CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214962Orig2s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	505(b)(2) NDA
Application Number(s)	NDA 214962
Priority or Standard	Standard
Submit Date(s)	12/18/2020
Received Date(s)	12/18/2020
PDUFA Goal Date	10/18/2021
Division/Office	Division of Neurology 2, Office of Neuroscience
Reviewer Name(s)	Laura Baldassari, MD, MHS
Review Completion Date	10/18/2021
Established/Proper Name	HND-020, Fingolimod orally dissolving tablet (ODT)
(Proposed) Trade Name	Tascenso ODT
Applicant	Handa Neuroscience
Dosage Form(s)	0.25mg (b) (4) ODT
Applicant Proposed Dosing Regimen(s)	0.25mg (≤40kg) (b) (4) orally once daily
Applicant Proposed Indication(s)/Population(s)	Fingolimod ODT is a sphingosine 1-phosphate receptor modulator indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, (b) (4)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, (b) (4)

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MS	Multiple Sclerosis
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event

NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
ODT	Oral Disintegrating Tablet
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
RMS	Relapsing Forms of Multiple Sclerosis
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Fingolimod oral disintegrating tablet (ODT; Tascenso ODT) was developed to treat relapsing forms of multiple sclerosis (RMS). The applicant submits a 505(b)(2) NDA for fingolimod ODT using fingolimod as the Reference Listed Drug (RLD). If an adequate pharmacokinetic/pharmacodynamic (PK/PD) bridge between fingolimod and fingolimod ODT is established, this application will therefore rely on the efficacy and safety data for fingolimod, supplemented with the safety findings from the PK/PD studies undertaken with fingolimod ODT.

Fingolimod (Gilenya, NDA 022527) was approved for treatment of RMS in adults on 9/21/2010 based on findings from two adequate and well-controlled clinical trials, and the indication was expanded to include pediatric patients ≥10 years of age on 5/11/2018 based on findings from an adequate and well-controlled trial in children. Fingolimod is an oral first-in-class sphingosine-1-phosphate (S1P) receptor modulator that is phosphorylated to the active moiety fingolimod-phosphate (fingolimod-P). Though the exact mechanism of clinical benefit in multiple sclerosis is unknown, the main pharmacodynamic effect of fingolimod is reduction of peripheral lymphocyte count. This effect is mediated by fingolimod-induced downregulation of S1P1 receptors on lymphocytes, therefore preventing their egress from lymph nodes. Reduction in peripheral lymphocytes is thought to limit the number of autoreactive lymphocytes that have potential to enter the central nervous system and lead to inflammation.

1.2. Conclusions on the Substantial Evidence of Effectiveness

This NDA is a 505(b)(2) submission and therefore does not include efficacy data for fingolimod ODT. If an adequate PK/PD bridge is established, fingolimod ODT will rely on the RLD, fingolimod, for substantial evidence of effectiveness.

Fingolimod (NDA 022527) was approved for treatment of RMS in adults on 9/21/2010. The basis for the original approval in adults was 2 adequate, well-controlled clinical trials (Studies 2301 and 2302), which demonstrated that fingolimod reduced the annualized relapse rate (ARR) compared to those on placebo (Study 2301) or interferon beta-1a (Study 2302) in patients with RMS.

The pediatric indication (patients ≥10 years of age) for fingolimod was added on 5/18/2018. This approval was based upon a single adequate and well-controlled trial in RMS patients ≥10 years and <18 years of age. This trial provided substantial evidence that fingolimod (0.25 or 0.5mg daily) reduced the frequency of relapses compared to interferon beta-1a.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Fingolimod (Gilenya, NDA 022527) was approved for treatment of relapsing forms of multiple sclerosis in adults on 9/21/2010, and the indication was amended based on findings from an efficacy supplement to include pediatric patients ≥10 years of age on 5/11/2018. The risks and therapeutic benefits associated with fingolimod are well-known and established. Fingolimod oral disintegrating tablet, the subject of this review, was submitted as a 505(b)(2) application with 2 Phase 1 studies intended to demonstrate a PK-PD bridge to fingolimod, the reference listed drug. Although the studies conducted to establish the PK characteristics of fingolimod ODT in relation to fingolimod were not designed to establish an extensive safety profile, these PK studies did not raise any specific new clinical safety concerns. (b) (4) Fingolimod ODT may offer a potential alternative to an oral tablet in patients who may experience dysphagia or other difficulty swallowing tablets. Given the similarity in safety profile and PK findings, fingolimod ODT merits an approval for the same indication as fingolimod, the treatment of relapsing multiple sclerosis (b) (4)

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Multiple sclerosis (MS) is a chronic, immune-mediated, demyelinating, and neurodegenerative disease affecting the central nervous system. • Relapsing forms of MS are defined by the occurrence of clinical relapses, which are events characterized by new onset neurological symptoms associated with disability, from which there is variable recovery. Relapsing forms of MS include clinically isolated syndrome, relapsing remitting MS, and active secondary progressive	Treatment of relapsing forms of multiple sclerosis is intended to reduce the frequency of clinical relapses. Clinical relapses can be permanently disabling and reduce quality of life.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	MS. • The prevention of relapses is paramount to the treatment of patients with relapsing forms of MS, in order to prevent new neurological symptoms that can lead to disability.	
Current Treatment Options	• There are over a dozen products approved for treatment of relapsing forms of MS. • Currently approved MS therapeutics have demonstrated efficacy in reducing the risk of clinical relapse, which is presumed to be related to immunomodulatory mechanisms of action that impact the neuroinflammatory aspect of the disease. • Interferon beta products, including Plegridy, were among the earliest products approved for MS. Plegridy SC was approved in 2014, and was intended to reduce the weekly injection frequency required for Avonex. The applicant has developed an IM formulation of Plegridy.	Treatment of relapsing forms of multiple sclerosis generally involves immunomodulation intended to reduce the frequency of clinical relapse. Many therapies approved for the treatment of relapsing forms of MS are labeled to prevent accumulation of disability.
Benefit	• The basis for the original approval of fingolimod in adults was 2 adequate, well-controlled clinical trials (Studies 2301 and 2302), which demonstrated that fingolimod reduced the annualized relapse rate (ARR) compared to those on placebo (Study 2301) or interferon beta-1a (Study 2302) in patients with RMS. • The pediatric indication for fingolimod was added in 2018, and the approval was based upon a single adequate and well-controlled trial in RMS patients ≥10 years and <18 years of age. This trial provided substantial evidence that fingolimod (0.25 or 0.5mg daily) reduced the frequency of relapses compared to interferon beta-1a.	Given the demonstration of a PK-PD bridge between fingolimod and fingolimod ODT, fingolimod ODT is expected to have similar clinical benefit on the frequency of relapses as fingolimod.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• The risks of fingolimod are known to include bradyarrhythmia and atrioventricular blocks (particularly with first dose), infections, progressive multifocal leukoencephalopathy, macular edema, liver injury, posterior reversible encephalopathy syndrome, respiratory effects, fetal risk, severe increase in disability after stopping fingolimod, tumefactive MS, increased blood pressure, and malignancies.	Given the demonstration of a PK-PD bridge between fingolimod and fingolimod ODT, fingolimod ODT is expected to have a similar clinical safety profile to fingolimod. (b) (4) [redacted]

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

x	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	□	Clinical outcome assessment (COA) data, such as		
		x	Patient reported outcome (PRO)	Section 8.5.4, Palatability
		□	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify)		
□	Patient experience data that were not submitted in the application, but were considered in this review:			
		□	Input informed from participation in meetings with patient stakeholders	
		□	Patient-focused drug development or other stakeholder meeting summary reports	
		□	Observational survey studies designed to capture patient experience data	
		□	Other: (Please specify)	
□	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

Multiple sclerosis (MS) is a chronic, immune-mediated, demyelinating, and neurodegenerative disorder affecting the central nervous system. The cause of MS is unknown, but is

hypothesized to be related to a complex interaction of genetic and environmental risk factors.[1,2] MS is the most common cause of non-traumatic neurologic disability in young adults, and it is estimated that approximately 1 million people in the United States have MS.[3] Disease manifestations can be diverse, and include weakness, incoordination, visual impairment, sensory loss, gait dysfunction, fatigue, cognitive impairment, and bowel/bladder dysfunction.

Relapsing forms of MS are defined by the occurrence of clinical relapses, which are events characterized by new onset neurological symptoms associated with disability, from which there is variable recovery. Relapsing forms of MS include clinically isolated syndrome, relapsing remitting MS (RRMS), and active secondary progressive MS. The prevention of relapses is paramount to the treatment of patients with relapsing forms of MS; relapses degrade the quality of life in patients with MS, and prevention of relapses prevents new neurological symptoms that can lead to disability.

Relapsing-remitting MS is the most common MS phenotype, as it accounts for approximately 85% of MS cases at symptom onset.[4] Patients with RRMS present with clinical relapses, from which there is a spectrum of recovery. The median age of RRMS onset is approximately 28 to 30 years.[5-7] In general, the frequency of relapse decreases over time,[8,9] with an estimate of relapse decrease by 17% for every 5 years of disease duration.[8] The decrease in relapse risk is thought to be more pronounced in patients with older age of onset.

Over time, the majority of patients with RRMS transition from predominantly inflammatory to more neurodegenerative driving forces of the disease, with development of secondary progressive MS (SPMS).[10] The transition to SPMS is an age-dependent process,[11-13] and it is estimated that approximately 30 to 40% of patients with SPMS have relapses superimposed upon this typical gradual decline.[6,14] The time from RRMS diagnosis to SPMS conversion is age of onset-dependent, and ranges from 18.9 to 20 years for all patients per several natural history studies.[8,12,15,16] Generally, the younger a patient is at the time of RRMS onset, the longer the disease duration prior to SPMS conversion. However, several studies have demonstrated that patients who receive MS treatments have substantially decreased risk of and delayed conversion to SPMS compared to patients in the pre-treatment era.[17-23] Additionally, use of some therapies approved to treat MS has been shown to delay reaching disability milestones.[17,20-22]

2.2. Analysis of Current Treatment Options

There are over a dozen products approved for treatment of relapsing forms of MS, including clinically isolated syndrome, relapsing remitting MS, and active secondary progressive MS (Table 1). Currently approved MS therapeutics have demonstrated efficacy in reducing the risk of clinical relapse, which is presumed to be related to immunomodulatory mechanisms of action that impact the neuroinflammatory aspect of the disease.

Table 1 (Reviewer). FDA-Approved Treatments for Relapsing Forms of Multiple Sclerosis

Product Name	Relevant Indication (Current)	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety Issues
Interferon beta-1b (Betaseron)	Relapsing forms of MS[1]	1993	SC every other day	ARR[2] 0.9 vs. placebo 1.31	Injection site reactions, hepatotoxicity, depression
Interferon beta-1a (Avonex)	Relapsing forms of MS	1996	IM weekly	ARR 0.67 vs. placebo 0.82	Injection site reactions, hepatotoxicity, depression
Glatiramer acetate (Copaxone)	Relapsing forms of MS	1996	SC daily or three times a week	Relapse rate 0.6/2 years vs. placebo 2.4 in Study 1	Injection site reactions, lipoatrophy
Mitoxantrone (Novantrone)	SPMS, progressive relapsing, or worsening RRMS	2000	IV q 3 months, duration limited by cardiotoxicity	Reduction in # relapses (0.4 and 0.73 vs. 1.2 placebo) in study 1; reduction in Gd+ T1 lesions, ARR, EDSS change in Study 2	Leukemia, cardiotoxicity
Interferon beta-1a (Rebif)	Relapsing forms of MS	2002	SC three times a week	29 to 32% reduction in # relapses over 2 years vs. placebo	Injection site reactions, hepatotoxicity, depression
Natalizumab (Tysabri)	Relapsing forms of MS	2004	IV every 4 weeks	67% reduction in ARR vs. placebo	PML, hepatotoxicity
Interferon beta-1b (Extavia)	Relapsing forms of MS	2009	SC every other day	ARR 0.9 vs. placebo 1.31	Injection site reactions, hepatotoxicity, depression
Fingolimod (Gilenya)	Relapsing forms of MS, ages ≥10 years	2010	PO daily	ARR 0.18 vs 0.4 placebo; 0.16 vs. 0.33 Avonex	Macular edema, infection, bradycardia, respiratory effects, liver injury
Teriflunomide (Aubagio)	Relapsing forms of MS	2012	PO daily	22 to 36% reduction in ARR vs. placebo	Hepatotoxicity, peripheral neuropathy, teratogenicity
Dimethyl fumarate (Tecfidera)	Relapsing forms of MS	2013	PO twice daily	44 to 53% reduction in ARR vs. placebo	Lymphopenia, GI effects, flushing
Peginterferon beta-1a (Plegridy)	Relapsing forms of MS	2014	SC every 2 weeks	36% ARR reduction vs. placebo	Injection site reactions, hepatotoxicity, depression
Alemtuzumab (Lemtrada)	Relapsing remitting and active SPMS, patients who have failed ≥2 other MS treatments	2015	IV, 3 to 5 days 1 year apart	49 to 55% ARR reduction vs interferon beta-1a	Serious and fatal autoimmune conditions, infusion reactions, stroke, malignancy

Product Name	Relevant Indication (Current)	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety Issues
Ocrelizumab (Ocrevus)	Relapsing forms of MS; PPMS	2017	IV every 6 months	46 to 47% ARR reduction vs. interferon beta-1a	Infusion-related reactions, infection, possible breast cancer
Monomethyl fumarate (Bafiertam)	Relapsing forms of MS	2018	PO twice daily	See Tecfidera (505(b)(2))	Lymphopenia, GI effects, flushing
Siponimod (Mayzent)	Relapsing forms of MS	2019	PO daily	55% ARR reduction vs. placebo	Macular edema, infection, bradycardia, respiratory effects, liver injury
Cladribine (Mavenclad)	Relapsing forms of MS (excluding CIS), in patients who have failed another MS treatment	2019	2 PO courses 1 year apart	58% ARR reduction vs. placebo	Malignancies, teratogenicity, lymphopenia, infections, hematologic toxicity, liver injury
Diroximel fumarate (Vumerity)	Relapsing forms of MS	2019	PO twice daily	See Tecfidera (505(b)(2))	Lymphopenia, GI effects, flushing
Ozanimod (Zeposia)	Relapsing forms of MS	2020	PO daily	38 to 48% ARR reduction vs. interferon beta-1a	Macular edema, infection, bradycardia, respiratory effects, liver injury
Ofatumumab (Kesimpta)	Relapsing forms of MS	2020	SC every 4 weeks	51 to 59% ARR reduction vs. Teriflunomide	Infections, injection-related reactions, reduction in immunoglobulins, fetal risk
Ponesimod (Ponvory)	Relapsing forms of MS	2021	PO daily	30.5% ARR reduction vs. Teriflunomide	Macular edema, infection, bradycardia, respiratory effects, liver injury

[1]Relapsing forms of MS, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease
[2] ARR: Annualized relapse rate

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Fingolimod ODT is not currently marketed in the United States for any indication. The US FDA approved the RLD, fingolimod (Gilenya, NDA 022527), for treatment of RMS in adults on 9/21/2010, and the indication was expanded to include pediatric patients ≥10 years of age on 5/11/2018.

3.2. Summary of Presubmission/Submission Regulatory Activity

Initial Pre-IND (IND 130544) meeting request: May 18, 2016

Pre-IND meeting written response: July 14, 2016

Original IND submission: Not applicable, as the applicant did not formally open the IND.

Pediatric initial study plan agreement: September 29, 2020

Pre-NDA meeting: Not applicable.

NDA 214962 submission: December 18, 2020

3.3. Foreign Regulatory Actions and Marketing History

Fingolimod ODT is not approved or marketed anywhere in the world for any indication.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

No inspections were conducted as part of this NDA review.

4.2. Product Quality

Please refer to the Chemistry, Manufacturing, and Control (CMC) review.

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

Please refer to the Nonclinical Review.

4.5. Clinical Pharmacology

Please refer to the Clinical Pharmacology review.

4.6. Devices and Companion Diagnostic Issues

Not applicable.

4.7. Consumer Study Reviews

Not applicable.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Data from two Phase 1, single dose trials in healthy volunteers were submitted in this NDA (Trials FGL-P01 and FGL-P02). The characteristics of these trials are summarized in Table 2.

Table 2 (Reviewer). Listing of Clinical Trials Relevant to this NDA

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Clinical Pharmacology Studies							
FGL-P01 (HND-P5-777)	Single center, randomized, single dose parallel comparative Bioavailability study, comparing fingolimod ODT to fingolimod in healthy fasting adult volunteers	Treatment 1: 1mg fingolimod ODT PO with water in AM Treatment 2: 1mg fingolimod ODT PO without water in AM Treatment 3: 1mg fingolimod with water in AM	PK, safety	Single dose	75	Healthy volunteers	1 site in Canada
FGL-P02 (HND-P1-318)	Single center, randomized, single dose, 2-treatment parallel comparative bioavailability study, comparing fingolimod ODT to fingolimod in healthy fed adult volunteers	1mg fingolimod ODT (test) or 1mg fingolimod (reference) under fed conditions	PK, safety	Single dose	38	Healthy volunteers	1 site in Canada

5.2. Review Strategy

The data from Studies FGL-P01 and FGL-P02 were the primary sources of safety data for this NDA. Please refer to the Clinical Pharmacology Review for evaluation of PK/PD data and assessment for an adequate bridge. This review does not discuss efficacy data for fingolimod ODT because the applicant did not conduct efficacy trials due to the applicant's intention to use the 505(b)(2) pathway to demonstrate pharmacological similarity.

The safety population for Trials FGL-P01 and FGL-P02 was defined as "all subjects who received at least 1 dose of 1 of the IPs."

In the protocol for Trials FGL-P01 and FGL-P02, the applicant defined an adverse event (AE) as "any untoward medical occurrence in a subject administered an IP and which does not necessarily have a causal relationship with the treatment." AE severity was graded as mild, moderate, or severe, according to the definitions in each protocol.

In Trials FGL-P01 and FGL-P02, serious adverse events (SAEs) or reactions were defined as "any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability or incapacity (defined as a substantial disruption of a person's ability to conduct normal life functions),
- Is a congenital anomaly or birth defect,
- Is an important medical event that may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above (according to the medical judgment of an investigator).

In Trials FGL-P01 and FGL-P02, the applicant defined treatment-emergent adverse events (TEAEs) as AEs "occurring after initiation of study drug."

For Trials FGL-P01 and FGL-P02, the ADAE dataset included verbatim terms by the investigators (AETERM) and preferred terms (AEDECOD) to which these verbatim terms were coded under the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0. Events were coded by their primary System Organ Class (AESOC in ADAE).

Trials FGL-P01 and FGL-P02 included assessments of AEs, SAEs, vital signs, electrocardiograms (ECGs), laboratory parameters, and a palatability questionnaire, which were reviewed.

5.3. Discussion of Individual Studies

5.3.1. Trial FGL-P01 (HND-P5-777)

Study Title

Single Dose Parallel Comparative Bioavailability Study of Fingolimod 0.5mg Orally Disintegrating Tablets versus Fingolimod 0.5mg Capsules Following the Administration of a 1mg Dose in Healthy Adult Subjects Under Fasting Conditions.

Study Center

The clinical research unit was Altasciences, located at 1200 Beaumont Ave, Mount-Royal, Quebec, Canada H3P 3P1.

Study Objective

The primary objectives of this study were to compare the bioavailability between a new orally disintegrating tablet (ODT) formulation (Test, administered without water) of fingolimod and the Reference Gilenya® capsule and to compare the bioavailability between the Test administered with and without water after a single oral dose administration under fasting conditions.

The secondary objective of this study was to evaluate the safety and tolerability of the Test and Reference formulations in healthy subjects.

Methodology

This study was a single-center, randomized, single-period, 3-treatment arm, parallel design trial intended to evaluate the relative bioavailability of fingolimod ODT and fingolimod capsules after a single oral dose, under fasting conditions (10 hours). Healthy volunteers were randomized to receive either fingolimod ODT with water (Test), fingolimod ODT without water (Test), or fingolimod capsule (Reference) with water. Seventy-five subjects were randomized to one of these 3 treatment assignments, which are described in further detail later in this section.

Subjects were confined to the clinical site for at least 11 hours prior to drug administration and for 48 hours following drug administration. The total study duration was up to 35 days, including screening. Study assessments include pharmacokinetic blood sampling, safety laboratory monitoring (hematology and chemistry), vital sign monitoring, continuous cardiac monitoring (30 minutes prior to administration to 7 hours post-dose), and 12-lead ECG (at baseline, 6 hours, and 24 hours post-dose). Subjects in the Treatment-2 group (fingolimod ODT

without water) also completed a product evaluation questionnaire related to palatability, and underwent oral cavity examination.

Number of Subjects

Seventy-five subjects were planned for inclusion in the study, and all 75 were enrolled and completed the study.

Diagnosis and Main Criteria for Inclusion

Subjects were healthy adult male or females between the ages of 18 and 55 years, with a body mass index (BMI) between 18.5 and 30 kg/m^2. Females could not be of childbearing potential, and were either physiologically postmenopausal, surgically postmenopausal (bilateral oophorectomy), or status-post hysterectomy. All patients were non- or former smokers. Patients could not have any clinically significant disease, physical examination (including vital sign) abnormalities, or ECG abnormalities. Subjects were also required to have a positive screening for varicella zoster antibody.

Relevant exclusion criteria included pregnancy, tongue piercings, braces, partials, dentures, seated heart rate <60 or >100 bpm, seated blood pressure <105/60 mmHg, any prescription drug use, and known conditions that could interfere with drug absorption, distribution or metabolism. Additionally, subjects with any significant cardiovascular, pulmonary, hematologic, immunologic, or neoplastic conditions were excluded.

Demographics

Subject demographic characteristics are presented in Table 3, and other pertinent clinical characteristics are presented in Table 4.

Table 3 (Reviewer). Demographics, Trial FGL-P01

	Treatment Group			
	Treatment-1 [Fingolimod ODT, with water] (N=25) n (%)	Treatment-2 [Fingolimod ODT, without water] (N=25) n (%)	Treatment-3 [Fingolimod, with water] (N=25) n (%)	Total (N=75) n (%)
Sex				
Male	24 (96.0)	24 (96.0)	24 (96.0)	72 (96.0)
Female	1 (4.0)	1 (4.0)	1 (4.0)	3 (4.0)
Age				
Mean, (SD) (years)	37.1 (9.3)	37.6 (9.3)	40.9 (11.4)	38.5 (10.1)
Median (IQR) (years)	36 (15.5)	36 (15)	40 (19.5)	37 (17)
Min, max (years)	23, 53	23, 55	18, 55	18, 55
Age Group				
< 18 years	0 (0)	0 (0)	0 (0)	0 (0)
≥ 18 - < 30 years	6 (24.0)	6 (24.0)	5 (20.0)	17 (22.7)
≥ 30 - < 45 years	13 (52.0)	13 (52.0)	9 (36.0)	35 (46.7)
≥ 45 - < 75 years	6 (24.0)	6 (24.0)	11 (44.0)	23 (30.7)
≥ 75 years	0 (0)	0 (0)	0 (0)	0 (0)
Race				
White	21 (84.0)	22 (88.0)	21 (84.0)	64 (85.3)
Black or African American	2 (8.0)	1 (4.0)	1 (4.0)	4 (5.4)
Asian	1 (4.0)	1 (4.0)	1 (4.0)	3 (4.0)
American Indian or Alaska Native	0 (0)	0 (0)	1 (4.0)	1 (1.3)
Native Hawaiian or Other Pacific Islander	0 (0)	0 (0)	0 (0)	0 (0)
Other	1 (4.0)	1 (4.0)	1 (4.0)	3 (4.0)
Ethnicity				
Hispanic or Latino	8 (32.0)	9 (36.0)	5 (20.0)	22 (29.3)
Not Hispanic or Latino	17 (68.0)	16 (64.0)	20 (80.0)	53 (70.7)
Region				
United States	0 (0)	0 (0)	0 (0)	0 (0)
Rest of the World	25 (100)	25 (100)	25 (100)	75 (100)
Canada	25 (100)	25 (100)	25 (100)	75 (100)
South America	0 (0)	0 (0)	0 (0)	0 (0)
Europe	0 (0)	0 (0)	0 (0)	0 (0)
Asia	0 (0)	0 (0)	0 (0)	0 (0)
Africa	0 (0)	0 (0)	0 (0)	0 (0)

Table 4 (Reviewer). Other Clinical Characteristics, Trial FGL-P01

	Treatment Group			
	Treatment-1 [Fingolimod ODT, with water] (N=25)	Treatment-2 [Fingolimod ODT, without water] (N=25)	Treatment-3 [Fingolimod, with water] (N=25)	Total (N=75)
Height				
Mean (SD) (cm)	175.5 (8.4)	176.1 (7.9)	173.5 (5.9)	175.0 (7.5)
Median (IQR) (cm)	176.2 (11.4)	176.2 (9.5)	173.6 (5.7)	175.9 (8.7)
Min, max (cm)	160.4, 198	154.1, 190.1	159.2, 187	154.1, 198
Weight				
Mean (SD) (kg)	78.8 (10.4)	80.1 (7.9)	77.3 (9.8)	78.7 (9.4)
Median (IQR) (kg)	76.2 (8.0)	79.8 (7.0)	77.7 (16.6)	77.9 (10.2)
Min, max (kg)	60.6, 110.8	63.8, 100.6	62.8, 102.2	60.6, 110.8
BMI				
Mean (SD) (kg/m^2)	25.6 (2.6)	25.8 (2.1)	25.6 (2.5)	25.7 (2.4)
Median (IQR) (kg/m^2)	26.2 (4.4)	25.6 (2.4)	25.9 (4.0)	25.9 (3.4)
Min, max (kg/m^2)	19.5, 28.7	21.1, 29.9	20.3, 29.5	19.5, 29.9

Study Treatments

The applicant designated 3 treatment groups for this study:

Treatment-1 (Test): A single 1 mg dose of fingolimod ODT (Test product) (2 × 0.5 mg ODT) will be orally administered with 240 mL of water in the morning under fasting conditions. The tablets will be swallowed whole.

Treatment-2 (Test): A single 1 mg dose of fingolimod ODT (Test product) (2 × 0.5 mg ODT) will be orally administered without water in the morning under fasting conditions. These subjects will be given 20mL to wet their mouth and swallow, then a stainless steel spatula will be used to transfer the ODT to the subject's tongue. The subject will let the tablet completely dissolve, then swallow saliva.

Treatment-3 (Reference): A single 1 mg dose of fingolimod capsule (Reference product) (2 × 0.5 mg hard capsules) will be orally administered with 240 mL of water in the morning under fasting conditions.

Duration of Treatment

This study involved single doses of either fingolimod or fingolimod ODT. Subjects were confined to the clinical site for at least 11 hours prior to drug administration and for 48 hours following drug administration. The total study duration was up to 35 days, including screening.

Reference Product Dose, Duration, Mode of Administration, and Batch Number

The reference product was Gilenya (fingolimod) 0.5mg hard capsules, administered orally at a dose of 1mg (2 x 0.5mg hard capsules). The manufacturer was Novartis, and the batch number was AANA250.

Criteria for Evaluation

Pharmacokinetics

The primary study endpoints were the PK parameters C_{max} and AUC_{0-144} of fingolimod and fingolimod phosphate.

Safety

Safety was evaluated via assessment of adverse events, laboratory parameters, vital signs, 12-lead ECG, oral cavity examination, and physical examination.

Statistical Methods

The applicant indicated that comparison of C_{max} and AUC_{0-144} will be based on an analysis of variance (ANOVA) model, and that two-sided 90% confidence interval (CI) of the ratio of geometric least-square means will be obtained from the ln-transformed PK parameters. Additionally, statistical interference of fingolimod and fingolimod-phosphate will be based on comparative bioavailability results.

Safety data were summarized via descriptive statistics.

Results

Pharmacokinetic Results

The applicant stated that the results of FGL-P01 indicate bioequivalence of fingolimod ODT and Gilenya. Per the applicant's Clinical Study Report:

"For Treatment-1 *vs* Treatment-2 comparison, the results presented herein show that the criteria used to assess bioequivalence between the Test formulations taken with and without water were all fulfilled. The Treatment-1 to Treatment-2 ratio of geometric LSmeans and corresponding 90% CI for Cmax and AUC0-144 for fingolimod and fingolimod phosphate were all within the acceptance range of 80.00 to 125.00%."

"For Treatment-2 *vs* Treatment-3 comparison, the results presented herein show that the criteria used to assess bioequivalence between the Test (without water) and Reference formulations were all fulfilled for fingolimod. The Treatment-2 to Treatment-3 ratio of geometric LSmeans and corresponding 90% CI for Cmax and AUC0-144 for fingolimod were all within the acceptance range of 80.00 to 125.00%. For fingolimod phosphate, the Treatment-2 to Treatment-3 ratio of geometric LSmeans and corresponding 90% CI for Cmax and AUC0-144 were all within the acceptance range of 80.00 to 125.00%, with the exception of the lower bound of 90% CI of Cmax, which was just below the 80.00% limit."

Please refer to the Clinical Pharmacology Review for further analysis and discussion of these results.

Safety Results

No deaths, SAEs, or adverse events leading to study discontinuation occurred in Trial FGL-P01.

A total of 30 unique TEAEs occurred in 20 unique patients (26.7%). Of these 30 TEAEs, 10 occurred in the Treatment-1 group (10/25, 40.0%), 10 in Treatment-2 (10/25, 40.0%), and 10 in Treatment-3 (10/25, 40.0%). TEAEs are presented in Table 5. The outcome of all TEAEs was Recovered/Resolved.

All TEAEs were mild except for 4 moderate events: atrioventricular block second degree (n = 1, fingolimod ODT), dizziness (n = 1, fingolimod ODT), pain in extremity (n = 1, fingolimod), and headache (n = 1, fingolimod).

Table 5 (Reviewer). Treatment-Emergent Adverse Events (All), Trial FGL-P01

	Treatment-1 [Fingolimod ODT, with water] (N=25) n (%)	Treatment-2 [Fingolimod ODT, without water] (N=25) n (%)	Treatment-3 [Fingolimod, with water] (N=25) n (%)
Any adverse event	10 (40.0)	10 (40.0)	10 (40.0)
Cardiac disorders	4 (16.0)	2 (8.0)	3 (12.0)
Atrioventricular block first degree	3 (12.0)	2 (8.0)	1 (4.0)
Atrioventricular block second degree	1 (4.0)	2 (8.0)	2 (8.0)
Bradycardia	0 (0)	1 (4.0)	0 (0)
Nodal arrhythmia	2 (8.0)	0 (0)	0 (0)
Gastrointestinal disorders	0 (0)	0 (0)	1 (4.0)
Nausea	0 (0)	0 (0)	1 (4.0)
General disorders and administration site conditions	1 (4.0)	1 (4.0)	0 (0)
Chest discomfort	1 (4.0)	0 (0)	0 (0)
Vessel puncture site bruise	0 (0)	1 (4.0)	0 (0)
Injury, poisoning and procedural complications	0 (0)	0 (0)	1 (4.0)
Procedural dizziness	0 (0)	0 (0)	1 (4.0)
Musculoskeletal and connective tissue disorders	0 (0)	0 (0)	1 (4.0)
Pain in extremity	0 (0)	0 (0)	1 (4.0)
Nervous system disorders	2 (8.0)	3 (12.0)	3 (12.0)
Dizziness	1 (4.0)	2 (8.0)	0 (0)
Headache	1 (4.0)	1 (4.0)	2 (8.0)
Somnolence	0 (0)	0 (0)	2 (8.0)
Psychiatric disorders	0 (0)	1 (4.0)	0 (0)
Anxiety	0 (0)	1 (4.0)	0 (0)
Respiratory, thoracic and mediastinal disorders	1 (4.0)	0 (0)	0 (0)
Throat irritation	1 (4.0)	0 (0)	0 (0)

Source: OCS Analysis Studio, Safety Explorer; Filters: TRT01A = "Treatment-1" and SAFFL = "Y" (Treatment-1); TRT01A = "Treatment-2" and SAFFL = "Y" (Treatment-2); TRT01A = "Treatment-3" and SAFFL = "Y" (Treatment-3); TRTEMFL = "Y" (Adverse Events).

Please refer to Section 8 for a discussion of these safety findings, laboratory data, vital signs, and cardiac parameters.

5.3.2. Trial FGL-P02 (HND-P1-318)

Study 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

Study Center

The clinical research unit was Altasciences, located at 1200 Beaumont Ave, Mount-Royal, Quebec, Canada H3P 3P1.

Study Objective

The primary objective of this study was to compare the bioavailability between 2 different formulations of fingolimod after a single oral dose administration under fed conditions.

The secondary objective of this study was to evaluate the safety and tolerability of the Test and Reference formulations in healthy subjects.

Methodology

This study was a single-center, randomized, laboratory-blinded, 2-arm parallel trial intended to evaluate the relative bioavailability of a single dose of fingolimod ODT (test) and fingolimod (reference) in healthy volunteers under fed conditions. Forty subjects were randomized to one of these 2 treatment assignments, which are described in further detail later in this section.

Subjects were confined to the clinical site for at least 11 hours prior to drug administration and for 48 hours following drug administration. The total study duration was up to 35 days, including screening. Study assessments include pharmacokinetic blood sampling, safety laboratory monitoring (hematology and chemistry), vital sign monitoring, and 12-lead ECG (at baseline, 6 hours, and 24 hours post-dose). Subjects in the Test group (fingolimod ODT) also completed a product evaluation questionnaire related to palatability.

Number of Subjects

Forty subjects were planned for inclusion in the study, and 38 were enrolled and completed the study. In the Clinical Study Report, the applicant cited recruitment challenges as the reason for not meeting the enrollment target of 40. All enrolled subjects completed the study.

Diagnosis and Main Criteria for Inclusion

Subjects were healthy adult male or females between the ages of 18 and 55 years, with a body mass index (BMI) between 18.5 and 30 kg/m^2. Females could not be of childbearing potential, and were either physiologically postmenopausal, surgically postmenopausal (bilateral oophorectomy), or status-post hysterectomy. All patients were non- or former smokers. Patients could not have any clinically significant disease, physical examination (including vital sign) abnormalities, or ECG abnormalities. Subjects were also required to have a positive screening for varicella zoster antibody.

Relevant exclusion criteria included pregnancy, tongue piercings, braces, partials, dentures, seated heart rate <60 or >100 bpm, seated blood pressure <105/60 mmHg, any prescription drug use, and known conditions that could interfere with drug absorption, distribution or metabolism. Additionally, subjects with any significant cardiovascular, pulmonary, hematologic, immunologic, or neoplastic conditions were excluded.

Demographics

Subject demographic characteristics are presented in Table 6, and other pertinent clinical characteristics are presented in Table 7.

Table 6 (Reviewer). Demographics, Study FGL-P02

	Treatment Group		
	Treatment-1 [Fingolimod ODT] (N=19) n (%)	Treatment-2 [Fingolimod] (N=19) n (%)	Total (N=38) n (%)
Sex			
Male	18 (94.7)	18 (94.7)	36 (94.7)
Female	1 (5.3)	1 (5.3)	2 (5.3)
Age			
Mean, (SD) (years)	40.6 (8.7)	38.7 (10.8)	39.6 (9.7)
Median (IQR) (years)	41.0 (15.0)	38.0 (21.0)	38.5 (16.8)
Min, max (years)	27, 55	24, 55	24, 55
Age Group			
< 18 years	0 (0)	0 (0)	0 (0)
≥ 18 - < 30 years	2 (10.5)	5 (26.3)	7 (18.4)
≥ 30 - < 45 years	10 (52.6)	8 (42.1)	18 (47.4)
≥ 45 - < 75 years	7 (36.8)	6 (31.6)	34.2 (13)
≥ 75 years	0 (0)	0 (0)	0 (0)
Race			
White	15 (78.9)	16 (84.2)	31 (81.6)
Black or African American	3 (15.8)	2 (10.5)	5 (13.2)
Asian	1 (5.3)	1 (5.3)	2 (5.3)
American Indian or Alaska Native	0 (0)	0 (0)	0 (0)
Native Hawaiian or Other Pacific Islander	0 (0)	0 (0)	0 (0)
Other	0 (0)	0 (0)	0 (0)
Ethnicity			
Hispanic or Latino	6 (31.6)	6 (31.6)	12 (31.6)
Not Hispanic or Latino	13 (68.4)	13 (68.4)	26 (68.4)
Region			
United States	0 (0)	0 (0)	0 (0)
Rest of the World			
Canada	19 (100)	19 (100)	38 (100)
South America	0 (0)	0 (0)	0 (0)
Europe	0 (0)	0 (0)	0 (0)
Asia	0 (0)	0 (0)	0 (0)
Africa	0 (0)	0 (0)	0 (0)

Table 7 (Reviewer). Other Clinical Characteristics, Study FGL-P02

	Treatment Group		
	Treatment-1 [Fingolimod ODT] (N=19) n (%)	Treatment-2 [Fingolimod] (N=19) n (%)	Total (N=38) n (%)
Height			
Mean (SD) (cm)	174.4 (6.9)	173.3 (5.7)	173.9 (6.2)
Median (IQR) (cm)	175.8 (10.6)	173.8 (3.1)	174.1 (7.1)
Min, max (cm)	162.7, 187.8	160.2, 185.1	160.2, 187.8
Weight			
Mean (SD) (kg)	77.9 (8.7)	78.5 (9.4)	78.2 (8.9)
Median (IQR) (kg)	80.3 (15.4)	77.0 (15.2)	78.9 (13.6)
Min, max (kg)	60.6, 89.9	60.7, 93.7	60.6, 93.7
BMI			
Mean (SD) (kg/m^2)	25.6 (2.3)	26.1 (2.3)	25.8 (2.3)
Median (IQR) (kg/m^2)	26.0 (2.5)	26.0 (4.2)	26.0 (3.3)
Min, max (kg/m^2)	20.3, 29.6	21.8, 29.8	20.3, 29.8

Study Treatments

Subjects were randomized to receive a single dose of fingolimod ODT (Test) or fingolimod (Reference).

For fingolimod ODT (Test), subjects received a single 1mg dose (2 x 0.5mg) in the morning after a 10-hour overnight fast and 30 minutes after a high-fat, high-calorie breakfast. These subjects were given 20mL to wet their mouth and swallow, then a stainless steel spatula was used to transfer the ODT to the subject's tongue. The subject let the tablet completely dissolve, then swallowed saliva.

For fingolimod (Reference), subjects received a single 1mg dose (2 x 0.5mg) with 240mL of water in the morning after a 10-hour overnight fast and 30 minutes after a high-fat, high-calorie breakfast.

Duration of Treatment

This study involved single doses of either fingolimod or fingolimod ODT. Subjects were confined to the clinical site for at least 11 hours prior to drug administration and for 48 hours following drug administration. The total study duration was up to 35 days, including screening.

Reference Product Dose, Duration, Mode of Administration, and Batch Number

The reference product was Gilenya (fingolimod) 0.5mg hard capsules, administered orally at a dose of 1mg (2 x 0.5mg hard capsules). The manufacturer was Novartis, and the batch number was AANA250.

Criteria for Evaluation

Pharmacokinetics

The primary study endpoints were the PK parameters C_{max} and AUC_{0-144} of fingolimod and fingolimod phosphate.

Safety

Safety was evaluated via assessment of adverse events, laboratory parameters, vital signs, 12-lead ECG, oral cavity examination, and physical examination.

Statistical Methods

The applicant indicated that comparison of C_{max} and AUC_{0-144} will be based on an analysis of variance (ANOVA) model, and that two-sided 90% confidence interval (CI) of the ratio of geometric least-square means will be obtained from the ln-transformed PK parameters. Additionally, statistical interference of fingolimod and fingolimod-phosphate will be based on comparative bioavailability results.

Safety data were summarized via descriptive statistics.

Results

Pharmacokinetic Results

The applicant stated that the results of FGL-P02 indicate bioequivalence of fingolimod ODT and Gilenya. Per the applicant's Clinical Study Report:

"The results presented herein show that the criteria used to assess bioequivalence between the Test and Reference formulations were all fulfilled. The Test to Reference ratio of geometric LSmeans and corresponding 90% CI for Cmax and AUC0-144 for fingolimod and fingolimod phosphate were all within the acceptance range of 80.00 to 125.00%."

Please refer to the Clinical Pharmacology Review for further analysis and discussion of these results.

Safety Results

No deaths, SAEs, or adverse events leading to dropouts occurred in Study FGL-P02.

A total of 17 unique TEAEs occurred in 11 unique patients (28.9%). Of these 17 TEAEs, 8 occurred in the fingolimod ODT group (8/18, 44.4%), and 9 in the fingolimod reference group (9/18, 50.0%). TEAEs are presented in Table 8. The outcome of all TEAEs was Recovered/Resolved.

All TEAEs were mild except for 2 moderate events: musculoskeletal pain (n = 1, fingolimod ODT) and headache (n = 1, fingolimod ODT).

Table 8 (Reviewer). Treatment Emergent Adverse Events (All), Study FGL-P02

	Treatment-1 [Fingolimod ODT] (N=19) n (%)	Treatment-2 [Fingolimod] (N=19) n (%)
Any adverse event	5 (26.3)	6 (31.6)
Cardiac disorders	1 (5.3)	0 (0)
Atrioventricular block first degree	1 (5.3)	0 (0)
Atrioventricular block second degree	1 (5.3)	0 (0)
Ear and labyrinth disorders	1 (5.3)	0 (0)
Tinnitus	1 (5.3)	0 (0)
Gastrointestinal disorders	1 (5.3)	1 (5.3)
Abdominal distension	1 (5.3)	0 (0)
Duodenogastric reflux	1 (5.3)	0 (0)
Tongue discolouration	0 (0)	1 (5.3)
General disorders and administration site conditions	1 (5.3)	0 (0)
Chills	1 (5.3)	0 (0)
Infections and infestations	0 (0)	1 (5.3)
Oral herpes	0 (0)	1 (5.3)
Musculoskeletal and connective tissue disorders	1 (5.3)	2 (10.5)
Back pain	0 (0)	2 (10.5)
Musculoskeletal pain	1 (5.3)	0 (0)
Nervous system disorders	1 (5.3)	3 (15.8)
Dizziness	0 (0)	2 (10.5)
Headache	1 (5.3)	1 (5.3)
Somnolence	0 (0)	1 (5.3)
Skin and subcutaneous tissue disorders	0 (0)	1 (5.3)
Hyperhidrosis	0 (0)	1 (5.3)

Source: OCS Analysis Studio, Safety Explorer; Filters: TRT01A = "Reference" and SAFFL = "Y" (Reference); TRT01A = "Test" and SAFFL = "Y" (Test); TRTEMFL = "Y" (Adverse Events).

Please refer to Section 8 for a discussion of these safety findings, laboratory data, vital signs, and cardiac parameters.

6. Review of Relevant Individual Trials Used to Support Efficacy

This NDA was submitted via the 505(b)(2) regulatory pathway; therefore, the applicant did not conduct any studies intended to demonstrate substantial evidence of efficacy.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

As noted previously in this review, this NDA is a 505(b)(2) application in which data from 2 clinical pharmacology studies were submitted to demonstrate a PK/PD bridge. This NDA therefore relies on efficacy findings for the RLD, Gilenya (fingolimod). The applicant did not conduct any studies intended to demonstrate efficacy and did not collect efficacy data in the clinical pharmacology studies submitted in support of this application.

7.1.1. Primary Endpoints

Not applicable.

7.1.2. Secondary and Other Endpoints

Not applicable.

7.1.3. Subpopulations

Not applicable.

7.1.4. Dose and Dose-Response

Not applicable.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

Not applicable.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

The efficacy of fingolimod ODT is predicted to be equivalent to that of the listed drug, fingolimod (Gilenya).

7.2.2. Other Relevant Benefits

Not applicable.

7.3. Integrated Assessment of Effectiveness

The efficacy of fingolimod ODT is predicted to be equivalent to that of the reference listed drug,

fingolimod (Gilenya), pending demonstration of bioequivalence.

8. Review of Safety

8.1. Safety Review Approach

Please refer to Section 5.2 for discussion of safety review approach, which encompasses data from two Phase 1 studies that are discussed in Section 5.3. Additionally, this NDA utilizes the 505(b)(2) pathway and therefore relies on the reference listed product (Gilenya) to partially inform the safety of fingolimod ODT, assuming demonstration of bioequivalence.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Overall, 69 healthy volunteers were exposed to a single dose of fingolimod ODT across Studies FGL-P01 and FGL-P02. No patients or healthy volunteers have been exposed to multiple doses of fingolimod ODT.

If bioequivalence is demonstrated, data regarding chronic exposure to fingolimod ODT is not required because this 505(b)(2) application relies on the extensive safety database from clinical trials and postmarketing experience of the RLD, Gilenya. The safety profile of Gilenya has been well-characterized in both pre-marketing trials as well as in postmarketing experience.

8.2.2. Relevant characteristics of the safety population:

Please refer to Section 5.3 for demographic and relevant clinical characteristics of the safety population (Table 3, Table 4, Table 6, Table 7).

8.2.3. Adequacy of the safety database:

The adequacy of the safety database for fingolimod ODT is not pertinent because this application relies on the extensive safety database from clinical trials and postmarketing experience of the RLD, Gilenya. The safety profile of Gilenya is established and well-characterized.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

There are no apparent issues regarding data integrity and submission quality. The application is of sufficient quality to permit review.

The applicant reported minor protocol deviations for both studies. One major protocol deviation was reported in Study FGL-P01, where a pre-dose ECG was not performed for 1 subject (ID (b) (6)). This lapse did not lead to a cardiac adverse event.

In Study FGL-P01, 10 blood sampling time deviations occurred across 5 timepoints. Deviations ranged from 3 to 8 minutes. Twenty-two other minor deviations included dosing administration procedure not followed (n = 15), hematology test not done (n = 3), water restriction not followed (n = 1), blood sampling not done (n = 1), cardiac monitoring not performed as scheduled (n = 1), and medication restriction not followed (n = 1). These deviations were most commonly related to swallowing saliva >30 seconds after ODT was placed on the tongue.

In Study FGL-P02, 17 blood sampling time deviations occurred across 6 timepoints (majority at 1.00 hour post-dose). Deviations ranged from 3 to 26 minutes. Twelve other minor deviations included dosing administration procedure not followed (n = 8), IP administration procedure not followed (n = 2), medication restriction not followed (n = 1), and housing requirement not followed (n =1). These deviations were most commonly related to receiving IMP >1 minute after the designated time or swallowing saliva >30 seconds after ODT was placed on the tongue.

The applicant submitted an Investigation Report entitled "Determination of in vivo Disintegration Endpoint for Fingolimod Orally Disintegrating Tablets in Studies HND-P5-777 and HND-P1-318," in which the reported disintegration time-related protocol deviations were investigated. Specifically, all 5 subjects in one Group receiving fingolimod ODT without water in Study HND-P5-777 had disintegration times of >30 seconds. The applicant was concerned that the ODTs were not dissolving as intended. The applicant reported that drug administrators at Altasciences should have instructed patients to swallow at 30 seconds "regardless of [the] evaluated composition at that time." The applicant identified confusion among the drug administrators regarding the terms "disintegrate" versus "dissolve;" some drug administrators were waiting for the ODTs to completely dissolve/disappear until recording the time to swallowing.

> *Reviewer comment: Based on the description of these minor protocol deviations, it does not appear that the integrity of the study was significantly compromised. These deviations did not appear to impact safety reporting to an extent that requires further comment. However, this reviewer defers to Clinical Pharmacology for evaluation of the potential effects of these deviations on interpretation of the final study results.*

8.3.2. Categorization of Adverse Events

Please refer to Section 5.2 for definitions of adverse events (including TEAEs and SAEs) and severity.

8.3.3. Routine Clinical Tests

Clinical testing during Studies FGL-P01 and FGL-P02 included vital signs, electrocardiograms (ECGs), and laboratory parameters. The schedule of activities for Studies FGL-P01 and FGL-P02 are reproduced in Figure 1 and Figure 2, respectively.

Continuous cardiac monitoring occurred in Study FGL-P01 from at least 30 minutes prior to dosing until at least 7 hours post-dose.

Figure 1 (Applicant). Schedule of Activities, Study FGL-P01

	Screening	Study Period					End of Study
Day	**-28 to -1**	**-1**	**1**	**2**	**3-6**	**7**	**7**
Informed Consent [1]	X						
Eligibility criteria review	X	X	X				
Demographics	X						
Medical History	X						
Admission		X					
Vital signs [2]	X		X	X			X
Physical Examination	X						X
Clinical Laboratory Tests [3]	X			X	X		X
Serology	X						
12-lead ECG [4]	X		X	X			X
Continuous Cardiac Monitoring[5]			X				
Alcohol and Drugs of Abuse Screen	X	X					
Serum Pregnancy Test (females only)	X						
Treatment Administration			X				
Blood sampling for PK [6]			X	X	X	X	
Oral Cavity Examination[7]			X	X			
Formulation Acceptability and Palatability Questionnaire[8]			X				
Discharge [9]					X		
AE monitoring	X	X	X	X	X	X	X[10]

AE: Adverse event; ECG: Electrocardiogram; PK: Pharmacokinetic

[1] The latest version of the consent form must be signed prior to subject's inclusion (prior to study drug administration).

[2] Vital signs at screening and prior to dosing include blood pressure, pulse rate and body temperature. Vital signs measured following dosing and at end of study will include blood pressure and pulse rate. Scheduled time points for vital signs recording during the treatment period are detailed in section 6.1.3.

[3] Clinical laboratory parameters at screening are detailed in section 6.1.4.1. On-study clinical laboratory parameters are detailed in section 6.1.4.2. Clinical laboratory tests will be repeated with or after the collection of the last blood sample of the study; the parameters tested are detailed in section 6.1.4.3.

[4] On-study ECG scheduled time points during the treatment period are detailed in section 6.1.5.

[5] Continuous cardiac monitoring will be done from at least 30 minutes prior to dosing until at least 7 hours postdose.

[5] Blood sampling time points for PK determinations during the treatment period are pre-dose and 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 24, 28, 32, 36, 48, 60, 72, 96, 120, and 144 hours after drug administration as detailed in section 6.4.

Source: HND-P5-777 Protocol, Version 5.0 (6/30/2020)

Figure 2 (Applicant). Schedule of Activities, Study FGL-P02

	Screening	Study Period					End of Study
Day	**-28 to -1**	**-1**	**1**	**2**	**3-6**	**7**	**7**
Informed Consent [1]	X						
Eligibility criteria review	X	X	X				
Demographics	X						
Medical History	X						
Admission		X					
Physical Examination	X						X
Vital signs [2]	X		X	X			X
Clinical Laboratory Tests [3]	X			X	X		X
Serology	X						
12-lead ECG [4]	X		X	X			X
Alcohol and Drugs of Abuse Screen	X	X					
Serum Pregnancy Test (females only)	X						
Treatment Administration			X				
Blood sampling for PK [5]			X	X	X	X	
Formulation Acceptability and Palatability Questionnaire[6]			X				
Discharge [7]					X		
AE monitoring	X	X	X	X	X	X	X[8]

AE: Adverse event; ECG: Electrocardiogram; PK: Pharmacokinetic

[1] The latest version of the consent form must be signed prior to subject's inclusion (prior to study drug administration).

[2] Vital signs at screening and prior to dosing include blood pressure, pulse rate and body temperature. Vital signs measured following dosing and at end of study will include blood pressure and pulse rate. Scheduled time points for vital signs recording during the treatment period are detailed in section 6.1.3.

[3] Clinical laboratory parameters at screening are detailed in section 6.1.4.1. On-study clinical laboratory parameters are detailed in section 6.1.4.2. Clinical laboratory tests will be repeated with or after the collection of the last blood sample of the study; the parameters tested are detailed in section 6.1.4.3.

[4] On-study ECG scheduled time points are detailed in section 6.1.5.

[5] Blood sampling time points for PK determinations during the treatment period are pre-dose and 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 24, 28, 32, 36, 48, 60, 72, 96, 120, and 144 hours after drug administration as detailed in section 6.4.

Source: HND-P1-318 Protocol, Version 3.0 (6/3/2020)

8.4. Safety Results

8.4.1. Deaths

No deaths occurred in either Study FGL-P01 or FGL-P02.

8.4.2. Serious Adverse Events

No serious adverse events occurred in either Study FGL-P01 or FGL-P02.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

No dropouts or discontinuations due to adverse events occurred in either Study FGL-P01 or FGL-P02.

8.4.4. Significant Adverse Events

No significant adverse events occurred in Studies FGL-P01 or FGL-P02. Please refer to Sections 5.3 and 8.4.5 for discussion of TEAEs.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Please refer to Section 5.3 for tabulation of TEAEs that occurred in Studies FGL-P01 and FGL-P02. A summary tabulation of all TEAEs for both Studies FGL-P01 and FGL-P02 is provided in Table 9.

Table 9 (Reviewer). All Adverse Events, Studies FGL-P01 and FGL-P02

Adverse Event (Preferred Term)	Fingolimod ODT 1mg (n = 69)	Fingolimod (Gilenya) 1mg (n = 44)
Atrioventricular Block 1st degree	6 (8.7)[1]	1 (2.3)
Atrioventricular Block 2nd degree	4 (5.8)	2 (4.5)
Headache	3 (4.3)	3 (6.8)
Dizziness	3 (4.3)	2 (4.5)
Somnolence	0 (0)	3 (6.8)
Back pain	0 (0)	2 (4.5)
Nodal arrhythmia	2 (2.9)	0 (0)
Abdominal distension	1 (1.4)	0 (0)
Anxiety	1 (1.4)	0 (0)
Bradycardia	1 (1.4)	0 (0)
Chest discomfort	1 (1.4)	0 (0)
Chills	1 (1.4)	0 (0)
Duodenogastric reflux	1 (1.4)	0 (0)
Hyperhydrosis	0 (0)	1 (2.3)
Musculoskeletal pain	1 (1.4)	0 (0)
Nausea	0 (0)	1 (2.3)
Oral herpes	0 (0)	1 (2.3)
Pain in extremity	0 (0)	1 (2.3)
Procedural dizziness	0 (0)	1 (2.3)
Throat irritation	1 (1.4)	0 (0)
Tinnitus	1 (1.4)	0 (0)
Tongue discolouration	0 (0)	1 (2.3)
Vessel puncture site bruise	1 (1.4)	0 (0)

[1]Presented as n (%)

Reviewer comment: Overall, TEAEs were infrequent, generally mild, and not unexpected across both studies. The most commonly reported TEAEs were in the Cardiac Disorders and Nervous System Disorders System Organ Classes, and the frequency was similar

between fingolimod ODT and fingolimod. Cardiac TEAEs are expected with fingolimod, and are described in current fingolimod (Gilenya) labeling (Warnings and Precautions). Additionally, the potential adverse reactions of headache, dizziness, and back pain are described in current fingolimod (Gilenya) labeling. Somnolence occurred in 3 patients who received fingolimod (Gilenya), but is not addressed independently of cardiac- or liver-related events in current labeling.

8.4.6. Laboratory Findings

Laboratory safety monitoring for Studies FGL-P01 and FGL-P02 included complete blood count with differential, complete metabolic panel, and urinalysis. No clinical laboratory-related TEAEs were reported in either Study FGL-P01 or FGL-P02.

Given the known safety profile of fingolimod, this reviewer evaluated changes in white blood cell count (WBC), absolute lymphocyte count (ALC), absolute neutrophil count (ANC), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin (TB) following single doses of fingolimod ODT in Studies FGL-P01 and FGL-P02.

White blood cell count

In Study FGL-P01, white blood cell count was measured at screening, Days 2, 3, 4, 5, 6, and end of study (Day 7). All groups experienced a similar reduction in WBC count, which appeared to be most pronounced at Day 2 (Table 10; Figure 3; Figure 4).

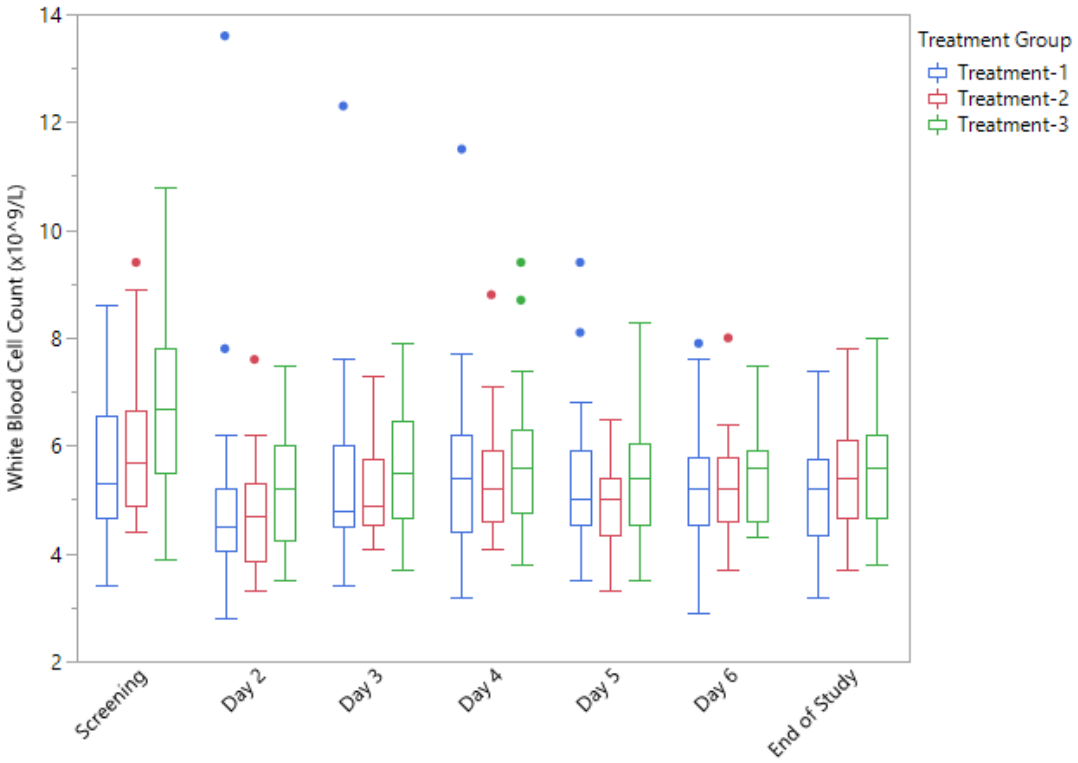
Two subjects (IDs (b) (6)), both of whom were in Treatment-1 group (fingolimod ODT with water), experienced WBC < 3.0 during the study, both on Day 2. One subject (ID (b) (6)) had WBC of 3.4 $x10^9$/L at screening, which is considered low. This subject experienced a nadir WBC of 2.8 $x10^9$/L on Day 2, peak WBC of 3.7 $x10^9$/L on Days 3 and 5, then 3.2 $x10^9$/L at end of study. The other subject (ID (b) (6)) had WBC of 4.2 $x10^9$/L at screening, experienced a nadir WBC of 2.9 $x10^9$/L on Day 2, improvement to WBC 3.7 $x10^9$/L on Day 3, and 3.6 $x10^9$/L at end of study.

Table 10 (Reviewer). White blood cell count ($x10^9$/L) by Treatment Group, Study FGL-P01

Time	Parameter	Treatment-1 [Fingolimod ODT, with water] (N=25)	Treatment-2 [Fingolimod ODT, without water] (N=25)	Treatment-3 [Fingolimod, with water] (N=25)
Screening	Mean (SD)	5.6 (1.4)	6.0 (1.3)	6.7 (1.6)
	Median (IQR)	5.3 (1.6)	5.7 (1.7)	6.7 (202)
	Min, Max	3.4, 8.6	4.4, 9.4	3.9, 10.8
Day 2	Mean (SD)	5.0 (2.1)	4.7 (1.0)	5.1 (1.1)
	Median (IQR)	4.5 (1.0)	4.7 (1.4)	5.2 (1.5)
	Min, Max	2.8, 13.6	3.3, 7.6	3.5, 7.5
	Mean (SD) change from baseline	-0.6 (1.6)	-1.3 (1.1)	-1.5 (1.0)
	Median (IQR) change from baseline	-0.9 (1.0)	-1.3 (1.1)	-1.4 (1.5)
	Min, Max change from baseline	-3.5, 5.4	-4.6, 0.8	-3.3, 0.1
Day 3	Mean (SD)	5.4 (1.8)	5.2 (0.9)	5.6 (1.1)
	Median (IQR)	4.8 (1.5)	4.9 (1.1)	5.5 (1.7)
	Min, Max	3.4, 12.3	4.1, 7.3	3.7, 7.9
	Mean (SD) change from baseline	-0.3 (1.3)	-0.8 (1.2)	-1.1 (1.1)
	Median (IQR) change from baseline	-0.6 (1.1)	-0.6 (1.5)	-0.8(1.6)
	Min, Max change from baseline	-2.6, 4.1	-4.8, 0.7	-3.3, 0.8
End of Study	Mean (SD)	5.2 (1.1)	5.4 (0.9)	5.6 (1.1)
	Median (IQR)	5.2 (1.2)	5.4 (1.2)	5.6 (1.5)
	Min, Max	3.2, 7.4	3.7, 7.8	3.8, 8
	Mean (SD) change from baseline	-0.5 (1.0)	-0.6 (1.2)	-1.1 (1.0)
	Median (IQR) change from baseline	-0.5 (0.9)	-0.3 (0.7)	-1.0 (1.2)
	Min, Max change from baseline	-2.5, 1.5	-4.7, 1.1	-3.3, 0.6

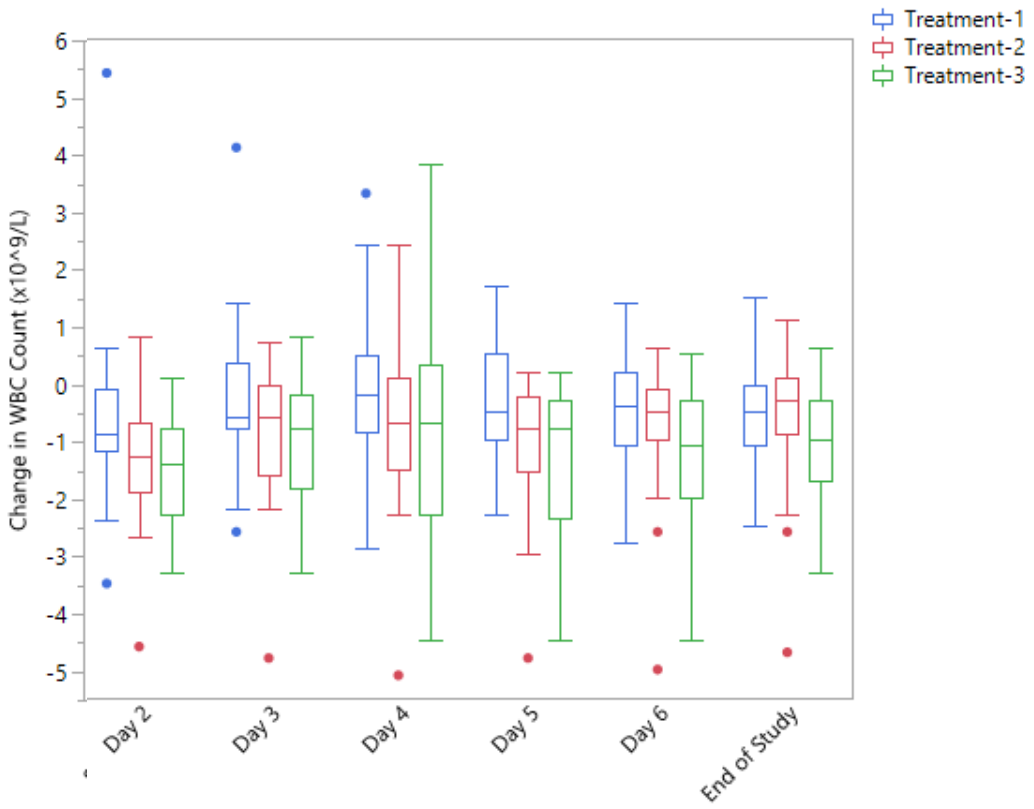
Source: ADLB where ANL01FL=Y, by TRT01A

Figure 3 (Reviewer). White Blood Cell Count (x10^9/L) Over Time by Treatment Group, Study FGL-P01



Treatment-1 = Fingolimod ODT with water; Treatment-2 = Fingolimod ODT without water; Treatment-3 = Fingolimod (reference)

Figure 4 (Reviewer). Change in White Blood Cell Count (x10^9/L) Over Time by Treatment Group, Study FGL-P01



Treatment-1 = Fingolimod ODT with water; Treatment-2 = Fingolimod ODT without water; Treatment-3 = Fingolimod (reference)

In Study FGL-P02, white blood cell count was measured at screening, Days 2, 3, 4, 5, 6, and end of study (Day 7). All groups experienced a reduction in WBC count, which appeared to be most pronounced at Day 2 (Table 11; Figure 5; Figure 6).

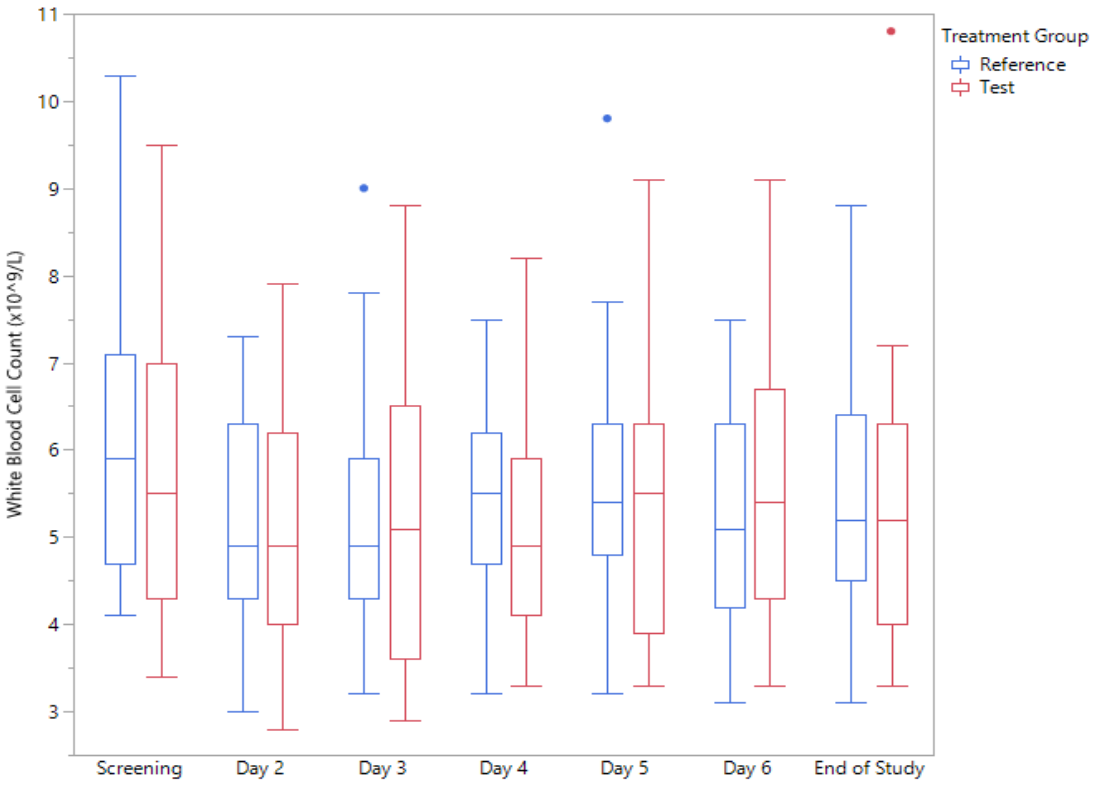
Two subjects (IDs (b) (6)), both of whom were in Test group (fingolimod ODT), experienced single events of WBC < 3.0 x10^9/L during the study, on days 2 and 3, respectively. Subject ID (b) (6) WBC count increased to 3.3 x10^9/L at end of study. Subject ID (b) (6) WBC count increased to 4.0 x10^9/L at end of study.

Table 11 (Reviewer). White blood cell count ($x10^9$/L) by Treatment Group, Study FGL-P02

Time	Parameter	Reference [Fingolimod] (N=19)	Test [Fingolimod ODT] (N=19)
Screening	Mean (SD)	6.2 (1.7)	5.9 (1.8)
	Median (IQR)	5.9 (2.2)	5.5 (2.2)
	Min, Max	4.1, 10.3	3.4, 9.5
Day 2	Mean (SD)	5.0 (1.2)	5.0 (1.4)
	Median (IQR)	4.9 (1.8)	4.9 (1.9)
	Min, Max	3.0, 7.3	2.8, 7.9
	Mean (SD) change from baseline	-1.2 (0.9)	-0.9 (1.1)
	Median (IQR) change from baseline	-1.0 (1.1)	-0.8 (1.4)
	Min, Max change from baseline	-3.5, 0.3	-3.2, 1.2
Day 3	Mean (SD)	5.2 (1.5)	5.2 (1.7)
	Median (IQR)	4.9 (1.6)	5.1 (2.6)
	Min, Max	3.2, 9.0	2.9, 8.8
	Mean (SD) change from baseline	-1.0 (0.8)	-0.7 (1.3)
	Median (IQR) change from baseline	-1.0 (0.9)	-0.4 (1.4)
	Min, Max change from baseline	-2.6, 0.7	-4.7, 0.9
End of Study	Mean (SD)	5.4 (1.3)	5.5 (1.8)
	Median (IQR)	5.2 (1.8)	5.2 (2.3)
	Min, Max	3.1, 8.8	3.3, 10.8
	Mean (SD) change from baseline	-0.8 (1.1)	-0.4 (1.3)
	Median (IQR) change from baseline	-0.9 (1.0)	-0.2 (1.2)
	Min, Max change from baseline	-2.6, 1.7	-3.8, 1.3

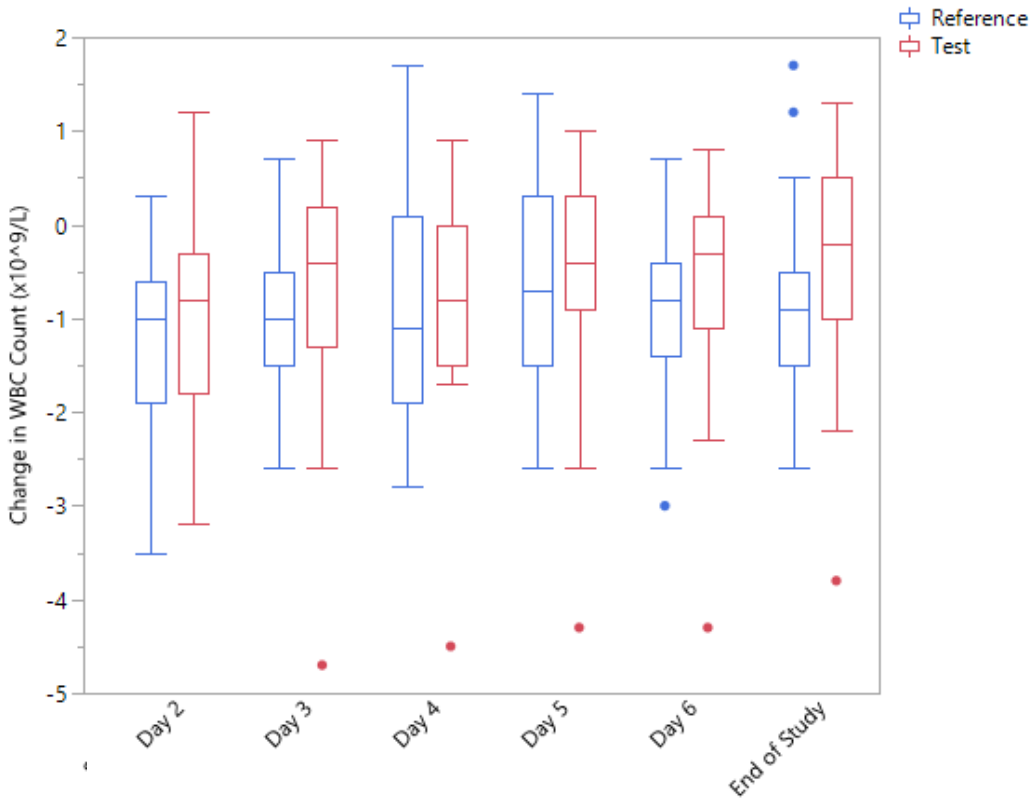
Source: ADLB where ANL01FL=Y, by TRT01A

Figure 5 (Reviewer). White Blood Cell Count (x10^9/L) Over Time by Treatment Group, Study FGL-P02



Reference = Fingolimod; Test = Fingolimod ODT

Figure 6 (Reviewer). Change in White Blood Cell Count (x10^9/L) Over Time by Treatment Group, Study FGL-P02



Reference = Fingolimod; Test = Fingolimod ODT

Reviewer comment: Overall, these WBC count data appear consistent with the known pharmacodynamic effects of fingolimod, and fingolimod ODT appears to have similar effects as fingolimod.

Lymphocyte Count

The mechanism of action of fingolimod is to reduce circulating lymphocytes via preventing egress from lymph nodes. Therefore, a decrease in absolute lymphocyte count is a desired pharmacodynamic effect of fingolimod. This effect has been observed within 4 to 6 hours of the first dose of fingolimod 0.5 mg.

In Study FGL-P01, lymphocyte count was measured at screening, Days 2, 3, 4, 5, 6, and end of study (Day 7). All groups experienced a reduction in WBC count, which appeared to be most pronounced at Day 2 (Table 12; Figure 7; Figure 8). The lowest ALC value recorded was 0.6 x10^9/L, which occurred in 2 subjects (Subjects (b) (6)) who received fingolimod (Treatment-3).

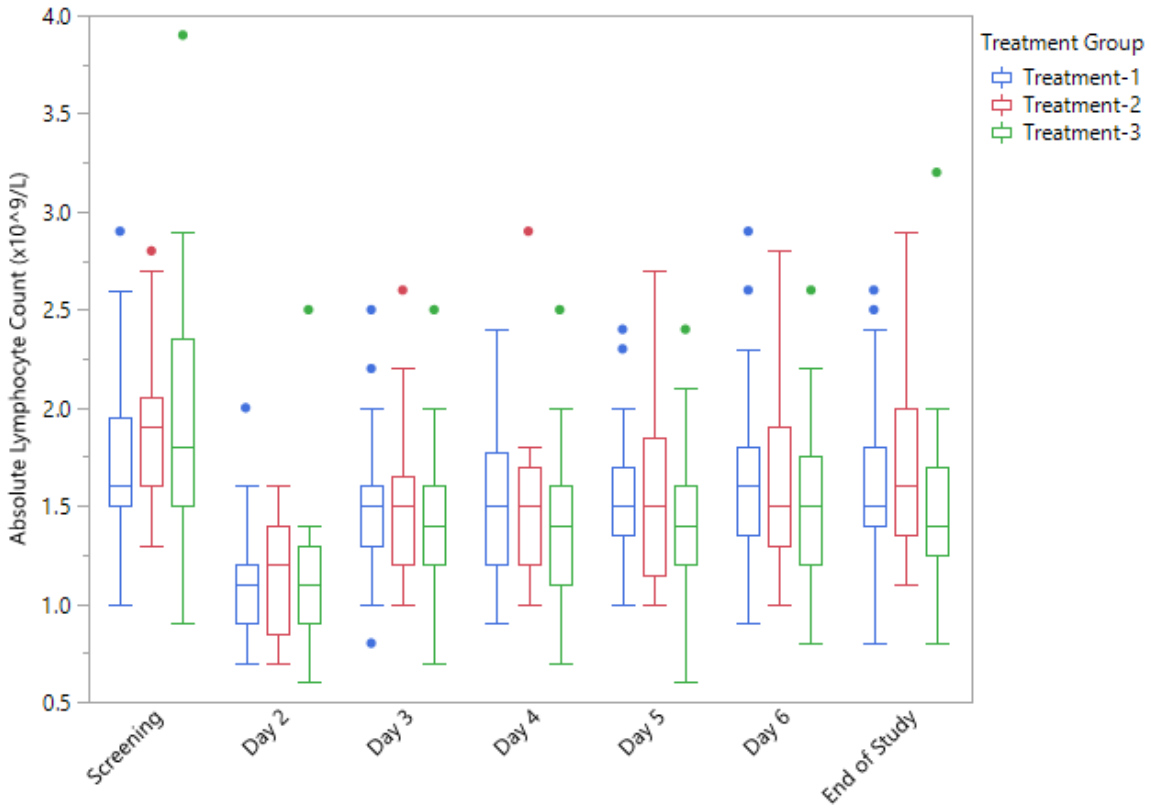
Reviewer comment: Subjects who received fingolimod ("Treatment-3") appeared to experience a slightly more pronounced decrease in ALC compared to the groups who received fingolimod ODT, but this difference is difficult to interpret in the setting of small sample size and high statistical variance. This observation may also be driven by the 2 subjects in the Treatment-3 group (fingolimod) with the lowest ALC values.

Table 12 (Reviewer). Absolute Lymphocyte Count ($x10^9$/L) by Treatment Group, Study FGL-P01

Time	Parameter	Treatment-1 [Fingolimod ODT, with water] (N=25)	Treatment-2 [Fingolimod ODT, without water] (N=25)	Treatment-3 [Fingolimod, with water] (N=25)
Screening	Mean (SD)	1.7 (0.4)	1.9 (0.4)	1.9 (0.7)
	Median (IQR)	1.6 (0.4)	1.9 (0.4)	1.8 (0.8)
	Min, Max	1.0, 2.9	1.3, 2.8	0.9, 3.9
Day 2	Mean (SD)	1.1 (0.3)	1.1 (0.3)	1.1 (0.4)
	Median (IQR)	1.1 (0.3)	1.2 (0.5)	1.1 (0.4)
	Min, Max	0.7, 2.0	0.7, 1.6	0.5, 2.5
	Mean (SD) change from baseline	-0.6 (0.4)	-0.8 (0.4)	-0.8 (0.5)
	Median (IQR) change from baseline	-0.6 (0.5)	-0.7 (0.3)	-0.8 (0.7)
	Min, Max change from baseline	-1.4, 0.1	-1.5, -0.2	-1.6, 0.1
Day 3	Mean (SD)	1.5 (0.4)	1.5 (0.4)	1.4 (0.4)
	Median (IQR)	1.5 (0.3)	1.5 (0.4)	1.4 (0.4)
	Min, Max	0.8, 2.5	1.0, 2.6	0.7, 2.5
	Mean (SD) change from baseline	-0.3 (0.4)	-0.4 (0.3)	-0.5 (0.5)
	Median (IQR) change from baseline	-0.2 (0.6)	-0.4 (0.4)	-0.6 (0.6)
	Min, Max change from baseline	-1.1, 0.7	-1.1, 0.2	-1.6, 0.6
End of Study	Mean (SD)	1.6 (0.4)	1.7 (0.4)	1.5 (0.5)
	Median (IQR)	1.5 (0.4)	1.6 (0.6)	1.4 (0.4)
	Min, Max	0.8, 2.6	1.1, 2.9	0.8, 3.2
	Mean (SD) change from baseline	-0.1 (0.4)	-0.2 (0.3)	-0.4 (0.5)
	Median (IQR) change from baseline	-0.1 (0.6)	-0.2 (0.3)	-0.3 (0.7)
	Min, Max change from baseline	-0.9, 1.0	-0.9, 0.3	-1.6, 0.4

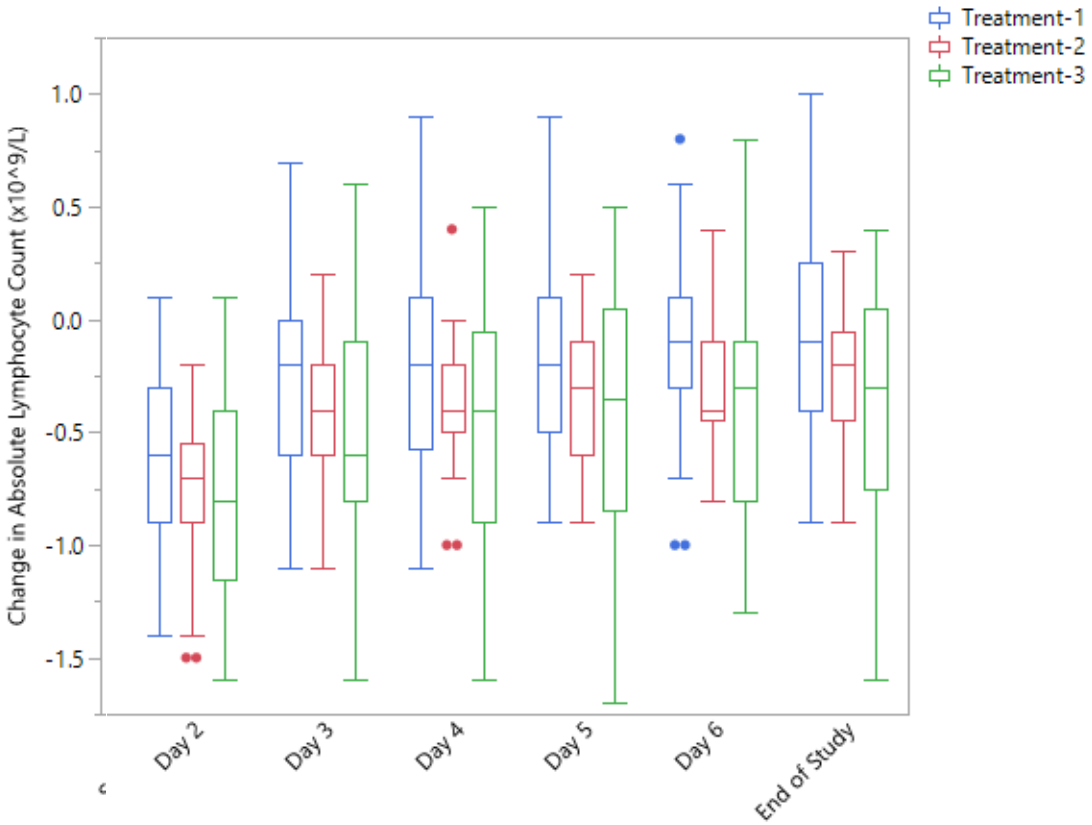
Source: ADLB where ANL01FL=Y, by TRT01A

Figure 7 (Reviewer). Absolute Lymphocyte Count (x10^9/L) Over Time by Treatment Group, Study FGL-P01



Treatment-1 = Fingolimod ODT with water; Treatment-2 = Fingolimod ODT without water; Treatment-3 = fingolimod (reference)

Figure 8 (Reviewer). Change in Absolute Lymphocyte Count (x10^9/L) Over Time by Treatment Group, Study FGL-P01



Treatment-1 = Fingolimod ODT with water; Treatment-2 = Fingolimod ODT without water; Treatment-3 = fingolimod (reference)

In Study FGL-P02, lymphocyte count was measured at screening, Days 2, 3, 4, 5, 6, and end of study (Day 7). All groups experienced a reduction in WBC count, which appeared to be most pronounced at Day 2 (Table 13; Figure 9; Figure 10). The lowest ALC value recorded was 0.6 x10^9/L, which occurred in 1 subject (ID (b) (6)) who received fingolimod ODT (Test). Otherwise, no subjects experienced ALC <0.7 x10^9/L.

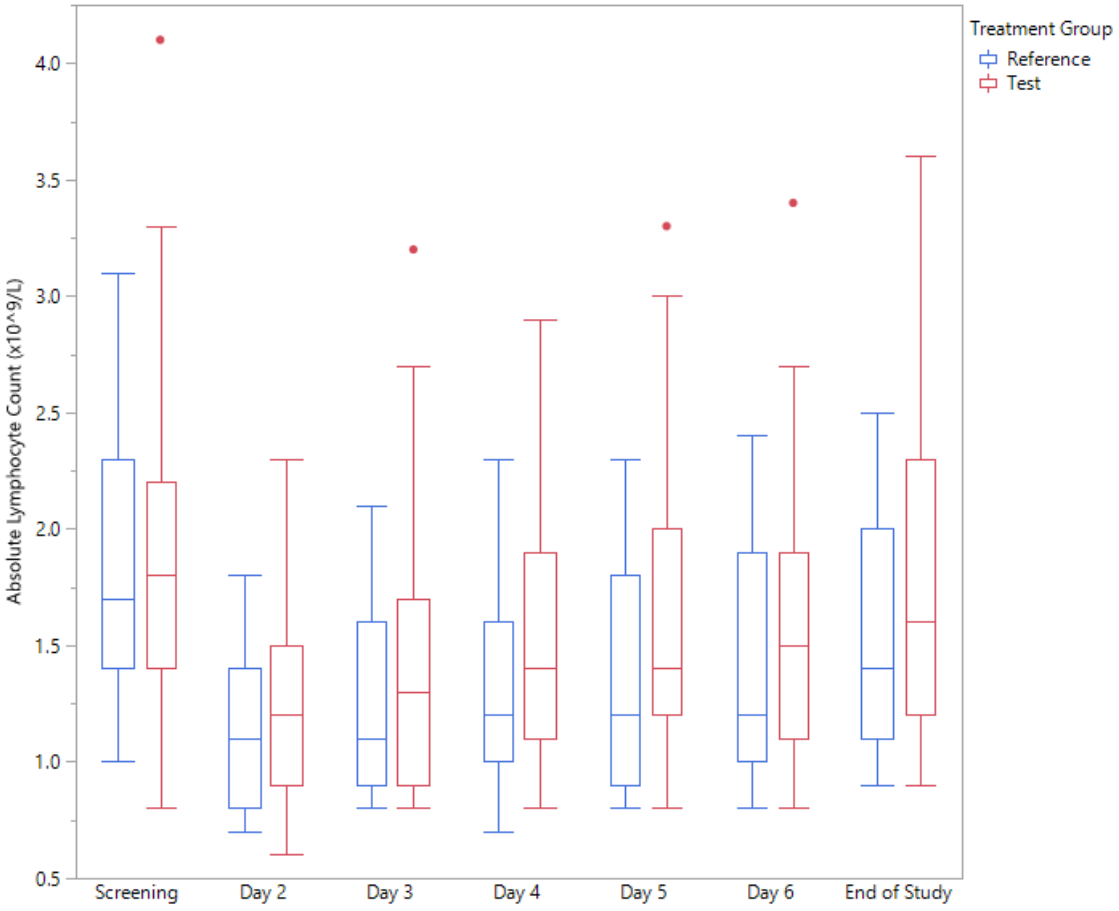
> *Reviewer comment: Again, it appears that subjects who received fingolimod ("Reference") appeared to experience a slightly more pronounced decrease in ALC compared to the groups who received fingolimod ODT, as the median ALC was consistently lower in patients on fingolimod ("Reference") at each timepoint.*

Table 13 (Reviewer). Absolute Lymphocyte Count ($x10^9/L$) by Treatment Group, Study FGL-P02

Time	Parameter	Reference [Fingolimod] (N=19)	Test [Fingolimod ODT] (N=19)
Screening	Mean (SD)	1.8 (0.6)	1.9 (0.8)
	Median (IQR)	1.7 (0.8)	1.8 (0.8)
	Min, Max	1.0, 3.1	0.9, 4.1
Day 2	Mean (SD)	1.1 (0.3)	1.3 (0.5)
	Median (IQR)	1.1 (0.6)	1.2 (0.6)
	Min, Max	0.7, 1.8	0.6, 2.3
	Mean (SD) change from baseline	-0.7 (0.4)	-0.6 (0.5)
	Median (IQR) change from baseline	-0.7 (0.4)	-0.5 (0.5)
	Min, Max change from baseline	-1.4, -0.1	-1.9, 0
Day 3	Mean (SD)	1.3 (0.4)	1.5 (0.6)
	Median (IQR)	1.1 (0.6)	1.3 (0.7)
	Min, Max	0.8, 2,1	0.8, 3.2
	Mean (SD) change from baseline	-0.5 (0.4)	-0.4 (0.4)
	Median (IQR) change from baseline	-0.5 (0.3)	-0.4 (0.4)
	Min, Max change from baseline	-1.4, 0.3	-1.3, 0.1
End of Study	Mean (SD)	1.5 (0.5)	1.7 (0.8)
	Median (IQR)	1.4 (0.9)	1.6 (0.9)
	Min, Max	0.9, 2.5	0.9, 3.6
	Mean (SD) change from baseline	-0.3 (0.3)	-0.2 (0.3)
	Median (IQR) change from baseline	-0.3 (0.5)	-0.2 (0.4)
	Min, Max change from baseline	-1.0, 0.3	-1.0, 0.5

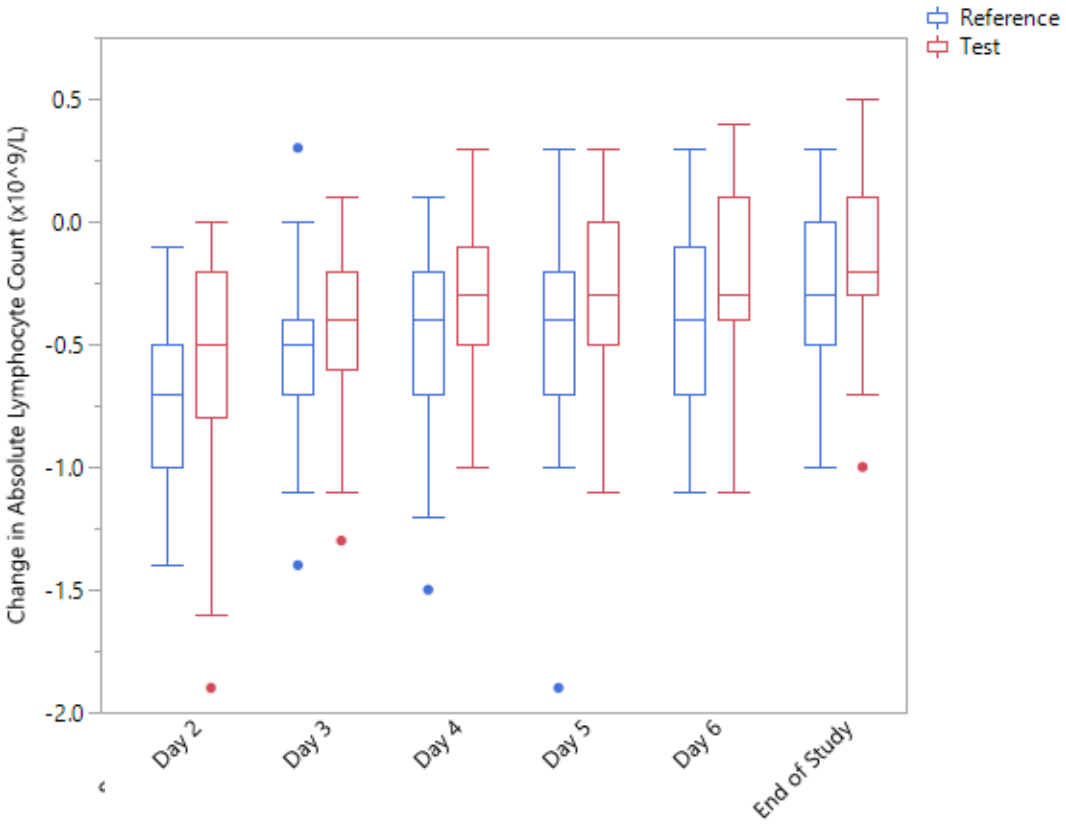
Source: ADLB where ANL01FL=Y, by TRT01A

Figure 9 (Reviewer). Absolute Lymphocyte Count (x10^9/L) Over Time By Treatment Group, Study FGL-P02



Reference = Fingolimod; Test = Fingolimod ODT

Figure 10 (Reviewer). Change in Absolute Lymphocyte Count (x10^9/L) Over Time By Treatment Group, Study FGL-P02



Reference = Fingolimod; Test = Fingolimod ODT

Neutrophil Count

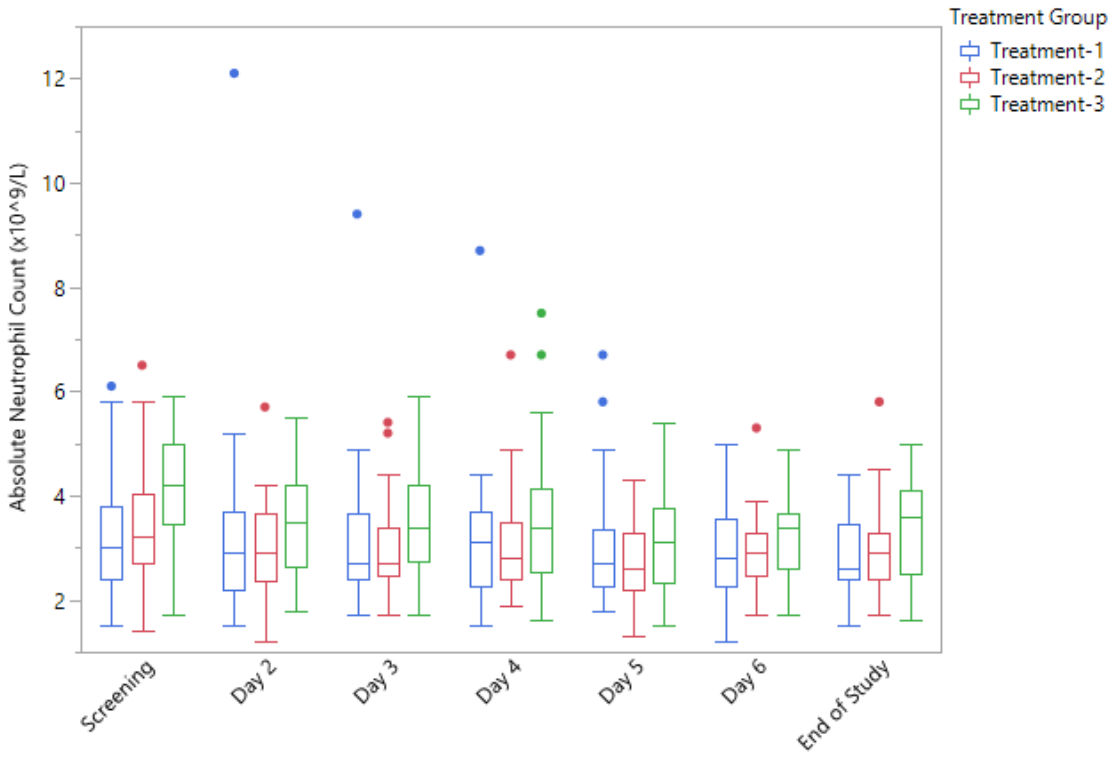
Chronic fingolimod use is known to lead to a mild decrease in neutrophil count to approximately 80% of baseline. Due to observations of ANC <1.5x10^9/L in both studies, neutrophil count was examined in further detail for this review.

In Study FGL-P01, neutrophil count was measured at screening, Days 2, 3, 4, 5, 6, and end of study (Day 7). ANC by treatment group over time is depicted in Figure 11, with change from baseline in Figure 12.

Two subjects who received fingolimod ODT, one in Treatment-2 (ID (b) (6)) and one in Treatment-1 (ID (b) (6)) experienced ANC < 1.5 x10^9/L, and the lowest reported ANC was 1.2 x 10^9/L. Subject ID (b) (6) had a low ANC of 1.4 x10^9/L at screening, which decreased to 1.2 x10^9/L (nadir) on Day 2 then improved to 1.8 x10^9/L at end of study. Subject ID (b) (6) had a borderline ANC of 1.5 x10^9/L at screening, which decreased to 1.2 x 10^9/L on Day 6, then improved to 1.5 x

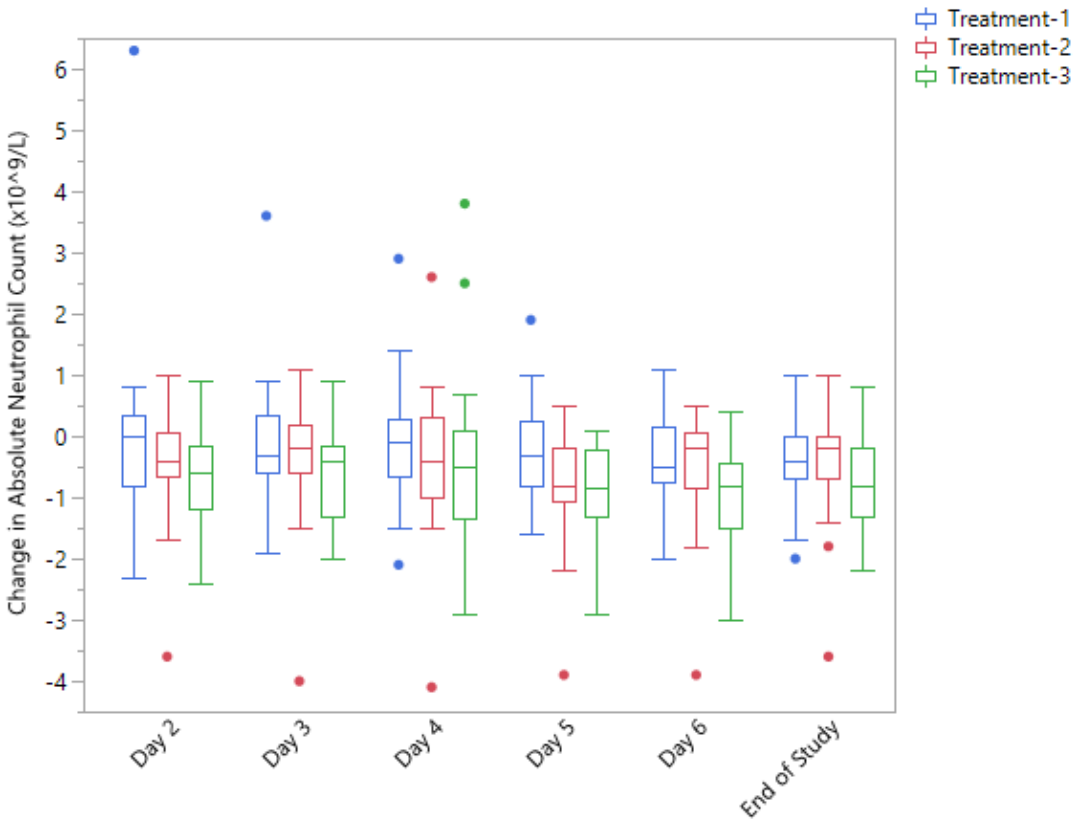
10^9/L at end of study.

Figure 11 (Reviewer). Absolute Neutrophil Count (x10^9/L) Over Time by Treatment Group, Study FGL-P01



Treatment-1 = Fingolimod ODT with water; Treatment-2 = Fingolimod ODT without water; Treatment-3 = Fingolimod (reference)

Figure 12 (Reviewer). Change in Absolute Neutrophil Count (x10^9/L) Over Time by Treatment Group, Study FGL-P01



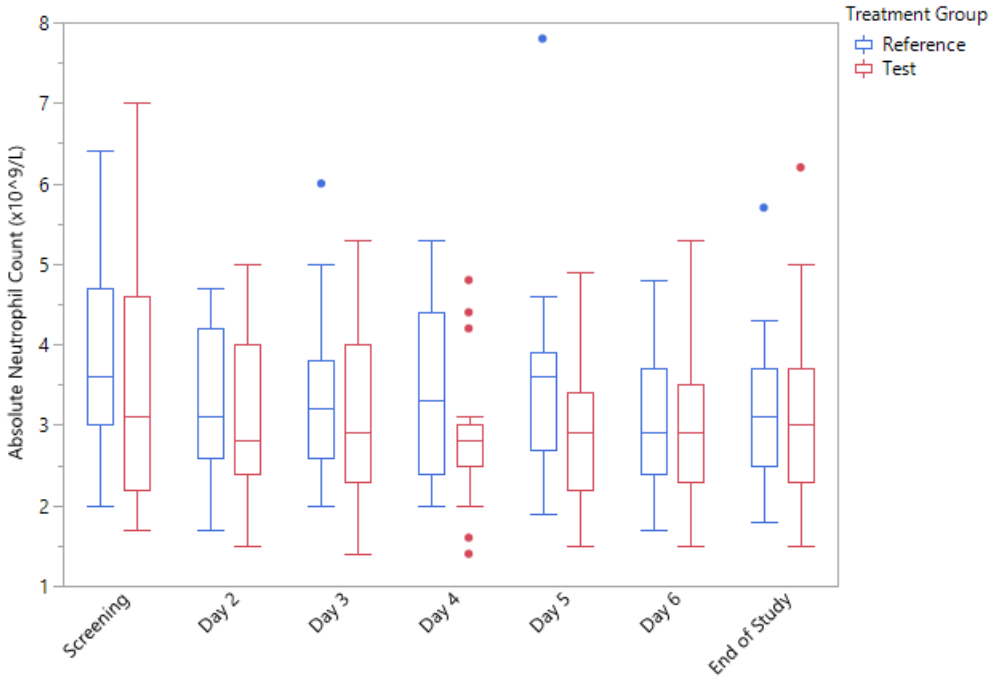
Treatment-1 = Fingolimod ODT with water; Treatment-2 = Fingolimod ODT without water; Treatment-3 = Fingolimod (reference)

> *Reviewer comment: In Study FGL-P01, it appears that subjects who received fingolimod (Treatment-3) experienced a more pronounced decrease in ANC, but it should be noted that this group had a higher median baseline ANC (Figure 11). The differences do not appear to be clinically meaningful after a single dose exposure.*

In Study FGL-P02, neutrophil count was measured at screening, Days 2, 3, 4, 5, 6, and end of study (Day 7). ANC by treatment group over time is depicted in Figure 13, and change from baseline in Figure 14.

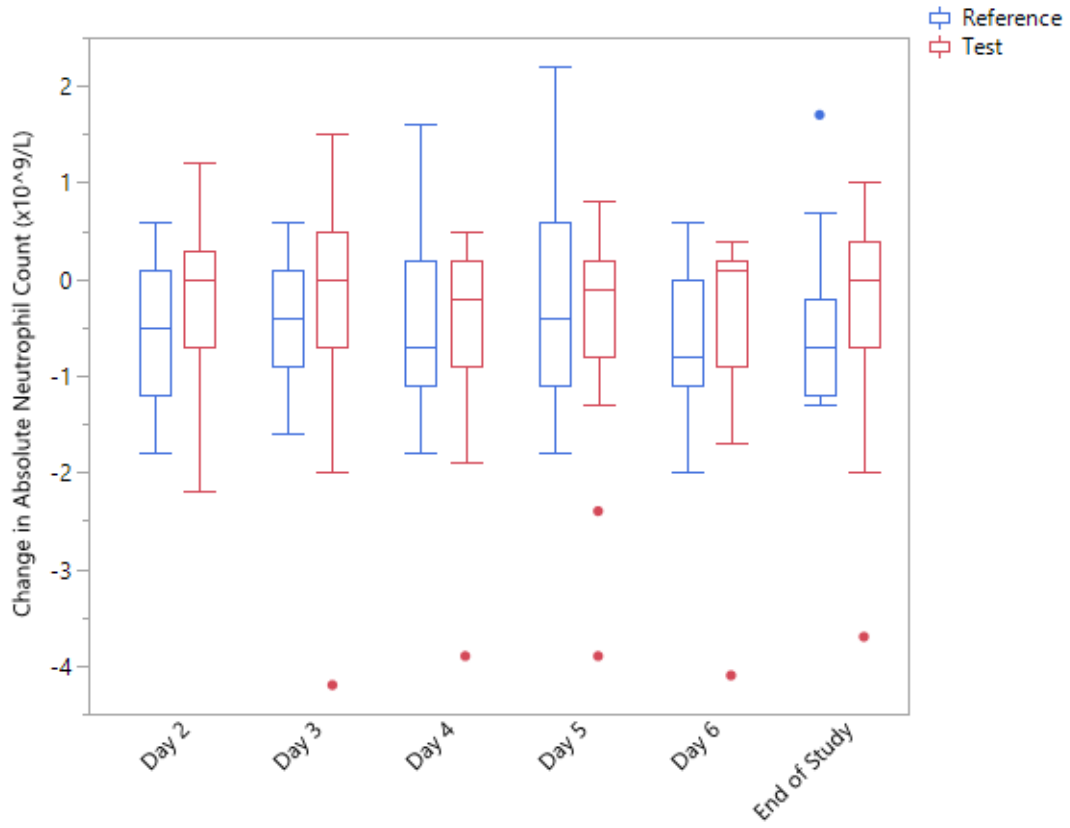
One subject who received fingolimod ODT (ID (b) (6)) experienced 2 instances of ANC < 1.5 x10^9/L, and the lowest reported ANC was 1.4 x 10^9/L. This subject had an ANC of 2.2 x10^9/L at screening, which decreased to 1.4 x10^9/L (nadir) on Days 3 and 4, then improved to 1.5 x10^9/L at end of study.

Figure 13 (Reviewer). Absolute Neutrophil Count (x10^9/L) Over Time by Treatment Group, Study FGL-P02



Reference = Fingolimod; Test = Fingolimod ODT

Figure 14 (Reviewer). Change in Absolute Neutrophil Count (x10^9/L) Over Time by Treatment Group, Study FGL-P02



Reference = Fingolimod; Test = Fingolimod ODT

Reviewer comment: In Study FGL-P02, it appears that subjects who received fingolimod ("Reference") experienced a more pronounced decrease in ANC, but it should be noted that this group had a higher median baseline ANC (Figure 13). This finding was also observed in Study FGL-P01. However, no clinically significant decreases in ANC occurred in either study.

Alanine aminotransferase

In Study FGL-P01, clinical biochemistry, including ALT, was assessed at screening and end of study. ALT values at screening and end of study (including change from baseline) are presented by treatment group in Table 14. No subjects experienced ALT >2x ULN during the study. No trends suggestive of increasing ALT in any treatment group were observed during this study.

Table 14 (Reviewer). Alanine aminotransferase by Treatment Group, Study FGL-P01

Time	Parameter	Treatment-1 [Fingolimod ODT, with water] (N=25)	Treatment-2 [Fingolimod ODT, without water] (N=25)	Treatment-3 [Fingolimod, with water] (N=25)
Screening	Mean (SD)	24.5 (13.4)	24.4 (11.1)	27.6 (15.4)
	Median (IQR)	21.0 (14.0)	22.0 (17.0)	25.0 (13.0)
	Min, Max	10, 63	10, 48	10, 66
End of Study	N	25	25	25
	Mean (SD)	22.9 (13.3)	22.4 (12.7)	26.8 (14.4)
	Median (IQR)	17.0 (12.0)	19.0 (13.0)	24.0 (19.0)
	Min, Max	10, 67	10, 70	10, 65
	Mean (SD) change from baseline	-1.0 (6.0)	-2.0 (7.1)	-0.3 (9.0)
	Median change from baseline	-1.0 (4.0)	-2.0 (7.0)	0.0 (9.0)
	Min, Max change from baseline	-13, 21	-15, 22	-30, 14
	% (n) of patients with ALT >2x ULN	0 (0)	0 (0)	0 (0)

Source: ADLB where ANL01FL=Y, by TRT01A

In Study FGL-P02, clinical biochemistry, including ALT, was assessed at screening and end of study. No subjects experienced ALT >2x ULN during the study. No trends suggestive of increasing ALT in any treatment group were observed during this study.

Table 15 (Reviewer). Alanine aminotransferase by Treatment Group, Study FGL-P02

Time	Parameter	Reference [Fingolimod] (N=19)	Test [Fingolimod ODT] (N=19)
Screening	Mean (SD)	26.8 (13.8)	23.7 (11.9)
	Median (IQR)	23.0 (26.5)	19.0 (16.5)
	Min, Max	10, 48	10, 51
End of Study	Mean (SD)	26.8 (13.8)	23.7 (11.9)
	Median (IQR)	23.0 (26.5)	19.0 (16.5)
	Min, Max	10, 48	10, 51
	Mean (SD) change from baseline	3.6 (8.0)	-1.5 (8.9)
	Median (IQR) change from baseline	2.0 (8.5)	0 (5.5)
	Min, Max change from baseline	-5, 25	-31, 9
	% (n) of patients with ALT >2x ULN	0 (0)	0 (0)

Source: ADLB where ANL01FL=Y, by TRT01A

Aspartate aminotransferase

In Study FGL-P01, clinical biochemistry, including AST, was assessed at screening and end of study. AST values at screening and end of study (including change from baseline) are presented

by treatment group in Table 16. No subjects experienced AST >2x ULN during the study. No trends suggestive of increasing AST in any treatment group were observed during this study.

Table 16 (Reviewer). Aspartate aminotransferase by Treatment Group, Study FGL-P01

Time	Parameter	Treatment-1 [Fingolimod ODT, with water] (N=25)	Treatment-2 [Fingolimod ODT, without water] (N=25)	Treatment-3 [Fingolimod, with water] (N=25)
Screening	Mean (SD)	22.7 (5.4)	24.3 (10.1)	23.7 (7.7)
	Median (IQR)	22.0 (4.0)	22.0 (9.0)	23.0 (7.0)
	Min, Max	14, 43	13, 64	13, 39
End of Study	N	25	25	25
	Mean (SD)	21.8 (6.5)	20.2 (5.7)	21.8 (7.0)
	Median (IQR)	20.0 (4.0)	19.0 (2.0)	21.0 (7.0)
	Min, Max	15, 47	13, 40	11, 42
	Mean (SD) change from baseline	-0.8 (3.4)	-2.8 (5.0)	-1.9 (4.0)
	Median change from baseline	-1.0 (5.0)	-2.0 (4.0)	-1.0 (5.0)
	Min, Max change from baseline	-9, 6	-17, 8	-13, 5
	% (n) of patients with AST >2x ULN	0 (0)	0 (0)	0 (0)

Source: ADLB where ANL01FL=Y, by TRT01A

In Study FGL-P02, clinical biochemistry, including AST, was assessed at screening and end of study. AST values at screening and end of study (including change from baseline) are presented by treatment group in Table 17. No subjects experienced AST >2x ULN during the study. No trends suggestive of increasing AST in any treatment group were observed during this study.

Table 17 (Reviewer). Aspartate aminotransferase by Treatment Group, Study FGL-P02

Time	Parameter	Reference [Fingolimod] (N=19)	Test [Fingolimod ODT] (N=19)
Screening	Mean (SD)	23.3 (6.8)	22.3 (6.0)
	Median (IQR)	22.0 (7.5)	21.0 (10.0)
	Min, Max	15, 40	13, 35
End of Study	Mean (SD)	22.9 (7.4)	21.0 (4.7)
	Median (IQR)	20.0 (10.0)	21.0 (7.5)
	Min, Max	14, 38	12, 29
	Mean (SD) change from baseline	-0.4 (0.6.8)	-1.3 (3.9)
	Median (IQR) change from baseline	-1.0 (4.5)	0.0 (4.5)
	Min, Max change from baseline	-12, 14	-10, 4
	% (n) of patients with AST >2x ULN	0 (0)	0 (0)

Source: ADLB where ANL01FL=Y, by TRT01A

Total Bilirubin

In Study FGL-P01, clinical biochemistry, including total bilirubin (in µmol/L), was assessed at screening and end of study. Total bilirubin values at screening and end of study (including change from baseline) are presented by treatment group in Table 18. One subject had an elevated total bilirubin (44 µmol/L) at screening, which normalized to 24 µmol/L at end of study. No subjects experienced a clinically significant (i.e., >1.5x ULN) treatment-emergent increase in total bilirubin.

Table 18 (Reviewer). Total bilirubin by Treatment Group, Study FGL-P01

Time	Parameter	Treatment-1 [Fingolimod ODT, with water] (N=25)	Treatment-2 [Fingolimod ODT, without water] (N=25)	Treatment-3 [Fingolimod, with water] (N=25)
Screening	Mean (SD)	12.8 (8.8)	11.9 (5.4)	9.6 (3.6)
	Median (IQR)	11.0 (4.0)	11.0 (6.0)	9.0 (6.0)
	Min, Max	5, 44	4, 26	4, 18
End of Study	N	25	25	25
	Mean (SD)	11.1 (5.5)	7.8 (3.0)	8.2 (3.6)
	Median (IQR)	10.0 (7.0)	7.0 (3.0)	8.0 (5.0)
	Min, Max	4, 24	3, 15	4, 19
	Mean (SD) change from baseline	-0.8 (4.0)	-4.0 (4.0)	-1.4 (3.6)
	Median change from baseline	-1.0 (3.0)	3.0 (6.0)	-1.0 (4.0)
	Min, Max change from baseline	-15, 6	-14, 1	-10, 5
	% (n) of patients with TB >1.5x ULN	0 (0)	0 (0)	0 (0)

Source: ADLB where ANL01FL=Y, by TRT01A

In Study FGL-P02, clinical biochemistry, including total bilirubin, was assessed at screening and end of study. Total bilirubin values at screening and end of study (including change from baseline) are presented by treatment group in Table 19. One subject experienced total bilirubin >1.5x ULN (39 µmol/L) at screening, but none had total bilirubin >1.5x ULN at end of study.

Table 19 (Reviewer). Total bilirubin by Treatment Group, Study FGL-P02

Time	Parameter	Reference [Fingolimod] (N=19)	Test [Fingolimod ODT] (N=19)
Screening	Mean (SD)	11.8 (8.2)	9.7 (5.1)
	Median (IQR)	9.0 (8.0)	9.0 (3.5)
	Min, Max	5, 39	3, 28
End of Study	Mean (SD)	9.1 (4.7)	8.7 (5.4)
	Median (IQR)	8.0 (4.5)	7.0 (5.0)
	Min, Max	3, 20	3, 25
	Mean (SD) change from baseline	-1.7 (4.1)	-0.9 (2.8)
	Median (IQR) change from baseline	-1.0 (5.0)	-1.0 (4.0)
	Min, Max change from baseline	-12, 5	-5, 4
	% (n) of patients with total bilirubin >1.5x ULN	0 (0)	0 (0)

Source: ADLB where ANL01FL=Y, by TRT01A

Other Laboratory Findings

Review of additional laboratory data for Studies FGL-P01 and FGL-P02 did not demonstrate clinically significant or consistent abnormalities in hemoglobin, hematocrit, platelets, monocyte count, eosinophil count, sodium, potassium, chloride, creatinine, glucose, protein, alkaline phosphatase, urine leukocytes, urine occult blood, urine protein, urine ketones, or urine bilirubin.

8.4.7. Vital Signs

Vital sign measurements occurred at screening, pre-dose, at 1, 2, 3, 4, 5, 6, 8, 12, 14, and 24 hours post-dose, then at end of study. Please refer to Section 8.3.3 for schedule of assessments for both studies.

Heart Rate

Bradycardia and atrioventricular (AV) block are known safety concerns with fingolimod, particularly at the time of treatment initiation. Post-dose heart rate changes from baseline were compared between patients who received fingolimod ODT and fingolimod in Studies FGL-P01 and FGL-P02. Please refer to Section 8.5.1 for cardiac TEAEs that occurred in Studies FGL-P01 and FGL-P02.

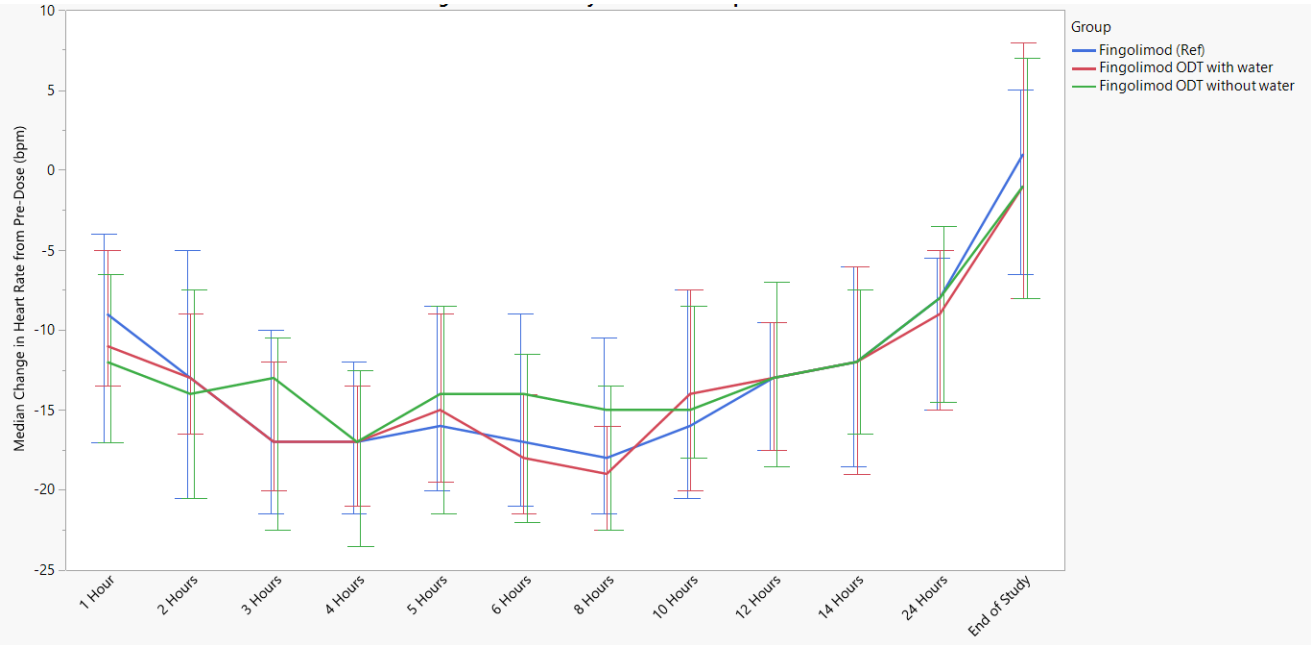
In Study FGL-P01, reductions in heart rate were observed following administration of study drug in all treatment groups, as anticipated. It appears that the heart rate nadir occurred at 8 hours post-dose, then gradually increased back to baseline through hour 24. Changes in heart rate at representative time points are presented in Table 20 and Figure 15.

Table 20 (Reviewer). Heart Rate Over Time by Treatment Group, Study FGL-P01

		Treatment-1 (Fingolimod ODT) [n = 25]	Treatment-2 (Fingolimod ODT) [n = 25]	Treatment-3 (Fingolimod) [n = 25]
Pre-Dose	Mean (SD)	71.0 (18.7)	66.6 (9.1)	69.5 (11.7)
	Median (IQR)	68.0 (11)	64.0 (11)	68.0 (18)
	Min, Max	46, 149	54, 92	53, 106
1 hour Post-Dose	Mean (SD)	60.9 (11.2)	56.7 (7.0)	59.8 (7.6)
	Median (IQR)	60.0 (11)	56.0 (8)	570 (8)
	Min, Max	46, 100	42, 77	49, 82
Change from Pre-Dose	Mean (SD)	-8.9 (10.5)	-12.4 (9.2)	-10.3 (8.4)
	Median (IQR)	-11.0 (8.0)	-12.0 (9.0)	-9.0 (13.0)
	Min, Max	-38, 20	-39, 4	-24, 4
2 hours Post-Dose	Mean (SD)	57.4 (12.01)	53.9 (7.1)	56.2 (8.3)
	Median (IQR)	55.0 (9.0)	52.0 (8.0)	55.0 (12.0)
	Min, Max	44, 109	42, 72	42, 73
Change from Pre-Dose	Mean (SD)	-12.4 (10.7)	-15.2 (11.1)	-13.9 (9.7)
	Median (IQR)	-13.0 (7.0)	-14.0 (12.0)	-13.0 (15.0)
	Min, Max	-38, 29	-52, 0	-33, 4
4 hours Post-Dose	Mean (SD)	52.4 (9.7)	50.7 (6.3)	52.1 (6.1)
	Median (IQR)	51.0 (8.0)	50.0 (8.0)	51.0 (9.0)
	Min, Max	42, 93	40, 63	42, 65
Change from Pre-Dose	Mean (SD)	-17.3 (9.6)	-18.4 (9.0)	-18.0 (8.0)
	Median (IQR)	-17.0 (7.0)	-17.0 (10.0)	-17.0 (9.0)
	Min, Max	-46, 13	-48, -4	-39, -3
6 hours Post-Dose	Mean (SD)	51.4 (7.8)	51.8 (6.4)	53.2 (7.1)
	Median (IQR)	52.0 (10.0)	51.0 (9.0)	51.0 (11.0)
	Min, Max	40, 73	38, 65	42, 67
Change from Pre-Dose	Mean (SD)	-18.3 (7.8)	-17.2 (9.8)	-16.9 (9.0)
	Median (IQR)	-18.0 (6.0)	-14.0 (9.0)	-17.0 (12.0)
	Min, Max	-47, -5	-47, -5	-40, -5
8 hours Post-Dose	Mean (SD)	50.2 (7.0)	51.0 (6.0)	52.8 (6.5)
	Median (IQR)	50.0 (9.0)	50.0 (9.0)	51.0 (9.0)
	Min, Max	40, 69	41, 67	43, 66
Change from Pre-Dose	Mean (SD)	-19.6 (6.6)	-18.0 (9.5)	-17.3 (8.8)
	Median (IQR)	-19.0 (6.0)	-15.0 (7.0)	-18.0 (10.0)
	Min, Max	-45, -11	-47, -4	-38, 2
24 hours Post-Dose	Mean (SD)	59.4 (10.8)	58.8 (7.1)	60.2 (7.6)
	Median (IQR)	60.0 (12.0)	58.0 (10.0)	57.0 (12.0)
	Min, Max	44, 89	47, 73	51, 76
Change from Pre-Dose	Mean (SD)	-10.3 (8.8)	-10.2 (10.4)	-9.9 (7.6)
	Median (IQR)	-9.0 (10.0)	-8.0 (9.0)	-8.0 (8.0)
	Min, Max	-38, 8	-42, 8	-29, 3
End of Study	Mean (SD)	70.6 (16.5)	68.3 (9.8)	69.3 (10.8)
	Median (IQR)	67.0 (15.0)	67.0 (9.0)	68.0 (13.0)
	Min, Max	40, 131	51, 91	51, 89
Change from Pre-Dose	Mean (SD)	0.8 (15.4)	-0.8 (14.2)	-0.8 (9.9)
	Median (IQR)	-1.0 (15.0)	-1.0 (13.0)	1.0 (9.0)
	Min, Max	-33, 51	-32, 29	-18, 20

Source: ADVS where ANFL01=Y, by TRT01A

Figure 15 (Reviewer). Median Change in Heart Rate Over Time by Treatment Group, Study FGL-P01



Error bars = Interquartile range

In Study FGL-P02, similar reductions in heart rate following study drug administration were observed. Again, the heart rate nadir appeared to occur at 8 hours post-dose, with gradual increase through 24 hours. Changes in heart rate at representative time points are presented in Table 21 and Figure 16.

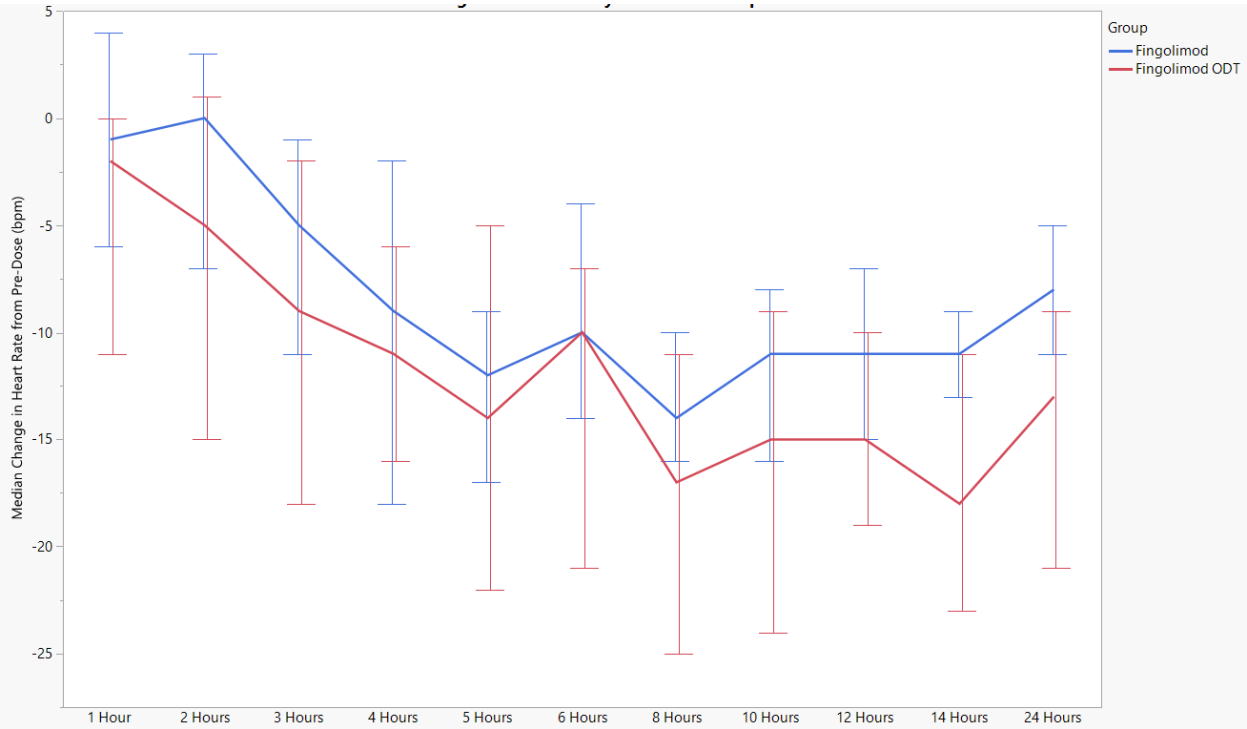
Table 21 (Reviewer). Heart Rate Over Time by Treatment Group, Study FGL-P02

		Reference (Fingolimod) [n = 19]	Test (Fingolimod ODT) [n = 19]
Pre-Dose	Mean (SD)	65.1 (7.7)	70.4 (13.9)
	Median (IQR)	66.0 (9.0)	68.0 (16.5)
	Min, Max	53, 78	53, 106
1 hour Post-Dose	Mean (SD)	65.6 (5.8)	67.5 (8.1)
	Median (IQR)	64.0 (5.5)	67.0 (11.0)
	Min, Max	57, 78	50, 83
Change from Pre-Dose	Mean (SD)	-1.0 (6.7)	-5.4 (10.3)
	Median (IQR)	-1.0 (8.5)	-2.0 (9.0)
	Min, Max	-14, 13	-33, 8
2 hours Post-Dose	Mean (SD)	64.1 (6.1)	65.2 (11.0)
	Median (IQR)	64.0 (6.5)	63.0 (13.0)
	Min, Max	53, 76	50, 90
Change from Pre-Dose	Mean (SD)	-2.4 (7.8)	-7.7 (14.2)
	Median (IQR)	0 (9.5)	-5.0 (12.5)
	Min, Max	-22, 10	-39, 19
3 hours Post-Dose	Mean (SD)	60.4 (8.7)	62.6 (11.4)
	Median (IQR)	58.0 (12.0)	62.0 (11.5)
	Min, Max	47, 77	43, 88
Change from Pre-Dose	Mean (SD)	-6.2 (8.9)	-10.3 (14.9)
	Median (IQR)	-5.0 (7.0)	-9.0 (14.0)
	Min, Max	-31, 6	-42, 17
4 hours Post-Dose	Mean (SD)	57.8 (9.4)	59.4 (8.8)
	Median (IQR)	56.0 (12.0)	61.0 (10.0)
	Min, Max	44, 78	45, 82
Change from Pre-Dose	Mean (SD)	-8.7 (8.7)	-13.5 (13.4)
	Median (IQR)	-9.0 (13.0)	-11.0 (9.5)
	Min, Max	-22, 6	-42, 14
5 hours Post-Dose	Mean (SD)	53.7 (5.1)	57.6 (8.6)
	Median (IQR)	54.0 (7.0)	59.0 (10.5)
	Min, Max	45, 63	46, 76
Change from Pre-Dose	Mean (SD)	-12.8 (7.4)	-15.3 (13.7)
	Median (IQR)	-12.0 (8.0)	-14 (14.5)
	Min, Max	-33, 3	-47, 8
6 hours Post-Dose	Mean (SD)	56.7 (7.0)	58.1 (7.8)
	Median (IQR)	57.0 (8.0)	57.0 (8.0)
	Min, Max	47, 74	44, 75
Change from Pre-Dose	Mean (SD)	-9.8 (7.4)	-14.8 (11.2)
	Median (IQR)	-10.0 (9.5)	-10.0 (13.0)
	Min, Max	-30, 2	-42, 0
8 hours Post-Dose	Mean (SD)	52.8 (5.9)	54.5 (7.9)
	Median (IQR)	52.0 (8.0)	55.0 (9.5)
	Min, Max	42, 66	43, 74
Change from Pre-Dose	Mean (SD)	-13.7 (6.4)	-18.4 (11.6)
	Median (IQR)	-14.0 (5.5)	-17.0 (12.0)
	Min, Max	-31, -3	-47, 0
10 hours Post-Dose	Mean (SD)	54.0 (6.0)	55.4 (8.2)
	Median (IQR)	54.0 (4.0)	55.0 (12.0)
	Min, Max	43, 67	43, 71

Change from Pre-Dose	Mean (SD)	-12.5 (8.2)	-17.5 (12.2)
	Median (IQR)	-11.0 (7.0)	-15.0 (14.0)
	Min, Max	-35, -2	-48, 0
12 hours Post-Dose	Mean (SD)	53.9 (5.5)	57.6 (11.7)
	Median (IQR)	55.0 (8.0)	55.0 (8.5)
	Min, Max	47, 68	42, 91
Change from Pre-Dose	Mean (SD)	-12.6 (6.5)	-15.3 (13.3)
	Median (IQR)	-11.0 (6.5)	-15 (8.5)
	Min, Max	-31, -5	-44, 12
14 hours Post-Dose	Mean (SD)	54.8 (7.4)	54.6 (6.4)
	Median (IQR)	54.0 (6.0)	54.0 (10.0)
	Min, Max	45, 78	44, 66
Change from Pre-Dose	Mean (SD)	-11.7 (6.3)	-18.3 (11.0)
	Median (IQR)	-11.0 (4.0)	-18.0 (10)
	Min, Max	-26, 3	-49, -4
24 hours Post-Dose	Mean (SD)	57.3 (5.0)	58.4 (8.3)
	Median (IQR)	58.0 (6.0)	55.0 (14.5)
	Min, Max	50, 68	45, 71
Change from Pre-Dose	Mean (SD)	-9.2 (5.4)	-14.5 (10.7)
	Median (IQR)	-8.0 (5.0)	-13.0 (9.5)
	Min, Max	-24, -3	-47, 1
End of Study	Mean (SD)	65.2 (8.2)	69.8 (10.1)
	Median (IQR)	63.0 (10.0)	69.0 (9.0)
	Min, Max	54, 90	52, 96
Change from Pre-Dose	Mean (SD)	-1.3 (8.7)	-3.1 (10.8)
	Median (IQR)	0.0 (9.0)	1.0 (13.5)
	Min, Max	-15, 24	-32, 10

Source: ADVS where ANFL01=Y, by TRT01A

Figure 16 (Reviewer). Median Change in Heart Rate Over Time by Treatment Group, Study FGL-P02



Error bars = Interquartile range

Reviewer comment: Though the heart rate nadir appeared to occur at 8 hours post-dose (similar to Study FGL-P01), another decrease in median heart rate in the fingolimod ODT group appeared to occur at 14 hours post-dose. This observation appears to be driven by 2 subjects: one with a maximum heart rate decrease of 49 beats per minute (subject ID (b) (6) *experienced a nadir heart rate of 51 bpm at hour 14 post-dose, from a baseline of 100 bpm), and one with a maximum heart rate decrease of 39 bpm (subject ID* (b) (6) *experienced a nadir heart rate of 57 bpm at hour 14 post-dose, from a baseline of 96 bpm). These two subjects, who had relatively high baseline heart rates, likely contributed to the consistently larger decrease in heart rate observed in subjects who received fingolimod ODT. Overall, there does not appear to be a clinically significant difference in the decrease in heart rate observed with fingolimod and fingolimod ODT.*

Blood Pressure

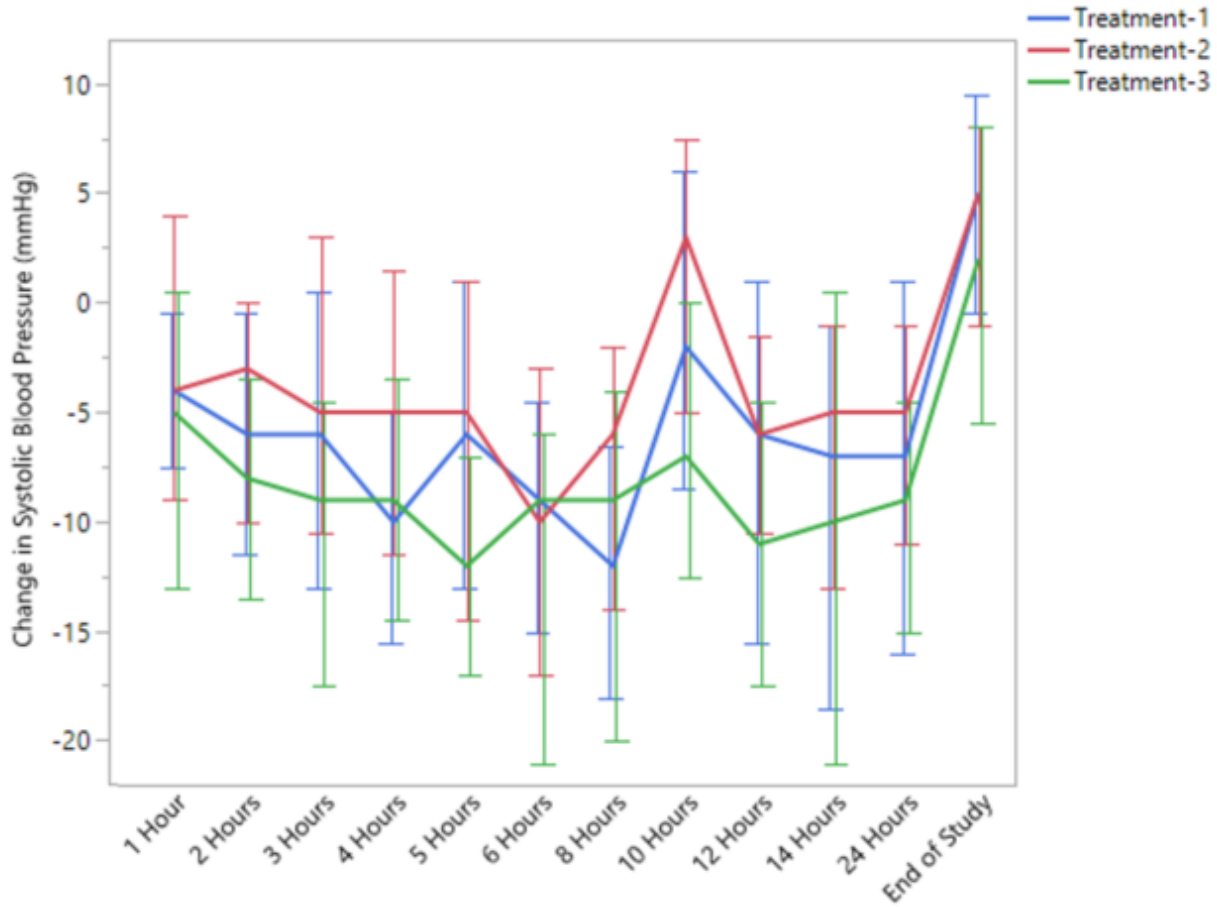
Increased blood pressure is included as a Warnings and Precautions section for the RLD (fingolimod). In controlled trials, adult patients who received fingolimod had a mean increase of 3 mmHg of systolic and 2 mmHg diastolic blood pressure compared to placebo, and this change was detected after approximately 1 month of treatment initiation. Hypertension was reported

as a TEAE in 8% of patients on fingolimod, versus 4% of those on placebo. Additionally, previous studies of fingolimod have reported a decline in blood pressure noted in the first 6 hours after the initial dose.

Systolic Blood Pressure

In Study FGL-P01, no subjects experienced systolic blood pressure (SBP) <90 mmHg or >160 mmHg during study participation. Median change in SBP over time is presented in Figure 17. Through 24 hours post-dose, SBP was generally lower than that at baseline (i.e., mean and median change from baseline were <0), with a gradual reduction between hours 1 and 6 to 8. Changes in SBP from baseline appeared to be similar between treatment groups.

Figure 17 (Reviewer). Median Change in Systolic Blood Pressure Over Time, Study FGL-P01



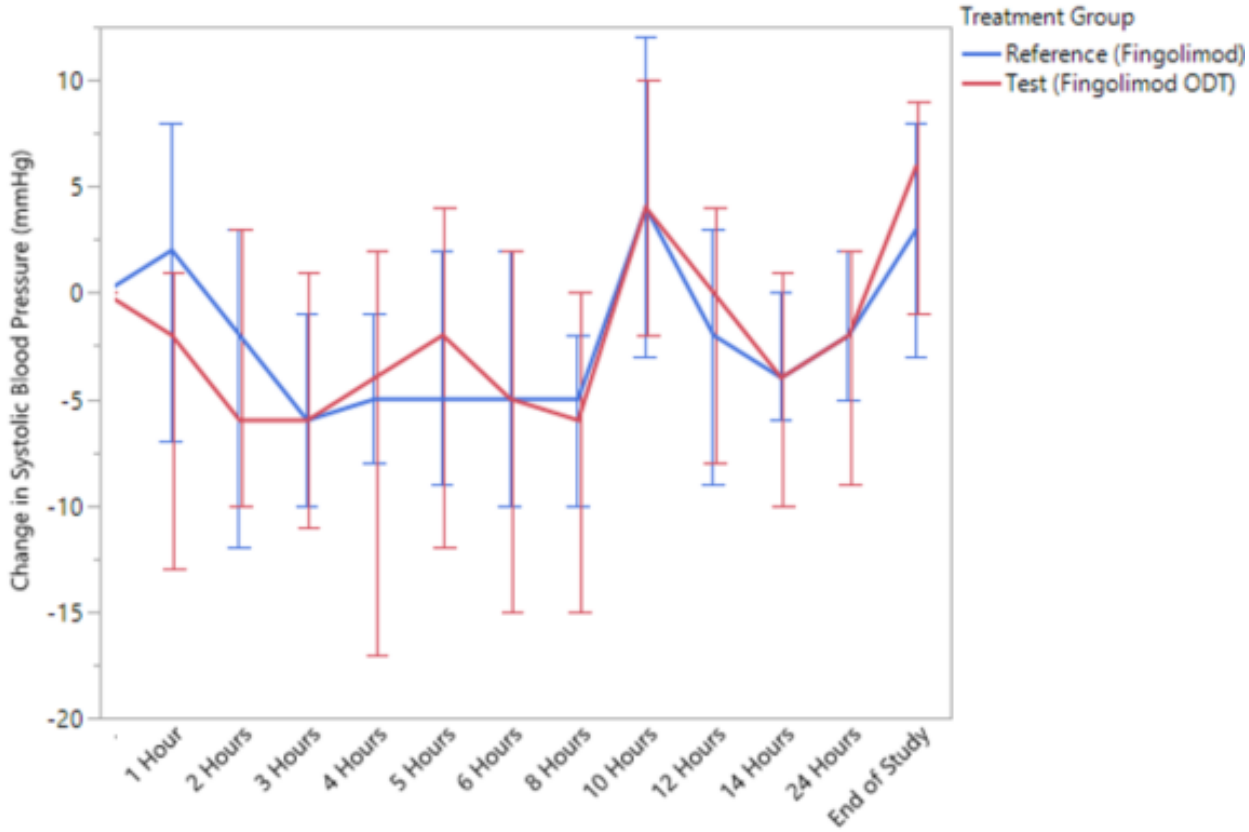
Error bars = Interquartile range; Treatment-1 = Fingolimod ODT with water; Treatment-2 = Fingolimod ODT without water; Treatment-3 = Fingolimod (reference)

Patients who experienced SBP >140 mmHg during the study all had a screening or pre-dose SBP >140 mmHg, except for 1 patient (Subject ID (b) (6)) who had a pre-dose SBP of 135 mmHg and

experienced a maximum SBP of 144 mmHg at 4 hours post-dose. This subject's SBP at end of study was 125 mmHg.

In Study FGL-P02, no subjects experienced systolic blood pressure (SBP) <85 mmHg or >160 mmHg during study participation. Median change in SBP over time is presented in Figure 18. Through 24 hours post-dose, SBP was generally lower than that at baseline (i.e., mean and median change from baseline were <0), except at 10 hours post-dose. Again, SBP decreased from baseline between hours 1 and 6 to 8 post-dose, as expected. Changes in SBP appeared to be similar between treatment groups.

Figure 18 (Reviewer). Median Change in Systolic Blood Pressure Over Time, Study FGL-P02



Error bars = Interquartile range

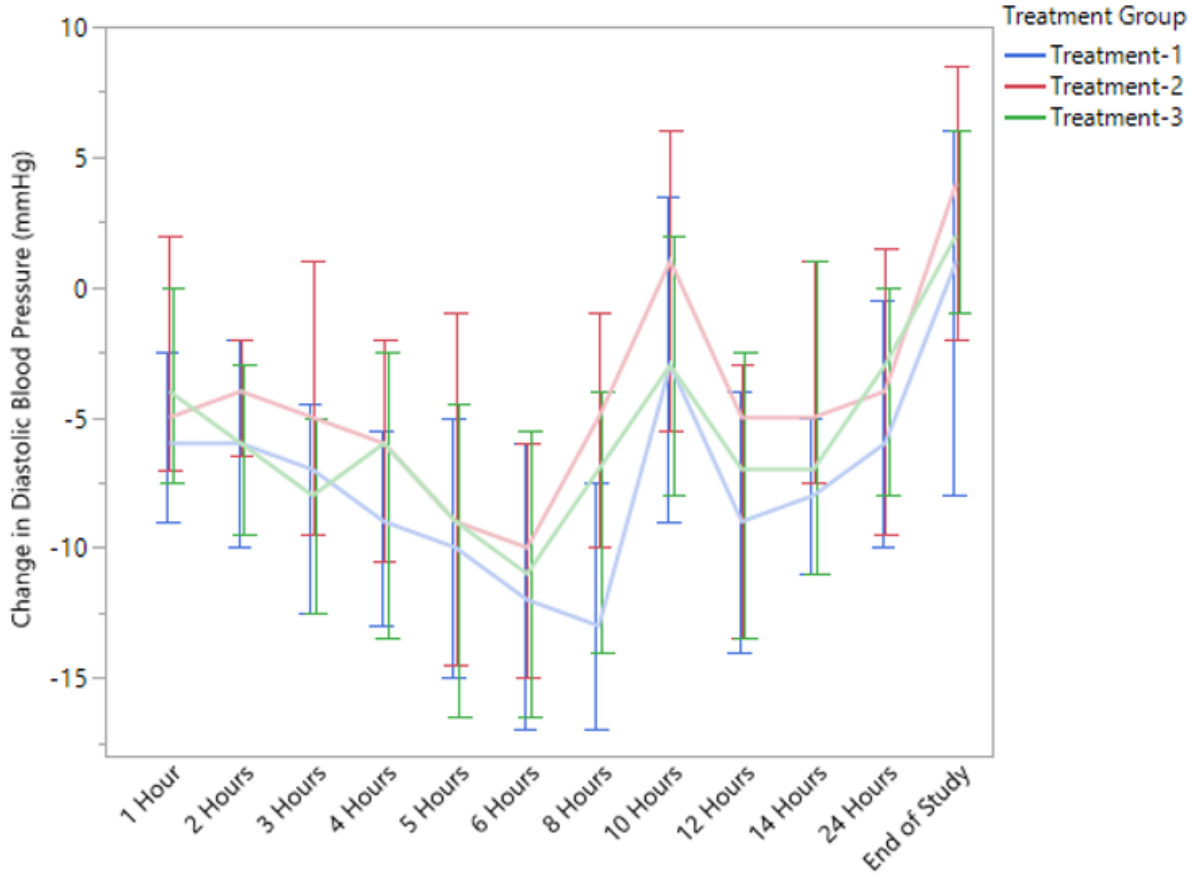
Four patients experienced SBP >140 mmHg during the study, one of whom (subject ID (b) (6), on fingolimod ODT) had SBP >140 mmHg at screening. One subject (ID (b) (6), on fingolimod ODT) had baseline SBP of 139 mmHg, so the observed increase in SBP to 141 and 143 mmHg at 12 and 14 hours post-dose is not clinically significant. Subject ID (b) (6) (on fingolimod) experienced SBP of 146 mmHg at 12 hours post-dose, from a baseline value of 126 mmHg. This observation

appears to be isolated, as all other values for this subject were <133 mmHg. Subject ID (b) (6) (on fingolimod ODT) experienced SBP of 145 mmHg at 24 hours post-dose, from a baseline value of 128 mmHg. This observation appears to be isolated, as all other values for this subject were <140 mmHg. At end of study, this subject's SBP was 114 mmHg.

Diastolic Blood Pressure

In Study FGL-P01, no subjects experienced diastolic blood pressure (DBP) >100 mmHg during study participation. Median DBP over time is presented in Figure 19, and it appears that DBP decreased through hour 8 post-dose and then increased in a manner similar to that of heart rate.

Figure 19 (Reviewer). Median Change in Diastolic Blood Pressure Over Time, Study FGL-P01



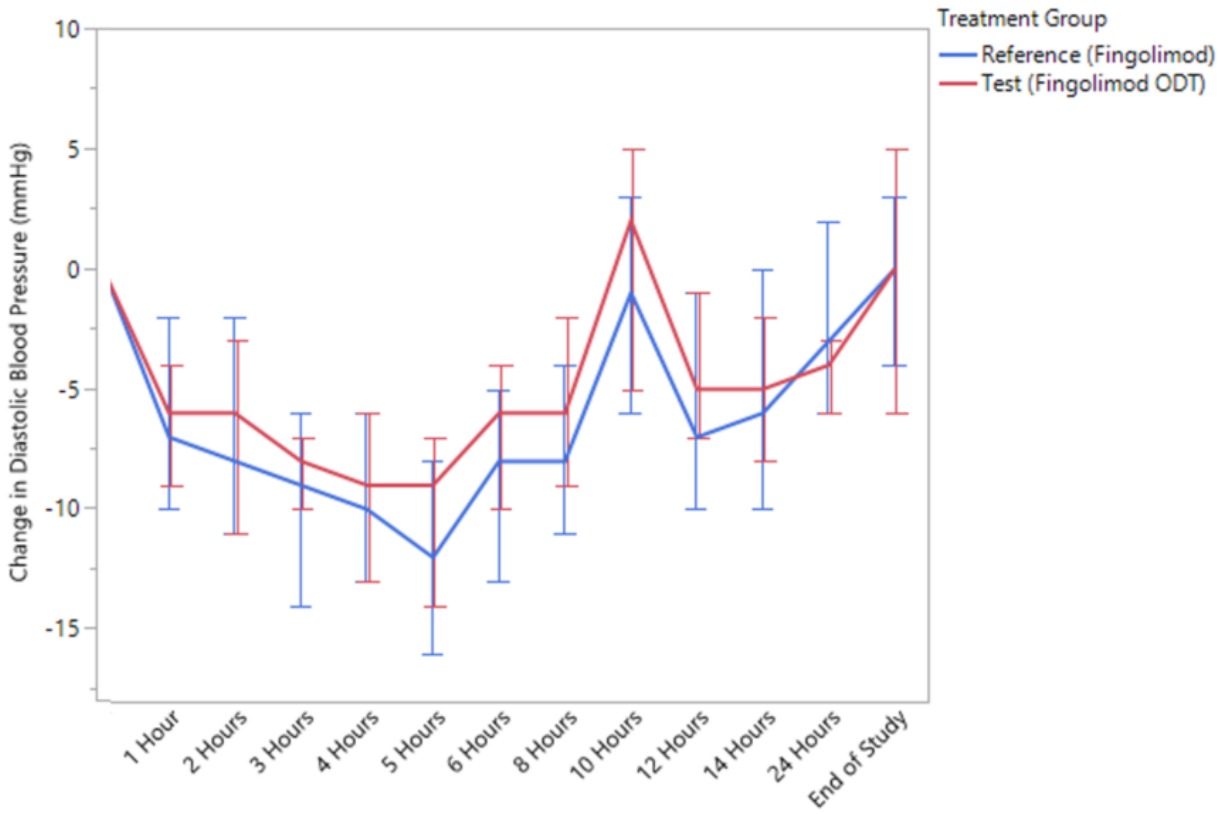
Error bars = Interquartile range; Treatment-1 = Fingolimod ODT with water; Treatment-2 = Fingolimod ODT without water; Treatment-3 = Fingolimod (reference)

Five patients in Study FGL-P01 experienced DBP <50 mmHg, which represented a 20 to 49 mmHg decrease from baseline. Four of these patients received Treatment-2 (Fingolimod ODT

without water), 1 received Treatment-1 (Fingolimod ODT with water), and 1 received Treatment-3 (Fingolimod). However, there does not appear to be a consistent trend for clinically significant DBP reduction demonstrated in Figure 19.

In Study FGL-P02, no subjects experienced diastolic blood pressure (DBP) >100 mmHg during study participation. Median DBP over time is presented in Figure 20, and it appears that DBP decreased through hour 5 post-dose and then increased in a manner similar to that of heart rate.

Figure 20 (Reviewer). Median Change in Diastolic Blood Pressure Over Time, Study FGL-P02



Error bars = Interquartile range

Reviewer comment: Neither Study FGL-P01 nor FGL-P02 suggest a trend for clinically significant consistent increases or decreases in systolic or diastolic blood pressure following a single dose of fingolimod or fingolimod ODT. The apparent increases in SBP and DBP at hour 10 post-dose observed in both studies in both treatment groups do not appear to be clinically significant. The existing labeling for Gilenya (fingolimod) describes a risk of hypertension, and the negotiated labeling for fingolimod ODT will similarly describe this risk.

Temperature

Temperature was recorded at screening and pre-dose. No subjects in Study FGL-P01 or FGL-P02 experienced temperature > 38.1°C during study participation.

8.4.8. Electrocardiograms (ECGs)

Fingolimod is known to have effects on heart rate and cardiac conduction at the first dose. ECG data was reviewed for abnormalities in PR interval, heart rate (discussed in Section 8.4.7), QTc interval (discussed in Section 8.4.9), and events of bradycardia and conduction abnormalities.

In Studies FGL-P01 and FGL-P02, ECGs were obtained at screening, pre-dose, 6 hours post-dose, 24 hours post-dose, and end of study.

PR interval

PR interval data, including changes from baseline, were reviewed for Studies FGL-P01 and FGL-P02.

In Study FGL-P01, the mean and median PR interval increased across all treatment groups, particularly at 6 hours post-dose (Table 22). This increase appeared to be similar between fingolimod and fingolimod ODT groups, and similar proportions of patients experienced PR interval >200 msec at 6 hours. The frequency of PR interval >200 msec decreased at 24 hours post-dose, and only one subject (on fingolimod ODT without water) had PR interval >200 msec at end of study (220 msec).

Table 22 (Reviewer). PR Interval on ECG, Study FGL-P01

Time	Parameter	Treatment-1 [Fingolimod ODT, with water] (N=25)	Treatment-2 [Fingolimod ODT, without water] (N=25)	Treatment-3 [Fingolimod, with water] (N=25)
Pre-Dose	Mean (SD)	161.4 (25.2)	168.0 (20.1)	161.0 (21.5)
	Median (IQR)	158.0 (32.0)	165.0 (24.5)	162.0 (28.0)
	Min, Max	110, 218	136, 208	112, 202
	N (%) of patients with PR >200 msec	2 (8.0)	1 (4.0)	1 (4.0)
6 Hours	Mean (SD)	170.2 (42.4)	170.4 (27.8)	169.8 (38.7)
	Median (IQR)	160.0 (30.0)	170.0 (28.0)	168.0 (44.0)
	Min, Max	114, 290	122, 228	116, 290
	Mean (SD) change from baseline	8.8 (25.8)	2.2 (16.4)	8.7 (27.1)
	Median (IQR) change from baseline	4.0 (18.0)	0 (14.0)	5.0 (36.0)
	Min, Max change from baseline	-30, 98	-38, 42	-36, 88
	N (%) of patients with PR >200 msec	4 (16.0)	5 (20.0)	4 (16.0)
24 Hours	Mean (SD)	156.4 (26.5)	164.9 (25.0)	159.4 (22.5)
	Median (IQR)	154.0 (40.0)	160.0 (22.0)	162.0 (32.0)
	Min, Max	122, 226	120, 226	112, 218
	Mean (SD) change from baseline	-5.0 (17.0)	-3.3 (11.9)	-1.5 (15.6)
	Median (IQR) change from baseline	-4.0 (16.0)	-2.0 (12.0)	-2.0 (22.0)
	Min, Max change from baseline	-56, 26	-32, 18	-34, 22
	N (%) of patients with PR >200 msec	2 (8.0)	3 (12.0)	1 (4.0)
End of Study	Mean (SD)	152.4 (22.1)	161.9 (20.0)	155.8 (18.5)
	Median (IQR)	150.0 (30.0)	170.0 (22.0)	154.0 (26.0)
	Min, Max	110, 194	122, 220	120, 190
	Mean (SD) change from baseline	-9.0 (9.1)	-6.2 (12.8)	-5.1 (10.0)
	Median (IQR) change from baseline	-8.0 (10.0)	-6.0 (24.0)	-4.0 (12.0)
	Min, Max change from baseline	-26, 16	-30, 14	-28, 20
	N (%) of patients with PR >200 msec	0 (0)	1 (4.0)	0 (0)

Source: ADEG, where ANL01FL = Y, by TRT01A

In Study FGL-P02, the increases in PR interval were not as apparent, including at 6 hours post-dose (Table 23). However, similar proportions of subjects in each treatment group (10.5%) experienced PR interval >200 msec at 6 hours. No subjects experienced a PR interval >200 msec 24 hours post-dose or at end of study.

Table 23 (Reviewer). PR Interval on ECG, Study FGL-P02

Time	Parameter	Reference (Fingolimod) [n = 19]	Test (Fingolimod ODT) [n = 19]
Pre-Dose	Mean (SD)	161.6 (17.1)	161.7 (19.2)
	Median (IQR)	162.0 (24.0)	156.0 (27.0)
	Min, Max	124, 190	128, 194
	N (%) of patients with PR >200 msec	0 (0)	0 (0)
6 Hours	Mean (SD)	163.5 (26.0)	168.5 (35.6)
	Median (IQR)	162.0 (33.0)	158.0 (33.0)
	Min, Max	116, 212	124, 272
	Mean (SD) change from baseline	1.9 (15.2)	6.8 (28.7)
	Median (IQR) change from baseline	0 (24.0)	-2.0 (10.0)
	Min, Max change from baseline	-20, 30	-12, 116
	N (%) of patients with PR >200 msec	2 (10.5)	2 (10.5)
24 Hours	Mean (SD)	160.3 (21.3)	158.6 (15.4)
	Median (IQR)	160.0 (29.0)	160.0 (19.0)
	Min, Max	108, 190	122, 190
	Mean (SD) change from baseline	-1.3 (9.9)	-3.1 (11.3)
	Median (IQR) change from baseline	-2.0 (13.0)	-4.0 (8.0)
	Min, Max change from baseline	-16, 22	-30, 24
	N (%) of patients with PR >200 msec	0 (0)	0 (0)
End of Study	Mean (SD)	159.5 (19.6)	160.3 (21.3)
	Median (IQR)	158.0 (31.0)	158.0 (34.0)
	Min, Max	114, 188	126, 200
	Mean (SD) change from baseline	-2.1 (9.0)	-1.4 (11.4)
	Median (IQR) change from baseline	-2.0 (9.0)	-4.0 (10.0)
	Min, Max change from baseline	-18, 18	-16, 36
	N (%) of patients with PR >200 msec	0 (0)	0 (0)

Source: ADEG, where ANL01FL = Y, by TRT01A

Overall Interpretation

The overall ECG interpretation was tabulated by treatment group for each study. In Study FGL-P01, no subjects had abnormal screening or pre-dose ECGs. As demonstrated in Table 24, between 0 and 16% of patients experienced ECG abnormalities at 6 hours post-dose, which was the most common timepoint at which to have an ECG abnormality in the study. All abnormalities except one case of sinus bradycardia with first degree AV block resolved by hour 24, and all ECGs were normal at end of study.

Table 24 (Reviewer). ECG Interpretations, Study FGL-P01

Finding	Treatment-1 (Fingolimod ODT) [n = 25] N (%)	Treatment-2 (Fingolimod ODT) [n = 25] N (%)	Treatment-3 (Fingolimod) [n = 25] N (%)
Screening			
Normal	25 (100.0)	25 (100.0)	25 (100.0)
Abnormal (CS[1])	0 (0)	0 (0)	0 (0)
Pre-Dose			
Normal	25 (100.0)	25 (100.0)	25 (100.0)
Abnormal (CS)	0 (0)	0 (0)	0 (0)
6 Hours			
Normal	21 (84.0)	25 (100.0)	22 (88.0)
Abnormal (CS)	4 (16.0)	0 (0)	3 (12.0)
Severe bradycardia with nodal escape	2 (8.0)	0 (0)	0 (0)
Sinus bradycardia with 1st degree AV block	2 (8.0)	0 (0)	0 (0)
Sinus bradycardia with 2nd degree AV block Mobitz I	0 (0)	0 (0)	1 (4.0)
Unusual P axis 2nd degree AV block	0 (0)	0 (0)	1 (4.0)
PR CS Asymptomatic	0 (0)	0 (0)	1 (4.0)
24 Hours			
Normal	24 (96.0)	25 (100.0)	25 (100.0)
Abnormal (CS)	1 (4.0)	0 (0)	0 (0)
Sinus bradycardia with 1st degree AV block	1 (4.0)	0 (0)	0 (0)
End of Study			
Normal	25 (100.0)	25 (100.0)	25 (100.0)
Abnormal (CS)	0 (0)	0 (0)	0 (0)
Unscheduled			
1st Degree AV Block	0 (0)	1 (4.0)	0 (0)
Sinus rhythm with 1st degree AV block	1 (4.0)	0 (0)	0 (0)

[1]CS: Clinically significant; Source: ADEG, where ANL01FL = Y, by TRT01A

In Study FGL-P02, no subjects had abnormal screening or pre-dose ECGs. As demonstrated in Table 25, 1 subject who received fingolimod ODT was noted to have sinus bradycardia with 1st degree AV block on ECG at 6 hours post-dose. No other clinically significant abnormal ECGs were reported in this study.

Table 25 (Reviewer). ECG Interpretations, Study FGL-P02

Finding	Reference (Fingolimod) [n = 19] N (%)	Test (Fingolimod ODT) [n = 19] N (%)
Screening		
Normal	19 (100.0)	19 (100.0)
Abnormal (CS[1])	0 (0)	0 (0)
Pre-Dose		
Normal	19 (100.0)	19 (100.0)
Abnormal (CS)	0 (0)	0 (0)
6 Hours		
Normal	19 (100.0)	18 (94.7)
Abnormal (CS)	0 (0)	1 (5.3)
Sinus bradycardia with 1st degree AV block	0 (0)	1 (5.3)
24 Hours		
Normal	19 (100.0)	19 (100.0)
Abnormal (CS)	0 (0)	0 (0)
End of Study		
Normal	19 (100.0)	19 (100.0)
Abnormal (CS)	0 (0)	0 (0)

[1]CS: Clinically significant; Source: ADEG, where ANL01FL = Y, by TRT01A

Reviewer comment: The observed abnormalities are consistent with the known safety profile of fingolimod, and clinically significant abnormalities occurred at similar frequencies between the fingolimod ODT and fingolimod groups. These abnormalities are captured in the TEAEs discussed in Sections 5.3.1 and 8.5.1. The current approved labeling for Gilenya (fingolimod) conveys these risks adequately. The negotiated labeling for fingolimod ODT will align with the Gilenya (fingolimod) labeling with respect to cardiac risks.

8.4.9. QT

Given the known impact on heart rate, fingolimod has the potential to prolong QTc as well. ECG data from each study were reviewed for evidence of QTc prolongation utilizing QT interval corrected via Fridericia's Correction formula at each available ECG timepoint.

In Study FGL-P01, the mean change from baseline in QTcF at 6 hours post-dose was 0.7 (SD 9.1) msec for those who received fingolimod ODT with water, -1.2 (SD 9.8) msec for those who received fingolimod ODT without water, and -1.7 (SD 10.6) msec for those who received fingolimod.

In Study FGL-P02, the mean change from baseline in QTcF at 6 hours post-dose was -0.5 (SD

5.8) msec for those who received fingolimod, and 2.1 (SD 12.7) msec for those who received fingolimod ODT.

No subjects in Studies FGL-P01 or FGL-P02 experienced QTc > 450 msec during study participation.

Reviewer comment: Overall, the QTcF changes observed in patients enrolled in Studies FGL-P01 and FGL-P02 were comparable between the groups and were not clinically significant.

8.4.10. Immunogenicity

Not applicable.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Cardiac Effects

Subjects in both studies experienced cardiac-related TEAEs that warrant further discussion, particularly given the known safety profile of fingolimod. The first dose of fingolimod necessitates monitoring due to the known risks of bradycardia and cardiac conduction abnormalities, both of which were observed in patients in Studies FGL-P01 and FGL-P02. A summary tabulation of all potential cardiac-related TEAEs is provided in Table 26.

Table 26 (Reviewer). All Cardiac-Related TEAEs, Studies FGL-P01 and FGL-P02

Adverse Event (Preferred Term)	Fingolimod ODT 1mg (n = 69)	Fingolimod (Gilenya) 1mg (n = 44)
Cardiac Disorders SOC	7 (10.1)[1]	3 (6.8)
Atrioventricular Block 1st degree	6 (8.7)	1 (2.3)
Atrioventricular Block 2nd degree	4 (5.8)	2 (4.5)
Dizziness	3 (4.3)	2 (4.5)
Nodal arrhythmia	2 (2.9)	0 (0)
Bradycardia	1 (1.4)	0 (0)
Chest discomfort	1 (1.4)	0 (0)

[1]Presented as n (%)

As discussed in Section 8.4.7, subjects experienced a decrease in heart rate, with a nadir at hour 8, following administration of study drug in both Studies FGL-P01 and FGL-P02. Overall, no clinically significant difference in decreases in heart rate were observed between fingolimod

and fingolimod ODT. Please see Sections 8.4.8 and 8.4.9 for ECG findings and QT interval-related findings, respectively.

The Division of Neurology 2 consulted the Division of Cardiology and Nephrology due to the observation of a slight numerical imbalance in the frequency of cardiac TEAEs between fingolimod and fingolimod ODT-treated subjects (particularly in Study FGL-P01), as demonstrated in Table 26. However, the consulting Division determined that this observation is not likely indicative of a significant differential safety signal between fingolimod and fingolimod ODT due to the small number of patients in each study, and the fact that the dose of fingolimod used in these studies (1mg) is higher than the approved dose in adults (0.5mg). Additionally, a determination of bioequivalence by Clinical Pharmacology further argues against a clinically meaningful differential safety profile.

> *Reviewer comment: Though there is an apparent numerical imbalance in cardiac TEAEs between fingolimod ODT and fingolimod, this does not likely represent a differential safety signal between the two products due to the small number of patients and the higher dose used in Studies FGL-P01 and FGL-P02. The cardiac risks of fingolimod are well-described in current labeling.*

8.5.2. Lymphopenia

No TEAEs related to cytopenias (including lymphopenia) were reported in either Study FGL-P01 or FGL-P02. Lymphopenia is the intended pharmacodynamic effect of fingolimod, as it reduces the number of circulating lymphocytes. Lymphopenia is unlikely to occur after a single dose of fingolimod. See Section 8.4.6 for detailed analysis of ALC in this submission.

8.5.3. Elevated Liver Enzymes

No TEAEs related to increased AST, ALT, ALP, or bilirubin were reported in either Study FGL-P01 or FGL-P02. No subjects in either study experienced AST or ALT > 2x ULN. A single dose of fingolimod is unlikely to cause significant liver toxicity in a healthy volunteer. See Section 8.4.6 for detailed analysis of liver enzyme data in this submission.

8.5.4. Palatability

The applicant administered product appreciation (palatability) questionnaires to subjects who received fingolimod ODT without water in Study FGL-P01, immediately post-dose then approximately 10 minutes post-dose. Immediately post-dose, subjects either somewhat or strongly agreed with the following statements: “I have a favorable overall opinion about the formulation” and “the formulation was easy to tolerate (did not cause discomfort during the administration) on the tongue/in the mouth. ” At 10 minutes post-dose, 16.0% of subjects strongly disagreed with the statement “there is no bitter after-taste left in my mouth after

intake."

In Study FGL-P02, the same questionnaire was administered to subjects who received fingolimod ODT. Again, immediately post-dose, all subjects either somewhat or strongly agreed with the statement "the formulation was easy to tolerate (did not cause discomfort during the administration) on the tongue/in the mouth. " At 10 minutes post-dose, most subjects had a favorable overall opinion about the formulation (84.2%), felt that the formulation was easy to tolerate (did not cause discomfort; 100%), and felt that there was no bitter aftertaste (94.7%).

Reviewer comment: Overall, it appears that this formulation was tolerated and considered "palatable" by subjects across Studies FGL-P01 and FGL-P02.

8.6. Safety Analyses by Demographic Subgroups

The size of demographic subgroups of interest within Studies FGL-P01 and FGL-P02 preclude meaningful conclusions regarding safety across these subgroups (Table 3; Table 6). Specifically, both studies had very few female, non-white subjects outside the 30 to 45 year age range.

8.7. Specific Safety Studies/Clinical Trials

Not applicable. As a 505(b)(2) submission, this NDA derives its safety database support from the application for the reference listed drug, Gilenya (fingolimod).

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Not applicable. Refer to the Clinical Review of Gilenya (fingolimod) NDA 022527 for discussion of nonclinical carcinogenicity studies.

8.8.2. Human Reproduction and Pregnancy

Not applicable. No pregnancies occurred in either Study FGL-P01 or FGL-P02. Refer to the Clinical Review of Gilenya (fingolimod) NDA 022527 for discussion of reproduction and pregnancy concerns.

8.8.3. Pediatrics and Assessment of Effects on Growth

Not applicable.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Not applicable. Fingolimod ODT is not currently marketed anywhere in the world.

8.9.2. Expectations on Safety in the Postmarket Setting

Expectations regarding safety are that the safety profile of fingolimod ODT will be identical to that of the reference listed drug, Gilenya (fingolimod).

8.9.3. Additional Safety Issues From Other Disciplines

No other safety issues were communicated at the time of submission of this review.

8.10. Integrated Assessment of Safety

Please refer to Table 9 for a summary tabulation of all TEAEs across both Phase 1 studies. Based upon this limited safety database across two Phase 1 studies, the safety profile of fingolimod ODT appears to be similar to that of the RLD, fingolimod.

9. Advisory Committee Meeting and Other External Consultations

Not applicable.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Please refer to final negotiated labeling.

10.2. Nonprescription Drug Labeling

Not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

Gilenya (fingolimod) does not have a REMS program, and no new safety issues were identified in this review that would necessitate a REMS program for fingolimod ODT.

12. Postmarketing Requirements and Commitments

No postmarketing requirements or commitments will be issued for this NDA.

13. Appendices

13.1. References

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13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): FGL-P01 and FGL-P02 (same investigators)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1 principal investigator, 10 sub-investigators		
Number of investigators who are Applicant employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator : 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐ (N/A)	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐ (N/A)	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0 (N/A)		
Is an attachment provided with the reason:	Yes ☐ (N/A)	No ☐ (Request explanation from Applicant)

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