Supplementary Appendix

Lublin et al, Oral fingolimod versus placebo in primary progressive multiple sclerosis: results of a large phase III, randomised trial, online appendix

Contents

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ADDITIONAL METHODOLOGICAL DETAILS

Inclusion and exclusion criteria

Inclusion criteria

General

1. Male or female

2. 25 through 65 years of age inclusive

3. Females of childbearing potential must:

- Have a negative pregnancy test at Baseline (prior to randomization) and
- Use simultaneously two forms of effective contraception during the treatment and 3-months after discontinuation of study medication

4. Sign written informed consent prior to participating in the study

Primary Progressive Multiple sclerosis

1. Diagnosis of primary progressive multiple sclerosis according to the 2005 Revised

McDonald criteria[1]

- One year of disease progression plus
    - Two of the following:
        - Positive brain MRI (nine T2 lesions or four or more T2 lesions with positive visual evoked potential)
        - Positive spinal cord MRI (2 focal T2 lesions)
        - Positive CSF
- Central review of the diagnostic criteria for PPMS will be required for all patients prior to randomization.

2. Duration of disease at Baseline

- Time since first reported symptoms between 2 and 10 years

3. Documented evidence of clinical disability progression in the 2 years prior to Screening

- Clinical disability progression should have been observed in each of the previous 2 years prior to Screening as per clinical judgment of the investigator.
- In addition, disability progression must be documented by an increase in the EDSS score of at least 0.5 points at any time point during the 2 years prior to Screening. Should documented EDSS scores not be available, a written summary of the clinical evidence of disability progression in the previous 2 years must be submitted for central review.

4. Disability status at Screening (V1 or V2)

- EDSS score of 3.5-6.0 inclusive
- Pyramidal functional system score of 2 or more
- 25'TWT less than 30 seconds.

Exclusion criteria

Patients who met any of the following exclusion criteria during the Pre-Randomization Phase were not eligible for enrollment in the study:

1. History of MS attack/relapse as per clinical judgement of the investigator.

2. Progressive disabling neurological disorder, other than PPMS.

3. Pure cerebellar progressive syndrome or pure visual progressive syndrome or a pure cognitive progressive syndrome.

4. Presence of cervical spinal cord compression on Screening MRI.

5. Relevant history of vitamin B12 deficit.

6. History of chronic active disease of the immune system other than MS which may require systemic immunosuppressive treatment or a known immunodeficiency syndrome.

7. History or presence of malignancy (except for successfully treated basal or squamous cell carcinoma of skin).

8. Known or 'new' diagnosis of diabetes mellitus (if Screening blood glucose is suspicious for diabetes (≥126 mg/dL or ≥7 mmol/L if fasting and ≥200 mg/dL or 11.1 mmol/L if random testing) a patient should be further evaluated for diabetes mellitus).

9. Diagnosis of macular oedema during Pre-randomization Phase (patients with a history of macular oedema will be allowed to enter the study provided that they do not have macular oedema at the ophthalmic Screening visit).

10. Evidence of syphilis, borreliosis, HIV, Hepatitis B, Hepatitis C infection or any other active systemic bacterial, viral or fungal infections.

11. Have received total lymphoid irradiation or bone marrow transplantation.

12. Have been treated with:

- Systemic corticosteroids or adrenocorticotropic hormones (ACTH) within 3 months prior to randomization
- Interferon-beta (IFN-b) or glatiramer acetate within 3 months prior to randomization
- Immunosuppressive medications such as azathioprine or methotrexate within 6 months prior to randomization
- Immunoglobulins and/or monoclonal antibodies within 6 months prior to randomization
- Any mitoxantrone during previous 5 years prior to randomization or evidence of cardiotoxicity following mitoxantrone or mitoxantrone at a total cumulative life-time dose of more than 60 mg/m^2
- Cladribine, cyclophosphamide at any time.

13. Any medically unstable condition, as assessed by the primary treating physician.

14. Any of the following cardiovascular conditions at screening:

- Myocardial infarction within the past 6 months prior to enrollment or current unstable ischemic heart disease
- History of angina pectoris due to coronary spasm or history of Raynaud's phenomenon
- Cardiac failure at time of Screening (Class III, according to NYHA Classification) or any severe cardiac disease as determined by the investigator
- History of cardiac arrest
- History of symptomatic bradycardia
- Resting pulse <55 bpm prior to randomization
- History of sick sinus syndrome or sino-atrial heart block
- History or presence of a second degree AV block or a third degree AV block or an increased QTc (Fridericia and Bazett) interval >440 ms on Screening ECG
- Arrhythmia requiring current treatment with Class III antiarrhythmic drugs (e.g., amiodarone, bretylium, sotalol, ibutilide, azimilide, dofetilide)
- History of a positive tilt test from workup for vasovagal syncope
- Hypertension, uncontrolled by medication.

15. Any of the following pulmonary conditions:

- Severe respiratory disease or pulmonary fibrosis
- Tuberculosis, except for history of successfully treated tuberculosis or history of prophylactic treatment after positive PPD skin reaction
- Abnormal chest x-ray, suggestive of active pulmonary disease

- Abnormal Pulmonary Function Tests: FEV_1 or FVC values lower than 70% of predicted value, D_LCO values lower than 60% of predicted value
- Patients receiving chronic (daily) therapies for asthma

16. Any of the following hepatic conditions:

- Known history of alcohol abuse, chronic liver or biliary disease
- Total or conjugated bilirubin greater than the upper limit of the normal range, unless in context of Gilbert's syndrome
- Alkaline phosphatase (AP) greater than 1.5 times the upper limit of the normal range
- AST (SGOT), ALT (SGPT) greater than 2 times the upper limit of the normal range
- Gamma-glutamyl-transferase (GGT) greater than 3 times the upper limit of the normal range

17. Any of the following abnormal laboratory values:

- Serum creatinine greater than 1.7 mg/dL (150 µmol/L)
- White blood cell (WBC) count <3,500/mm3 (<3.5 x 10^9/L)
- Lymphocyte count <800/mm3 (<0.8 x 10^9/L)

18. History of substance abuse (drug or alcohol) or any other factor (i.e., serious psychiatric condition) that may interfere with the subject's ability to cooperate and comply with the study procedures.

19. Unable to undergo MRI scans, including claustrophobia or history of hypersensitivity to gadolinium-DTPA.

20. Participation in any clinical research study evaluating another investigational drug or therapy within 6 months prior to randomization.

21. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.

22. Negative for varicella-zoster virus IgG antibodies at Screening.

23. Have received any live or live attenuated vaccines (including for varicella-zoster virus or measles) within 2 months prior to randomization.

Note: If a patient failed on one or more laboratory (or other) assessment criteria, as part of the Screening process, the assessment(s) may have been repeated at the discretion of the investigator provided the assessments are completed within the Screening period.

1. Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". Annals of neurology 2005;58:840-6.

Additional details on adverse events monitoring procedure

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. Study drug includes the investigational drug under evaluation and the comparator drug or placebo that is given during any phase of the study. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. All adverse events must be recorded on the Adverse Events eCRF with the following information:

- The severity grade (mild, moderate, severe)
- Its relationship to the study drug(s) (suspected/not suspected)
- Its duration (start and end dates or if continuing at final exam)
- Whether it constitutes a serious adverse event (SAE)

An SAE is defined as an event which:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
    - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of an SAE given above and not resulting in hospital admission
    - Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above.

Although MS attacks/relapses are considered medically significant and are frequently associated with hospitalization and thus, meet the definition for SAE, these events will be

reported on the MS attacks/relapse eCRF instead of the SAE form. However, if, in the judgment of the investigator, an MS attack/relapse is unusually severe and warrants specific notification, then an SAE form must be completed and submitted according the SAE reporting procedures.

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements. All adverse events should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e., further observation only); study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication given; non-drug therapy given; patient hospitalized/patient's hospitalization prolonged. The action taken to treat the adverse event should be recorded on the Adverse Event eCRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB) or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

Serious adverse event reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until 30 days after the patient has stopped study participation (defined as time of last dose of study drug taken or last visit whichever is later). Any SAEs experienced after this 30 day period should only be reported to Novartis if the investigator suspects a causal relationship to the study drug. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form. The investigator must assess the relationship to study drug, complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the local Novartis Clinical Safety & Epidemiology Department. The telephone and telecopy number of the contact persons in the local department of Clinical Safety and Epidemiology, specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported

SAE and giving the date of the original report. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation. If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study drug, a Clinical Safety & Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

Pregnancies

To ensure patient safety, each pregnancy in a patient on study drug must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the local Novartis Clinical Safety & Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

BASELINE CHARACTERISTICS ACCORDING TO COHORT AND STUDY GROUP

Characteristic	Fingolimod		Placebo (N=487)	Total (N=970)
	Cohort 1 1.25/0.5 mg (N=147)	Cohort 2 0.5 mg (N=336)		
Demographics				
Sex, n (%)				
Male	76 (51.7)	173 (51.5)	252 (51.7)	501 (51.6)
Female	71 (48.3)	163 (48.5)	235 (48.3)	469 (48.4)
Age (years)				
Median (range)	47.0 (25, 65)	49.0 (24, 65)	49.0 (27, 65)	49.0 (24, 65)
Mean (SD)	47.8 (8.5)	48.5 (8.6)	48.5 (8.3)	48.4 (8.4)
Age distribution (years), n (%)				
18–30	3 (2.0)	6 (1.8)	4 (0.8)	13 (1.3)
31–40	22 (15.0)	60 (17.9)	90 (18.5)	172 (17.7)
41–50	68 (46.3)	127 (37.8)	194 (39.8)	389 (40.1)
>50	54 (36.7)	143 (42.6)	199 (40.9)	396 (40.8)
Race, n (%)				
Caucasian	142 (96.6)	324 (96.4)	467 (95.9)	933 (96.2)
Black	0 (0)	7 (2.1)	6 (1.2)	13 (1.3)
Asian	1 (0.7)	0 (0)	4 (0.8)	5 (0.5)
Native American	1 (0.7)	0 (0)	0 (0)	1 (0.1)
Other	3 (2.0)	5 (1.5)	10 (2.1)	18 (1.9)
Clinical characteristics				
Disease duration since diagnosis, years				
Mean (SD)	2.72 (2.2)	2.80 (2.6)	2.91 (2.3)	2.84 (2.4)
Median (range)	2.02 (0.1, 9.9)	1.98 (0.1, 20.1)	2.35 (0.1, 10.4)	2.13 (0.1, 20.1)
Disease duration since onset of symptoms, years				
Mean (SD)	5.8 (2.5)	5.8 (2.5)	5.9 (2.4)	5.8 (2.4)
Median (range)	5.6 (2, 17)	5.4 (1, 20)	5.7 (2, 15)	5.6 (1, 20)
EDSS score				
Mean (SD)	4.55 (1.00)	4.70 (1.03)	4.66 (1.03)	4.66 (1.03)
Median (range)	4.5 (2.5, 6.5)	4.5 (2.0, 6.5)	4.5 (2.0, 6.5)	4.5 (2.0, 6.5)
25'TWT score (seconds)				
Mean (SD)	7.65 (3.14)	9.05 (5.61)	9.09 (7.62)	8.86 (6.46)
Median (range)	7.05 (3.8, 25.5)	7.23 (3.7, 41.0)	6.90 (3.1, 117.7)	7.05 (3.1, 117.7)
9-HPT score *(seconds)				
Mean (SD)	28.92 (11.86)	28.44 (11.47)	28.79 (16.45)	28.69 (14.23)
Median (range)	26.05 (15.2, 95.4)	25.26 (17.2, 115.8)	25.33 (13.9, 218.3)	25.33 (13.9, 218.3)
PASAT 3 score				

Mean (SD)	45.7 (12.8)	44.3 (13.0)	45.0 (12.5)	44.9 (12.7)
Median (range)	50.0 (0, 60)	48.0 (4, 60)	48.0 (0, 60)	48.5 (0, 60)
History of DMT use, n (%)				
Treatment naïve	120 (81.6)	272 (81.0)	372 (76.4)	764 (78.8)
Any IFN β	15 (10.2)	36 (10.7)	66 (13.6)	117 (12.1)
Natalizumab	0 (0.0)	3 (0.9)	2 (0.4)	5 (0.5)
Glatiramer acetate	5 (3.4)	26 (7.7)	33 (6.8)	64 (6.6)
Other MS medicines	11 (7.5)	19 (5.7)	36 (7.4)	66 (6.8)
MRI characteristics				
Gd-enhancing lesions				
N	147	336	484	967
Mean (SD)	0.2 (0.52)	0.3 (1.10)	0.3 (1.03)	0.3 (1.00)
Median (range)	0 (0, 4)	0 (0, 10)	0 (0, 14)	0 (0, 14)
n, (%) free of Gd+	130 (88.4)	290 (86.3)	423 (87.4)	843 (87.2)
Total volume of T2 lesions at baseline (mm^3)				
N	146	336	485	967
Mean (SD)	9594.2 (12446.2)	9442.7 (10179.7)	10038.2 (13030.9)	9764.2 (12014.4)
Median (range)	6041.5 (217, 110821)	6109.5 (145, 52484)	5271.0 (44, 91964)	5758.0 (44, 110821)
Normalized brain volume (cm^3)				
N	145	335	483	963
Mean (SD)	1493.4 (89.0)	1490.9 (86.5)	1491.7 (84.9)	1491.7 (86.0)
Median (range)	1497.0 (1256, 1752)	1491.0 (1243, 1725)	1498.0 (1206, 1725)	1494.0 (1206, 1752)

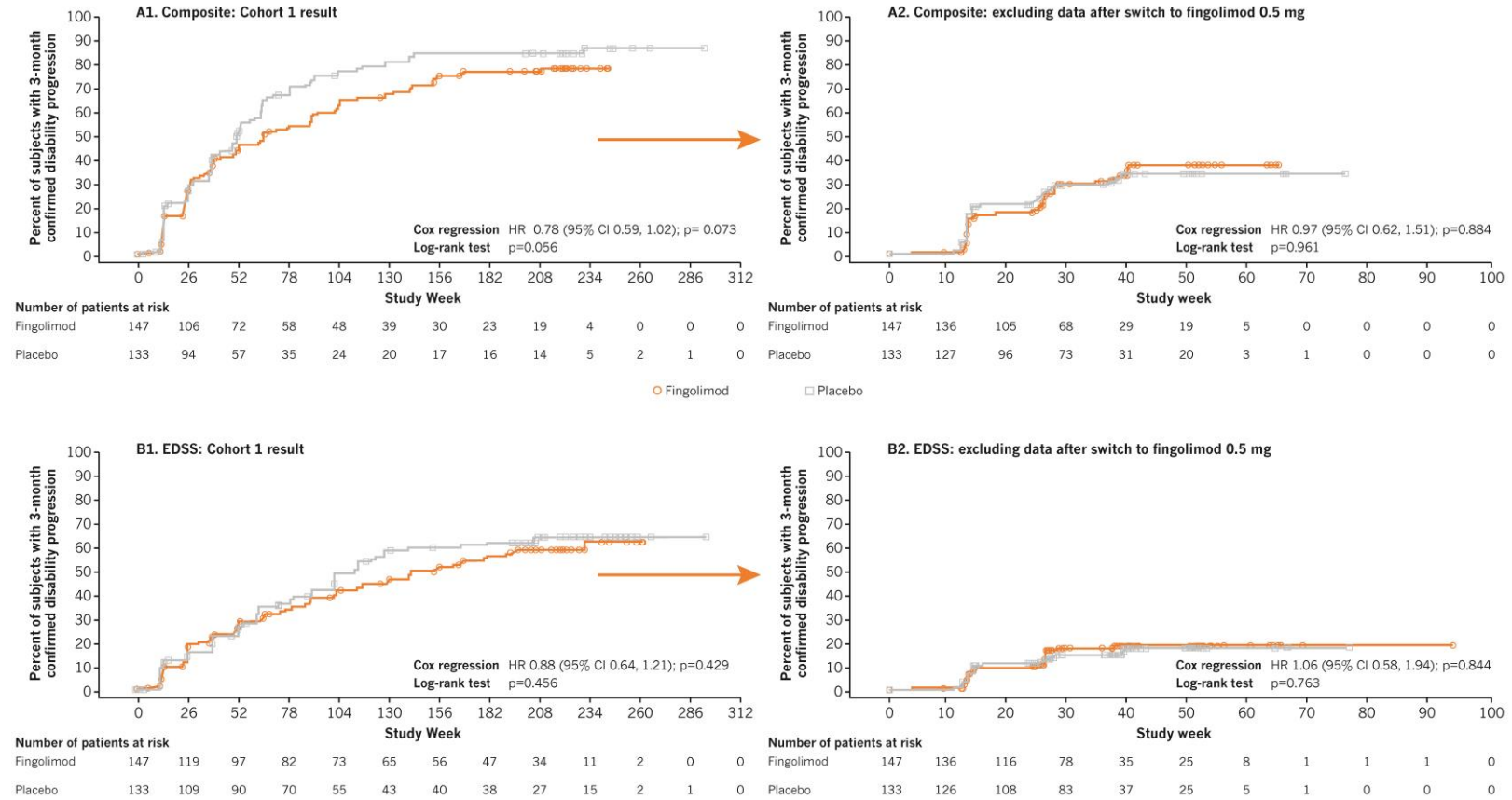
EFFICACY ACCORDING TO STUDY COHORT

The risk reductions (RRs) for 3-month confirmed disability progression according to the primary composite endpoint were 22.5% (p=0.073) and –4.00% (p>0.6) for Cohort 1 and Cohort 2, respectively. Notably, the result for Cohort 2 was similar to that of the overall efficacy cohort (RR 5.05%; p=0.544), strengthening the validity of combining the Cohort 1 and 2 placebo groups.

While the effect remained non-significant in both cohorts, and was underpowered to detect a difference in Cohort 1, it was deemed necessary to review the possibility that a higher dose may have had a stronger effect on the primary endpoint. Therefore, a *post hoc* analysis was performed for patients in Cohort 1 in which only data for the period when patients were receiving fingolimod 1.25 mg or placebo was included (Figure S1). This resulted in a much lower treatment difference (risk reduction 3.3%, p=0.884), arguing against a dose effect (Figure S1). Furthermore, the risk reductions in 3-month confirmed disability progression as assessed by EDSS did not support a dose effect (Cohort 1: 12.2%, p>0.4; Cohort 2: 6.5%, p>0.5).

The apparent dose effect is thought to be due to a random difference in the rate of progression between the placebo groups of Cohort 1 and Cohort 2 as measured by the primary composite endpoint. While the proportion of patients with 3-month confirmed disability progression at Month 60 was similar for fingolimod 1.25/0.5 mg in Cohort 1 and fingolimod 0.5 mg in Cohort 2 (78.6% and 77.2%, respectively), the rates for the respective placebo groups were 87.1% and 74.2%.

Figure S1. Efficacy in cohort 1



ADVERSE EVENTS ACCORDING TO COHORT AND TREATMENT GROUP

Event	Fingolimod		Placebo (n=487)
	Cohort 1 1.25/0.5 mg (n=147)	Cohort 2 0.5 mg (n=336)	
All events, n (%)			
At least one adverse event	144 (98.0)	324 (96.4)	463 (95.1)
Any adverse event leading to discontinuation of study drug*	33 (22.4)	52 (15.5)	36 (7.4)
Any serious adverse event	38 (25.9)	84 (25.0)	117 (24.0)
Abnormal laboratory value leading to discontinuation of study drug	9 (6.1)	27 (8.0)	6 (1.2)
Death	2 (1.4)	1 (0.3)	2 (0.4)
Most common AEs (>5% in any group, preferred term), n (%)			
Nasopharyngitis	40 (27.2)	78 (23.2)	135 (27.7)
Headache	28 (19.0)	56 (16.7)	77 (15.8)
Urinary tract infection	21 (14.3)	50 (14.9)	79 (16.2)
Fall	32 (21.8)	47 (14.0)	94 (19.3)
Hypertension	23 (15.6)	43 (12.8)	28 (5.7)
Alanine aminotransferase increased	17 (11.6)	39 (11.6)	9 (1.8)
Back pain	16 (10.9)	37 (11.0)	75 (15.4)
Upper respiratory tract infection	21 (14.3)	37 (11.0)	58 (11.9)
Gamma-glutamyltransferase increased	19 (12.9)	31 (9.2)	3 (0.6)
Arthralgia	13 (8.8)	30 (8.9)	49 (10.1)
Constipation	10 (6.8)	29 (8.6)	36 (7.4)
Influenza	14 (9.5)	29 (8.6)	43 (8.8)
Cough	8 (5.4)	28 (8.3)	34 (7.0)
Fatigue	16 (10.9)	25 (7.4)	44 (9.0)
Nausea	14 (9.5)	21 (6.3)	19 (3.9)
Pain in extremity	9 (6.1)	21 (6.3)	36 (7.4)
Dizziness	10 (6.8)	19 (5.7)	29 (6.0)
Lymphopenia	13 (8.8)	19 (5.7)	0 (0.0)
Pyrexia	8 (5.4)	18 (5.4)	21 (4.3)
Abdominal pain upper	3 (2.0)	17 (5.1)	12 (2.5)
Bronchitis	10 (6.8)	16 (4.8)	21 (4.3)
Melanocytic naevus	22 (15.0)	16 (4.8)	31 (6.4)

Blood cholesterol increased	8 (5.4)	15 (4.5)	16 (3.3)
Depression	11 (7.5)	15 (4.5)	39 (8.0)
Diarrhoea	13 (8.8)	15 (4.5)	18 (3.7)
Eczema	8 (5.4)	15 (4.5)	19 (3.9)
Gait disturbance	10 (6.8)	15 (4.5)	24 (4.9)
Dyspnoea	8 (5.4)	14 (4.2)	16 (3.3)
Gastroenteritis	10 (6.8)	14 (4.2)	23 (4.7)
Hypercholesterolaemia	10 (6.8)	13 (3.9)	19 (3.9)
Insomnia	8 (5.4)	12 (3.6)	29 (6.0)
Seborrhoeic keratosis	10 (6.8)	12 (3.6)	14 (2.9)
Cystitis	10 (6.8)	9 (2.7)	18 (3.7)
Adverse events of special interest, n (%)			
Cardiovascular disorders			
Bradycardia	2 (1.4)	5 (1.5)	1 (0.2)
Sinus Bradycardia	1 (0.7)	0	0
AV block first degree	0	3 (0.9)	6 (1.2)
AV block second degree	1 (0.7)	1 (0.3)	0
Myocardial infarction	1 (0.7)	1 (0.3)	0
Myocardial ischemia	0	1 (0.3)	0
Angina pectoris	0	1 (0.3)	3 (0.6)
Hypertensive crisis	0	0	1 (0.2)
Secondary hypertension	0	1 (0.3)	0
Hypotension	1 (0.7)	2 (0.6)	5 (1.0)
Syncope / Presyncope	3 (2.0)	7 (2.1)	9 (1.8)
Macular Oedema			
Macular Oedema	2 (1.4)	6 (1.8)	6 (1.2)
Cystoid ME	0	1 (0.3)	1 (0.2)
Infection and Infestations			
Bronchitis	10 (6.8)	16 (4.8)	21 (4.3)
Cystitis/*bacterial*	10 (6.8)	9 (2.7)	19 (3.9)
Tinea versicolour	5 (3.4)	6 (1.8)	8 (1.6)
Pneumonia/Bronchopneumonia	3 (2.0)	6 (1.8)	8 (1.6)
Rare Infection and Infestations			
Meningitis	0	0	1 (0.2)
Systemic mycosis	0	1 (0.3)	0
Pulmonary sepsis	0	0	1 (0.2)
Urosepsis	1 (0.7)	0	2 (0.4)
Serratia sepsis	0	0	1 (0.2)
Herpes zoster/VZV			
Herpes zoster	3 (2.0)	10 (3.0)	9 (1.8)
Herpes zoster meningomyelitis	0	1 (0.3)	0
Herpes zoster *neurological*	0	0	1 (0.2)
Herpes zoster oticus/ophthalmic	0	0	1 (0.2)
Hepatobiliary disorders			

Hepatocellular injury	0	2 (0.6)	0
Hepatic function abnormal	0	1 (0.3)	1 (0.2)
Hyperbilirubinemia	1 (0.7)	1 (0.3)	0
Drug-induced liver injury	1 (0.7)	0	0
Hepatitis toxic	1 (0.7)	0	0
Skin cancer			
Basal cell carcinoma	1 (0.7)	14 (4.2)	9 (1.8)
Squamous cell carcinoma/*of skin (comb.)*	0	6 (1.8)	1 (0.2)
Malignant melanoma/ *in situ (comb.)*	1 (0.7)	1 (0.3)	0
Other malignancies			
Breast cancer	2 (1.4)	1 (0.3)	0
Invasive ductal carcinoma	1 (0.7)	0	0
Invasive lobular breast carc.	0	0	1 (0.2)
B-cell lymphoma	0	1 (0.3)	0
Non-Hodgkin's lymphoma	1 (0.7)	1 (0.3)	0
Lung neoplasm malignant	0	1 (0.3)	0
Ovarian cancer	0	1 (0.3)	0
Prostate cancer	0	1 (0.3)	1 (0.2)
Respiratory			
Dyspnoea	8 (5.4)	14 (4.2)	16 (3.3)
Dyspnoea exertional	2 (1.4)	0	5 (1.0)
Nocturnal Dyspnoea	1 (0.7)	0	0
Seizures/Convulsions			
Convulsion	1 (0.7)	2 (0.6)	2 (0.4)
Epilepsy	0	1 (0.3)	0
Generalized tonic-clonic seizure	0	0	1 (0.2)
Status epilepticus	0	0	1 (0.2)
Investigations			
Blood cholesterol increased	8 (5.4)	15 (4.5)	16 (3.3)
Blood triglycerides increased	3 (2.0)	9 (2.7)	9 (1.8)
Low density lipoprotein increased	4 (2.7)	7 (2.1)	3 (0.6)
Weight increased	2 (1.4)	5 (1.5)	1 (0.2)
Carbon monoxide diffusion capacity decreased.	5 (3.4)	7 (2.1)	8 (1.6)

*Any adverse event leading to discontinuation of the study drug includes events occurring in patients whose primary or secondary reason for discontinuing the study drug was an adverse event (including abnormal laboratory findings).