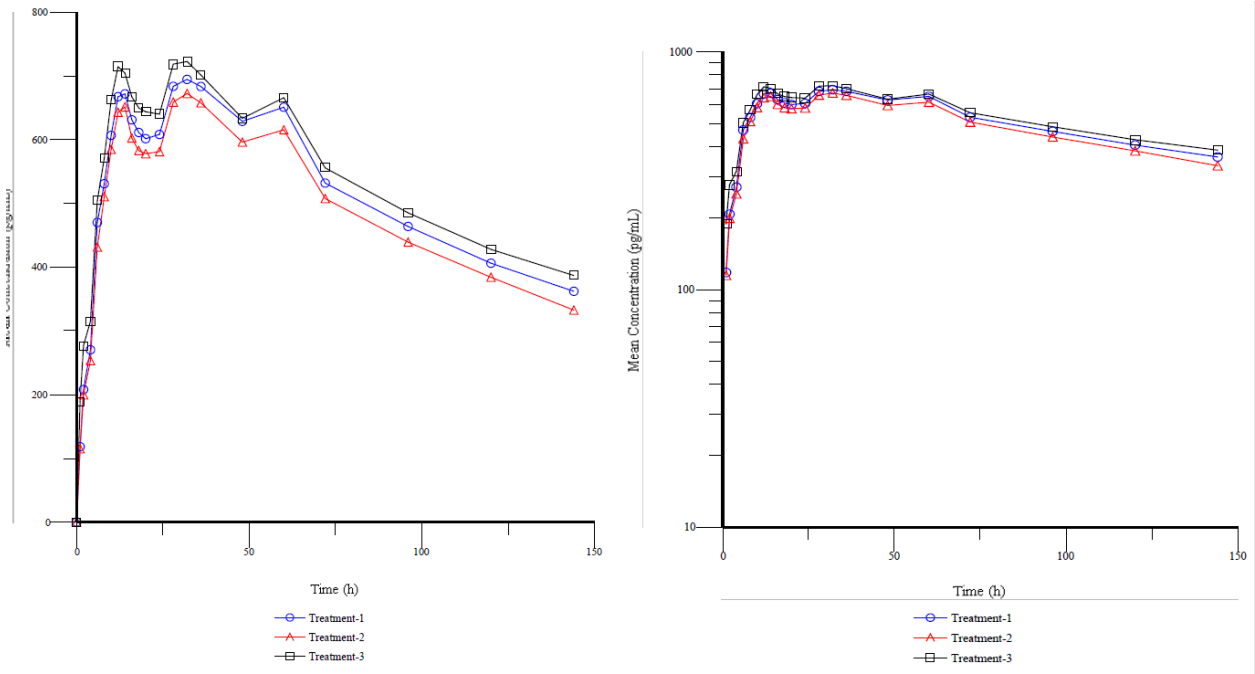
Based on the applicant's PK analysis, 75 (100%) subjects were included in the primary PK population. The PK and BA analysis conducted by the applicant are presented as below:

**Table 1: Study FGL-01: Summary of Whole Blood PK Parameters of Fingolimod (PK Population)**

| Parameters | Treatment-1 (N=25) | | Treatment-2 (N=25) | | Treatment-3 (N=25) | |
|---|---|---|---|---|---|---|
| | Mean | CV% | Mean | CV% | Mean | CV% |
| $C_{max}$ (pg/mL) | 722.68 | 17.6 | 689.03 | 13.9 | 761.64 | 14.8 |
| $T_{max}$ (h) | 32 | 12.00 – 59.82 | 32 | 10.00 – 58.87 | 32 | 12.00 – 59.03 |
| $AUC_{0-144h}$ (pg·h/mL) | 74521.65 | 20.4 | 70875.79 | 14.4 | 77952.08 | 15.4 |
| $T_{1/2}$ (h) | 134.05 | 36.0 | 129.79 | 48.2 | 142.2 | 40.1 |

Source: Based on Reviewer's analysis; $T_{max}$ is presented as Median and range (minimum-maximum)

**Figure 1: Study FGL-01: Mean Blood Concentration vs. Time Curve for Fingolimod**




Source: Study Report FGL-01; page number 36; figure 1

**Table 2: Study FGL-01: Geometric Mean Ratios (90% CI) of Fingolimod following a Single Dose of Test Product (T2) and Reference Product (T3) under a Fasting Condition**

| Parameter | Inter-subject CV (%) | Geometric LSmeans[a] | | Ratio (%) | 90% Confidence Limits (%) | |
|---|---|---|---|---|---|---|
| | | Treatment-2 (n=25) | Treatment-3 (n=25) | | Lower | Upper |
| $C_{max}$ | 14.5 | 682.5 | 753.8 | 90.54 | 84.54 | 96.98 |
| $AUC_{0-144}$ | 15.5 | 70155.9 | 77014.8 | 91.09 | 84.66 | 98.01 |

Abbreviations: CV = coefficient of variation; LSmeans = least-square means; n = number of subjects

a. units are pg/mL for $C_{max}$ and pg·h/mL for $AUC_{0-144}$.

Source: Study Report FGL-01; page number 35, Table 8

**Table 3: Study FGL-01: Geometric Mean Ratios (90% CI) of Fingolimod following a Single Dose of Test Product with Water (T1) and without Water (T2) under a Fasting Condition**

| Parameter | Inter-subject CV (%) | Geometric LSmeans[a] | | Ratio (%) | 90% Confidence Limits (%) | |
|---|---|---|---|---|---|---|
| | | Treatment-1 (n=25) | Treatment-2 (n=25) | | Lower | Upper |
| $C_{max}$ | 16.1 | 712.1 | 682.5 | 104.33 | 96.71 | 112.56 |
| $AUC_{0-144}$ | 17.6 | 73098.0 | 70155.9 | 104.19 | 95.89 | 113.21 |

Abbreviations: CV = coefficient of variation; LSmeans = least-squares means; n = number of subjects

a. units are pg/mL for $C_{max}$ and pg·h/mL for $AUC_{0-144}$.

Source: Study Report FGL-01; page number 35, Table 7

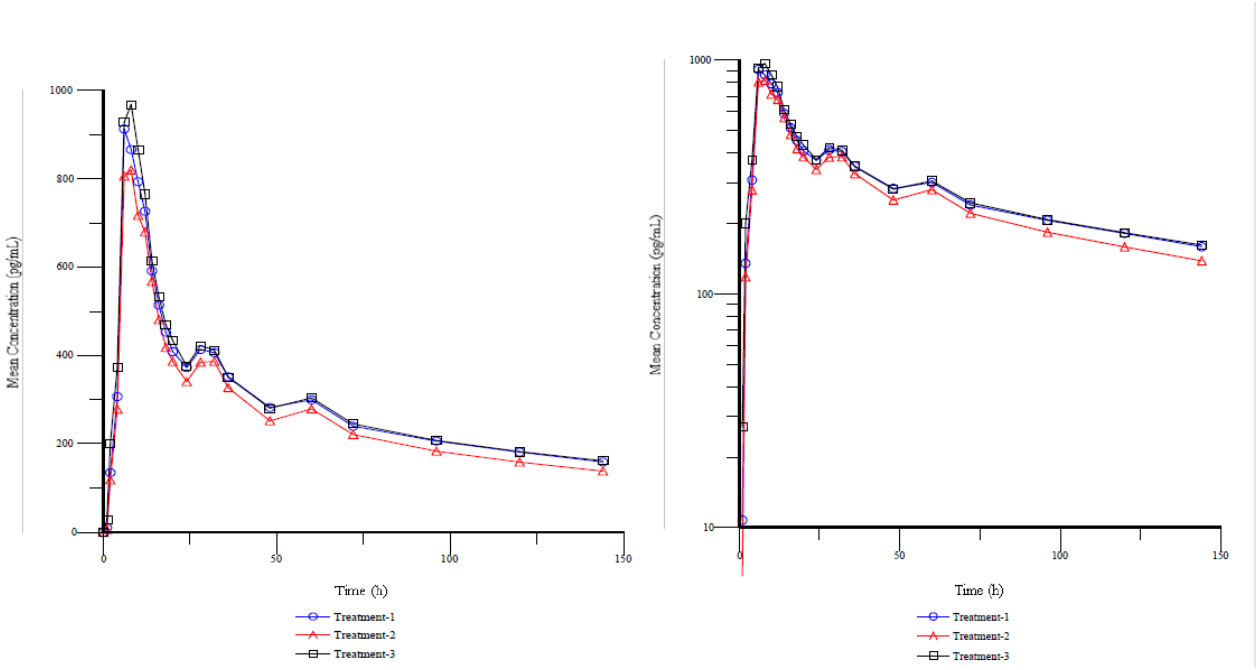
**Fingolimod-P:**

**Table 4: Study FGL-01: Summary of Whole Blood PK Parameters of Fingolimod-P (PK Population)**

| Parameters | Treatment-1 (N=25) | | Treatment-2 (N=25) | | Treatment-3 (N=25) | |
|---|---|---|---|---|---|---|
| | Mean | CV% | Mean | CV% | Mean | CV% |
| $C_{max}$ (pg/mL) | 975.29 | 24.0 | 899.03 | 28.9 | 1027.52 | 19.2 |
| $T_{max}$ (h) | 6 | 6-10.02 | 8 | 6-12 | 8 | 6-12 |
| $AUC_{0\text{-}144h}$ (pg·h/mL) | 41763.53 | 20.1 | 38077.01 | 21.1 | 42929.85 | 18.8 |
| $T_{1/2}$ (h) | 121.89 | 52.0 | 95.53 | 31.1 | 112.26 | 32.0 |

Based on Reviewer's analysis; $T_{max}$ is presented as Median and range (minimum-maximum)

**Figure 2: Study FGL-01: Mean Blood Concentration vs. Time Curve for Fingolimod-P**




Source: Study Report FGL-01; page number 39; Figure 2

**Table 5: Study FGL-01: Geometric Mean Ratios (90% CI) of Fingolimod-P following a Single Dose of Test Product (T2) and Reference Product (T3) under a Fasting Condition**

| Parameter | Inter-subject CV (%) | Geometric LSmeans[a] | | Ratio (%) | 90% Confidence Limits (%) | |
|---|---|---|---|---|---|---|
| | | Treatment-2 (n=25) | Treatment-3 (n=25) | | Lower | Upper |
| $C_{max}$ | 23.7 | 868.0 | 1008.7 | 86.06 | 77.03 | 96.14 |
| $AUC_{0-144}$ | 19.2 | 37366.1 | 42256.2 | 88.43 | 80.79 | 96.79 |

Abbreviations: CV = coefficient of variation; LSmeans = least-squares means; n = number of subjects

a. units are pg/mL for $C_{max}$ and pg·h/mL for $AUC_{0-144}$.

Source: Study Report FGL-01; page number 35, Table 11

**Table 6: Study FGL-01: Geometric Mean Ratios (90% CI) of Fingolimod-P following a Single Dose of Test Product with Water (T1) and without Water (T2) under a Fasting Condition**

| Parameter | Inter-subject CV (%) | Geometric LSmeans[a] | | Ratio (%) | 90% Confidence Limits (%) | |
|---|---|---|---|---|---|---|
| | | Treatment-1 (n=25) | Treatment-2 (n=25) | | Lower | Upper |
| $C_{max}$ | 26.4 | 946.8 | 868.0 | 109.07 | 96.42 | 123.38 |
| $AUC_{0-144}$ | 19.7 | 41026.0 | 37366.1 | 109.79 | 100.09 | 120.44 |

Abbreviations: CV = coefficient of variation; LSmeans = least-squares means; n = number of subjects

a. units are pg/mL for $C_{max}$ and pg·h/mL for $AUC_{0-144}$.

Source: Study Report FGL-01; page number 35, Table 10

## Discussion and Conclusion

The comparative bioavailability of fingolimod PK between ODT and LD (both administered under fasting conditions) met the standard BE criteria, while fingolimod-P PK did not. Specifically, the 90% CI of GMR between ODT and LD for $C_{max}$ and $AUC_{0-144h}$, were within 80-125%. The 90% CI of GMR between ODT and LD for fingolimod-P $AUC_{0-144h}$ was within 80-125%, but not for fingolimod-P $C_{max}$ (90% CI: 77.03-96.14). The $T_{max}$ of fingolimod and fingolimod-P, following the administration of fingolimod ODT, was comparable to that following the administration of LD under the fasting conditions.

Administration of fingolimod ODT with/without water did not affect the relative bioavailability of fingolimod and fingolimod-P. The 90% CI of GMR of fingolimod and fingolimod-P exposures (when administered with and without water), $C_{max}$ and $AUC_{0\text{-}144h}$ were within 80-125%. The $T_{max}$ was comparable following the administration of fingolimod ODT with or without water.

In conclusion, results from study FGL-01 established a PK bridging between fingolimod ODT and the LD, Gilenya oral capsules, both administered under fasting conditions. Fingolimod ODT can be taken with or without water.

*Reviewer's Comments:*

- *Fifteen of 25 subjects who received Treatment-2 (i.e., Fingolimod ODT, without water) had a protocol deviation related to dosing. Specifically, per protocol, the time to swallow the saliva was not to exceed a maximum of 30-second, and these subjects swallowed the saliva 30-505 seconds after placing the fingolimod ODT on the tongue. However, this protocol deviation is not expected to have any meaningful impact on the PK or safety assessments, because ODTs disintegrate rapidly in the oral cavity, and patients typically do not require liquids to ingest ODTs.*
- *The terminal half-lives of fingolimod and fingolimod-P are relatively long – 142 and 112 hours in study FGL-01, respectively). Consequently, the % AUC extrapolated relative to $AUC_{0\text{-}\infty}$ was approximately 45% for fingolimod and 37% for fingolimod-P following each of the three treatments. The last time point for PK sample collection was 144 hours and the intra-subject variability reported for fingolimod and fingolimod-P was low (<16%, based on the Gilenya NDA 022527 OCP review, dated Aug. 2010). Therefore, the statistical analysis for relative BA assessments based on truncated $AUC_{0\text{-}144hr}$ is acceptable.*
- *The reviewer was able to verify and confirm the applicant's analyses and results independently.*
- *Fingolimod is metabolized by sphingosine kinase to the active metabolite, fingolimod-phosphate (fingolimod-P). In study FGL-01, the GMR of fingolimod-P $C_{max}$ (between ODT and LD) did not meet the standard BE criteria (GMR: 0.86; 90% CI: 77.03-96.14). Specifically, the lower bound of 90% CI for fingolimod-P Cmax (77.03%) was 3% lower than the standard BE criteria (80%). The point estimate (LS means ratios) for $C_{max}$ is 0.86, but more importantly, AUC of fingolimod-P, and both $C_{max}$ and AUC for the parent drug fingolimod met the standard BE criteria. In the original Clinical Pharmacology Review of NDA 022527 (DARRTS dated Aug. 2010), it was noted that though the projected fingolimod-P steady-state exposures following administration of 0.25 mg QD Gilenya were approximately half of those following administration of 0.5 mg QD Gilenya, 0.25 mg QD was almost as effective as 0.5 mg QD. Considering all the information, the review team believes that the 3% lower exposure (77.03%)*

*relative to the standard BE criteria of lower bound of 90% CI (80%) for $C_{max}$ of fingolimod-P, is unlikely to be clinically relevant.*

## 4.2 Study FGL-02

**Title:** Single-dose, parallel, comparative bioavailability study of fingolimod 0.5 mg orally disintegrating tablets versus fingolimod 0.5 mg capsules following the administration of a 1 mg dose in healthy adult subjects under fed conditions

**Primary Objectives:**

- To compare the bioavailability between fingolimod ODT (Test) and Gilenya® capsule (Reference) under fed conditions

**Study Design and Methodology:**

The study was an open-label, randomized, single-dose, two-treatment, two-arm, parallel study in healthy male and female subjects. Following an overnight fast of at least 10 hours, subjects received a high-fat, high-calorie breakfast 30 mins before drug administration. The high-fat, high-calorie breakfast was estimated to have 1011 kcal, with 53% of total calories from fat. A total of 38 subjects were enrolled and randomized to 1:1 to receive one of the following treatments:

| | **Test Treatment** | **Reference Treatment** |
|---|---|---|
| Product Administered | Fingolimod ODT | Fingolimod Capsule (Gilenya) |
| Dose/Strength | 1 mg [0.5 mg] | 1 mg [0.5 mg] |
| Route of Administration | Oral | Oral |
| Other Characteristics | Administered without water | Administered with 240 mL of water |

**Number of Subjects (Planned and Analyzed)**

A total of 38 subjects enrolled in the study, and all subjects completed the study and were included in the PK population and statistical analysis.

**PK Sampling:**

Blood samples for PK determination were collected at pre-dose and post-dose at 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 24, 28, 32, 36, 48, 60, 72, 96, 120, and 144 hours. Whole blood concentrations of fingolimod and fingolimod-P were quantified using a validated LC-MS/MS assay (please refer to section 5).

**Criteria for Evaluation**

Statistical inference of fingolimod and fingolimod-P exposures was based on a comparative BA/BE approach using the following standards: The ratio of geometric LS means with corresponding 90% CI calculated from the exponential of the difference between the Test and Reference product for the ln-transformed parameters $C_{max}$, $AUC_{0-144}$ should all be within the 80.00 to 125.00%.

**Pharmacokinetics Results:**

**Fingolimod**

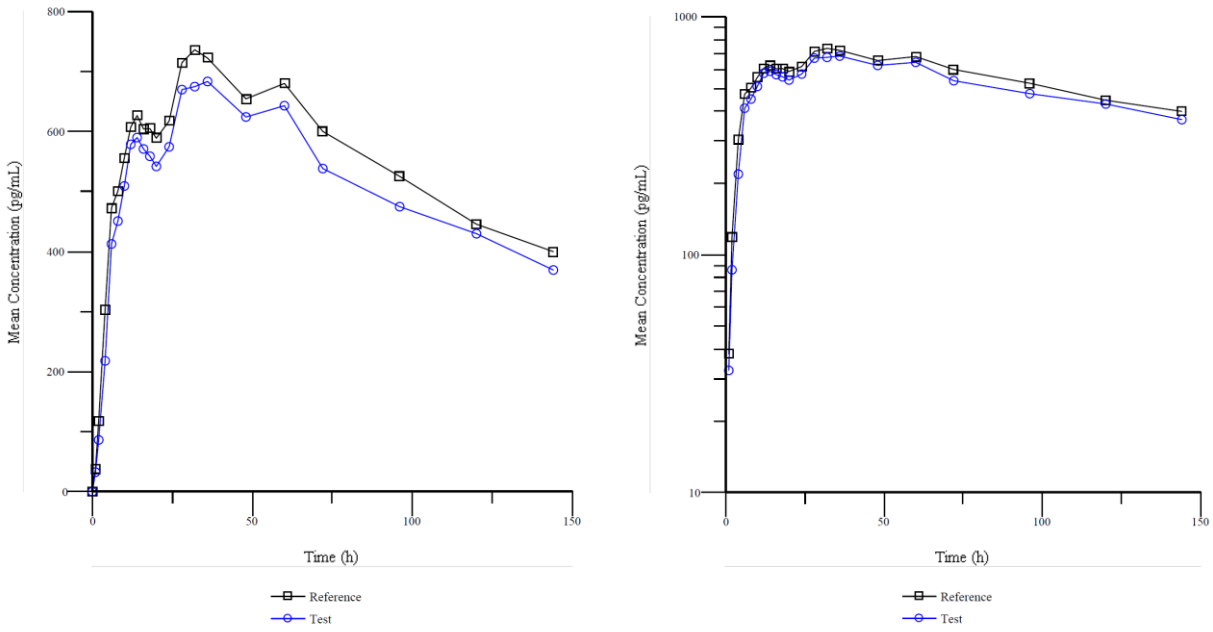
Based on the applicant's PK analysis, 38 (100%) subjects were included in the primary PK population. The PK and BA analysis conducted by the applicant are presented as below:

**Table 7: Study FGL-02: Summary of Whole Blood PK Parameters of Fingolimod (PK Population)**

| Parameters | Test (N=19) | | Reference (N=19) | |
|---|---|---|---|---|
| | Mean | CV% | Mean | CV% |
| $C_{max}$ (pg/mL) | 725.27 | 14.6 | 760.06 | 14.8 |
| $T_{max}$ (h) | 32 | 6-59.7 | 32 | 28-59.43 |
| $AUC_{0-144h}$ (pg·h/mL) | 73779.37 | 16.7 | 79550.82 | 17.6 |
| $T_{1/2}$ (h) | 128.19 | 32.0 | 124.1 | 43.5 |

Based on Reviewer's analysis; $T_{max}$ is presented as Median and range (minimum-maximum)

**Figure 3: Study FGL-02: Mean Blood Concentration vs. Time Curve for Fingolimod**




Source: Study Report FGL-02; appendix 16.2.6, P42 &43

**Table 8: Study FGL-02: Geometric Mean Ratios (90% CI) of Fingolimod-P following a Single Dose of Test Product and Reference Product under a Fed Condition**

| Parameter | Inter-subject CV (%) | Geometric LSmeans[a] | | Ratio (%) | 90% Confidence Limits (%) | |
|---|---|---|---|---|---|---|
| | | Test (n=19) | Reference (n=19) | | Lower | Upper |
| $C_{max}$ | 14.8 | 718.0 | 752.3 | 95.44 | 88.07 | 103.44 |
| $AUC_{0-144}$ | 17.2 | 72440.1 | 78202.0 | 92.63 | 84.35 | 101.73 |

Abbreviations: CV = coefficient of variation; LSmeans = least-square means; n = number of subjects.
a. units are pg/mL for $C_{max}$ and pg·h/mL for $AUC_{0-144}$.

Source: Study Report FGL-02; page number 35, Table 8

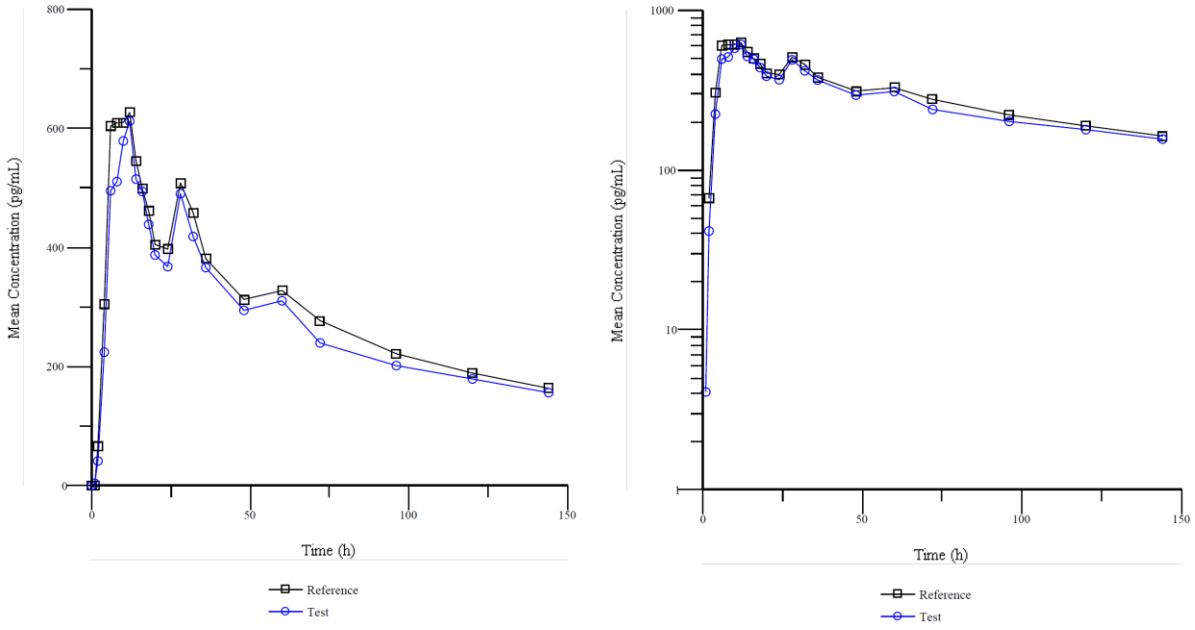
**Fingolimod-P:**

**Table 9: Study FGL-02: Summary of Whole Blood PK Parameters of Fingolimod-P (PK Population)**

| Parameters | Test (N=19) | | Reference (N=19) | |
|---|---|---|---|---|
| | Mean | CV% | Mean | CV% |
| $C_{max}$ (pg/mL) | 718.41 | 24.1 | 749.93 | 19.9 |
| $T_{max}$ (h) | 12 | 6-28 | 10 | 6-28.07 |
| $AUC_{0-144h}$ (pg·h/mL) | 39740.33 | 21.1 | 43058.84 | 18.0 |
| $T_{1/2}$ (h) | 104.03 | 31.1 | 108.42 | 48.2 |

Based on Reviewer's analysis; $T_{max}$ is presented as Median and range (minimum-maximum)

**Figure 4: Study FGL-02: Mean Blood Concentration vs. Time Curve for Fingolimod-P**




Source: Study Report FGL-02; Appendix 16.2.6; Page 174 & 175

**Table 10: Study FGL-02: Geometric Mean Ratios (90% CI) of Fingolimod-P following a Single Dose of Test Product and Reference Product under a Fed Condition**

| Parameter | Inter-subject CV (%) | Geometric LSmeans[a] | | Ratio (%) | 90% Confidence Limits (%) | |
|---|---|---|---|---|---|---|
| | | Test (n=19) | Reference (n=19) | | Lower | Upper |
| $C_{max}$ | 21.8 | 700.3 | 735.8 | 95.17 | 84.56 | 107.11 |
| $AUC_{0-144}$ | 20.3 | 38591.4 | 41995.9 | 91.89 | 82.32 | 102.59 |

Abbreviations: CV = coefficient of variation; LSmeans = least-squares means; n = number of subjects.

a. units are pg/mL for $C_{max}$ and pg·h/mL for $AUC_{0-144}$.

Source: Study Report FGL-02; page number 38, Table 10

## Discussion and Conclusion

The comparative bioavailability of fingolimod and fingolimod-P PK between ODT and LD (both administered under fed conditions) met the standard BE criteria. Specifically, the 90% CI of GMR between ODT and LD for fingolimod and fingolimod-P $C_{max}$ and $AUC_{0-144h}$ were within 80-125%. The $T_{max}$ for fingolimod and fingolimod-P, following the administration of ODT, was comparable to that following the administration of LD under the fed condition.

In conclusion, results from study FGL-02 supported a PK bridging between fingolimod ODT and the LD, Gilenya oral capsules under fed conditions. The dosing instruction fingolimod ODT, with or without food, is recommended the same as in the LD.

*Reviewer's Comments:*

- *Similar to the dosing deviation observed in Study FGL-01, 8 of 19 subjects who received ODT had the protocol deviation for swallowing the saliva 30-192 seconds after placing fingolimod ODT on the tongue, exceeding the 30-second maximum required by the protocol. However, this protocol deviation is not expected to have any impact on the PK or safety assessments.*
- *Similar to analyses in study FGL-01, the statistical analysis for BE assessment based on truncated AUC0-144hr is acceptable.*
- *The reviewer was able to verify and confirm the applicant's analyses and results independently.*

## 5. Summary of Bioanalytical Method Validation and Performance

Plasma concentrations of fingolimod and fingolimod-P were measured by a validated LC-MS/MS method in human whole blood in study FNO-V3-628. Whole blood samples from studies FGL-P01 and FGL-P02 were analyzed by (b) (4) . Because approval of fingolimod ODT relies on the pivotal relative BA studies FGL-P01 and FGL-P02, a routine inspection of the clinical and bioanalytical sites was requested via Office of Study Integrity and Surveillance (OSIS). Inspections at the clinical and analytical sites are not warranted at this time because OSIS inspected both sites in 2019 with No Action Indicated (refer to NDA 214962, Bioequivalence Establishment Inspection Report Review, DARRTS, 2/18/2021).

Description of method validation parameters (Validation Report # FNO-V3-628) are provided below:

## Table 1: Bioanalytical Method Validation for Fingolimod

| Information Requested | Data |
|---|---|
| **Bioanalytical method validation report location** | FNO-V3-628<br>Module 5.3.1.4 |
| **Analyte** | Fingolimod |
| **Internal standard (IS)** | Fingolimod-D4 |
| **Method description** | Double extraction (protein precipitation followed by solid-phase).<br>Reversed-phase HPLC with MS/MS detection |
| **Limit of quantitation** | 20.0 pg/mL |
| **Average recovery of drug (%)** | 60.1% |
| **Average recovery of IS (%)** | 63.1% |
| **Standard curve concentrations (units/mL)** | 20.0 pg/mL to 2000.0 pg/mL |
| **QC concentrations (units/mL)** | 20.0 pg/mL, 60.0 pg/mL, 1000.0 pg/mL and 1500.0 pg/mL |
| **QC Intraday precision range (%)** | 1.3% to 5.6% |
| **QC Intraday accuracy range (%)** | -4.0% to 9.0% |
| **QC Interday precision range (%)** | 2.1% to 7.5% |
| **QC Interday accuracy range (%)** | -2.0% to 0.8% |
| **Bench-top stability (hrs)** | 68.5 hours at 22°C nominal. |
| **Stock stability (days)** | 166 days for Fingolimod in MeOH at 100.00 µg/mL at 4°C nominal.<br><br>163 days for Fingolimod in MeOH at 2.00 ng/mL at 4°C nominal.<br><br>166 days for Fingolimod-D4 in MeOH at 100.00 µg/mL at 4°C nominal. |
| **Processed stability (hrs)** | 357.6 hours at 4°C nominal. |
| **Freeze-thaw stability (cycles)** | 4 cycles |
| **Long-term storage stability (days)** | 21 days at -20°C nominal<br><br>135 days at -80°C nominal. |
| **Dilution integrity** | 1500.0 pg/mL diluted 2-fold.<br><br>4000.0 pg/mL diluted 5-fold.<br><br>4000.0 pg/mL diluted 10-fold. |
| **Selectivity** | No significant interference observed in the 8 regular blank matrix lots screened for Fingolimod, in the 10 regular blank matrix lots screened for Fingolimod-D4, as well as in the lipemic matrix lot screened for Fingolimod and Fingolimod-D4. |

Source: Summary of Biopharmaceuticals, Module 2.7.1; page number 46

## Table 2: Bioanalytical Method Validation for Fingolimod Phosphate

| Information Requested | Data |
|---|---|
| **Bioanalytical method validation report location** | FNO-V3-628<br>Module 5.3.1.4 |
| **Analyte** | Fingolimod Phosphate |
| **Internal standard (IS)** | Fingolimod Phosphate-D4 |
| **Method description** | Double extraction (protein precipitation followed by solid-phase).<br>Reversed-phase UHPLC with MS/MS detection |
| **Limit of quantitation** | 70.0 pg/mL |
| **Average recovery of drug (%)** | 55.7% |
| **Average recovery of IS (%)** | 58.9% |
| **Standard curve concentrations (units/mL)** | 70.0 pg/mL to 1500.0 pg/mL |
| **QC concentrations (units/mL)** | 70.0 pg/mL, 210.0 pg/mL, 750.0 pg/mL and 1125.0 pg/mL |
| **QC Intraday precision range (%)** | 1.6% to 6.0% |
| **QC Intraday accuracy range (%)** | -10.3% to 5.5% |
| **QC Interday precision range (%)** | 3.4% to 6.6% |
| **QC Interday accuracy range (%)** | -6.3% to 3.5% |
| **Bench-top stability (hrs)** | 68.5 hours at 22°C nominal. |
| **Stock stability (days)** | 166 days for Fingolimod Phosphate in MeOH at 100.00 µg/mL at 4°C nominal.<br><br>163 days for Fingolimod Phosphate in MeOH at 100.00 ng/mL at 4°C nominal.<br><br>166 days for Fingolimod Phosphate-D4 in MeOH at 100.00 µg/mL at 4°C nominal. |
| **Processed stability (hrs)** | 165.2 hours at 4°C nominal |
| **Freeze-thaw stability (cycles)** | 4 cycles |
| **Long-term storage stability (days)** | 21 days at -20°C nominal.<br><br>135 days at -80°C nominal. |
| **Dilution integrity** | 1125.0 pg/mL diluted 2-fold.<br><br>3000.0 pg/mL diluted 5-fold.<br><br>3000.0 pg/mL diluted 10-fold. |
| **Selectivity** | No significant interference observed in the 8 regular blank matrix lots screened for Fingolimod Phosphate, in the 10 regular blank matrix lots screened for Fingolimod Phosphate-D4, as well as in the lipemic matrix lot screened for Fingolimod Phosphate and Fingolimod Phosphate-D4. |

Source: Summary of Biopharmaceuticals, Module 2.7.1; page number 47

*Reviewer's comments: Method validation and sample analysis were acceptable.*

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/s/

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XIAOHAN CAI
09/13/2021 10:52:08 AM

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