Efficacy and Safety of Teriflunomide in Patients With Relapsing Multiple Sclerosis and Treated With Interferon-beta (TERACLES)

ClinicalTrials.gov Identifier: NCT01252355

Recruitment Status : Terminated (Sponsor decision to prematurely stop the study, not linked to any safety concern.)
First Posted : December 3, 2010
Results First Posted : May 22, 2014
Last Update Posted : June 9, 2014

Sponsor:
Sanofi

Information provided by (Responsible Party):
Sanofi

Study Description

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Brief Summary:

The primary objective was to demonstrate the effect of teriflunomide, in comparison to placebo, on frequency of Multiple Sclerosis (MS) relapses in patients with relapsing forms of MS who are treated with Interferon-beta (IFN-beta).

The secondary objectives were:

- Assess the effect of teriflunomide, in comparison to placebo, when added to IFN-beta on:
  - Disease activity as measured by brain Magnetic Resonance Imaging (MRI)
  - Disability progression
  - Burden of disease and disease progression as measured by brain MRI
- Evaluate the safety and tolerability of teriflunomide when added to IFN-beta therapy
- Assess the pharmacokinetics of teriflunomide in use in addition to baseline IFN-beta therapy
- Assess associations between variations in genes and clinical outcomes (safety and efficacy)
- Assess other measures of efficacy of teriflunomide such as fatigue and health-related quality of life
- Assess measures of health economics (hospitalization due to relapse, including the length of stay and any admission to intensive care unit)

Condition or disease	Intervention/treatment	Phase
Multiple Sclerosis Relapse	Drug: Teriflunomide Drug: Placebo (for teriflunomide) Drug: Interferon-beta (IFN-beta)	Phase 3

Detailed Description:

The study period per patient was expected to be between 56 and 160 weeks depending on when the patient was randomized and this included the following:

- a screening period up to 4 weeks,
- a treatment period expected to be between 48 and 152 weeks,
- 4-week post rapid elimination follow-up period.

Patients were to continue on treatment until a fixed common end date which was approximately 48 weeks after randomization of the last patient.

For those patients who completed the treatment period, a long term extension study of approximately 1 year (including teriflunomide alone) was initially planned to be proposed.

Study Design

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Study Type : Interventional (Clinical Trial)

Actual Enrollment :	534 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Triple (Participant, Investigator, Outcomes Assessor)
Primary Purpose:	Treatment
Official Title:	A Multi-center Double-blind Parallel-group Placebo-controlled Study of the Efficacy and Safety of Teriflunomide in Patients With Relapsing Multiple Sclerosis Who Are Treated With Interferon-beta
Study Start Date :	January 2011
Actual Primary Completion Date :	April 2013
Actual Study Completion Date :	April 2013

Resource links provided by the National Library of Medicine

Genetics Home Reference related topics:
Multiple sclerosis

MedlinePlus related topics: Multiple Sclerosis

Drug Information available for: Interferon Interferon beta Teriflunomide

U.S. FDA Resources

Arms and Interventions

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Arm	Intervention/treatment
Experimental: Teriflunomide 7 mg + IFN-beta Teriflunomide 7 milligram (mg) once a day concomitantly with IFN-beta therapy.	Drug: Teriflunomide Film-coated tablet Oral administration Other Name: HMR1726 Drug: Interferon-beta (IFN-beta) Any of the IFN-beta which are approved for marketed use in the country where the patient is

	enrolled. Administration according to the package insert.
Experimental: Teriflunomide 14 mg + IFN-beta Teriflunomide 14 mg once a day concomitantly with IFN-beta therapy.	Drug: Teriflunomide Film-coated tablet Oral administration Other Name: HMR1726 Drug: Interferon-beta (IFN-beta) Any of the IFN-beta which are approved for marketed use in the country where the patient is enrolled. Administration according to the package insert.
Placebo Comparator: Placebo + IFN-beta Placebo (for teriflunomide) once a day concomitantly with IFN-beta therapy.	Drug: Placebo (for teriflunomide) Film-coated tablet Oral administration Drug: Interferon-beta (IFN-beta) Any of the IFN-beta which are approved for marketed use in the country where the patient is enrolled. Administration according to the package insert.

Outcome Measures

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Primary Outcome Measures :

1. Annualized Relapse Rate (ARR) (Poisson Regression Estimates) [Time Frame: Up to a maximum of 108 weeks depending on time of enrollment]

   ARR is the total number of confirmed relapses that occurred during the treatment period divided by the total number of patient-years treated. Each episode of relapse (appearance, or

worsening of a clinical symptom that was stable for at least 30 days, that persisted for a minimum of 24 hours in the absence of fever) was to be confirmed by an increase in Expanded Disability Status Scale (EDSS) score or Functional System scores. To account for the different treatment durations among participants, a Poisson regression model with robust error variance was used (total number of confirmed relapses as response variable; log-transformed treatment duration as "offset" variable; treatment group, region of enrollment and IFN-beta dose stratum, and number of relapses in the year prior to randomization as covariates).

Secondary Outcome Measures :

1. Brain Magnetic Resonance Imaging (MRI) Assessment: Number of Gadolinium Enhancing (Gd-enhancing) T1-lesions Per Scan (Poisson Regression Estimates) [Time Frame: Up to a maximum of 108 weeks depending on time of enrollment]

   Number of Gd-enhancing T1-lesions per scan is the total number of Gd-enhancing T1-lesions that occurred during the treatment period divided by the total number of scans performed during the treatment period. To account for the different number of scans among participants, a Poisson regression model with robust error variance was used (total number of Gd-enhancing T1-lesions as response variable; log-transformed number of scans as offset variable; treatment group, region of enrollment, IFN-beta dose stratum and baseline number of Gd-enhancing T1-lesions as covariates).

2. Time to 12-Week Sustained Disability Progression [Time Frame: Up to a maximum of 108 weeks depending on time of enrollment]

   The 12-week sustained disability progression was defined as an increase from baseline of at least 1-point in EDSS score (at least 0.5-point for participants with baseline EDSS score >5.5) that persisted for at least 12 weeks. Probability of disability progression was to be estimated using Kaplan-Meier method.

3. Brain MRI Assessment: Volume of Gd-enhancing T1-lesions Per MRI Scan [Time Frame: Up to a maximum of 108 weeks depending on time of enrollment]

   Total volume of Gd-enhancing T1-lesions per scan is the sum of the volumes of Gd-enhancing T1-lesions observed during the treatment period divided by the total number of scans performed during the treatment period.

4. Brain MRI Assessment: Change From Baseline in Total Lesion Volume (Burden of Disease) at

Week 24 [Time Frame: Baseline, Week 24]

The total lesion volume (burden of disease) is the total volumes of hyperintense on T2 plus hypointense on T1 as measured by MRI scan. Least-square means were estimated using a Mixed-effect model with repeated measures (MMRM) on cubic root transformed volume data with factors for treatment, region, IFN-beta dose stratum, visit, treatment-by-visit interaction, cubic root transformed baseline burden of disease, and baseline-by-visit interaction.

5. Time to Relapse: Kaplan-Meier Estimates of the Probability of no Relapse at Week 24, 48, and 72 [Time Frame: Up to a maximum of 108 weeks depending on time of enrollment]

   Probability of no relapse at 24, 48 and 72 weeks was estimated using Kaplan-Meier method on the time to relapse defined as the time from randomization to first EDSS confirmed relapse. Participants free of confirmed relapse (no EDSS confirmed relapse observed on treatment) were censored at the date of the last study drug intake. Kaplan-Meier method consists in computing probabilities of non-occurrence of event at any observed time of event and multiplying successive probabilities for time <=t by any earlier computed probabilities to estimate the probability of being event-free for the amount of time t.

6. Change From Baseline in Fatigue Impact Scale (FIS) Total Score at Week 24 [Time Frame: Baseline, Week 24]

   FIS is a participant-reported scale that qualifies the impact of fatigue on daily life in participants with MS.

7. Change From Baseline in Short Form Generic Health Survey - 36 Items, Version 2 (SF-36v2) Summary Scores at Week 24 [Time Frame: Baseline, Week 24]

   SF-36 scale is a generic, self-administered, health-related quality-of-life (QOL) instrument.

8. Resource Utilization When Relapse [Time Frame: Up to a maximum of 108 weeks depending on time of enrollment]

   Resource utilization each time a participant experiences an MS relapse, specifically the number of hospitalizations, the number of over night spent in the hospital and number of intensive care admissions if hospitalized were to be reported.

9. Overview of Adverse Events (AEs) [Time Frame: First study drug intake up to 28 days after last study drug intake, for up to 112 weeks]

AEs are any unfavorable and unintended sign, symptom, syndrome, or illness observed by the investigator or reported by the participant during the study.

Other Outcome Measures:

1. Liver Function: Number of Participants With Potentially Clinically Significant Abnormalities (PCSA) [Time Frame: First study drug intake up to 28 days after last study drug intake, for up to 112 weeks]

   PCSA values are abnormal values considered medically important by the Sponsor according to predefined criteria based on literature review. Hepatic parameters thresholds were defined as follows: Alanine Aminotransferase (ALT) >3, 5 or 10 Upper Limit of Normal (ULN); Aspartate Aminotransferase (AST) >3, 5 or 10 ULN; Alkaline Phosphatase >1.5 ULN; Total Bilirubin (TB) >1.5 ULN; and ALT >3 ULN and TB >2 ULN.

Eligibility Criteria

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Ages Eligible for Study:	18 Years to 55 Years (Adult)
Sexes Eligible for Study:	All
Accepts Healthy Volunteers:	No

Criteria

Inclusion criteria :

- Patient with relapsing forms of MS treated with IFN-beta
- Stable dose of IFN-beta (approved brand) for at least 6 months prior to randomization

- Disease activity in the 12 months prior to randomization and after first 3 months of IFN-beta treatment (defined by at least 1 relapse supported by EDSS or equivalent neurological examination, or, at least 1 brain or spinal cord MRI with at least one T1 gadolinium enhancing lesion)

Exclusion criteria:

- McDonald criteria for MS diagnosis not met at time of screening visit
- EDSS score greater than (>) 5.5 at randomization visit
- A relapse within 30 days prior randomization
- Persistent significant or severe infection
- Patients must not have used adrenocorticotrophic hormone or systemic corticosteroids for 2 weeks prior to randomization
- Prior or concomitant use of cytokine therapy (except baseline interferons), glatiramer acetate or intravenous immunoglobulins in the 3 months preceding randomization
- Liver function impairment or persisting elevations (confirmed by retest) of alanine aminotransferase (ALT), aspartate aminotransferase (AST), or direct bilirubin greater than 2 times the upper limit of normal range (ULN)
- Active hepatitis or hepatobiliary disease or known history of severe hepatitis
- Pregnant or breast-feeding women or those who were planning to become pregnant during the study
- Significantly impaired bone marrow function or significant anemia, leukopenia, or thrombocytopenia
- Human Immunodeficiency Virus (HIV) positive
- Known history of active tuberculosis not adequately treated
- Prior use within 2 years preceding randomization or concomitant use of cladribine and mitoxantrone
- Prior use within 6 months preceding randomization or concomitant use of natalizumab, or any other immunosuppressive agents such as azathioprine, cyclophosphamide, cyclosporine, methotrexate, mycophenolate, or fingolimod

The above information is not intended to contain all considerations relevant to a patient's potential participation in a clinical trial.

Contacts and Locations

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Information from the National Library of Medicine

To learn more about this study, you or your doctor may contact the study research staff using the contact information provided by the sponsor.

Please refer to this study by its ClinicalTrials.gov identifier (NCT number):
NCT01252355

Show 185 Study Locations

Sponsors and Collaborators

Sanofi

Investigators

Study Director: Clinical Sciences & Operations Sanofi

More Information

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Responsible Party:	Sanofi
ClinicalTrials.gov Identifier:	NCT01252355 History of Changes
Other Study ID Numbers:	EFC6058
	2010-023172-12 (EudraCT Number)
	U1111-1115-2414 (Other Identifier: UTN)
First Posted:	December 3, 2010 Key Record Dates
Results First Posted:	May 22, 2014
Last Update Posted:	June 9, 2014
Last Verified:	May 2014

Additional relevant MeSH terms:

Multiple Sclerosis
Sclerosis
Pathologic Processes
Demyelinating Autoimmune Diseases, CNS
Autoimmune Diseases of the Nervous System
Nervous System Diseases
Demyelinating Diseases
Autoimmune Diseases

Immune System Diseases
Interferons
Interferon-beta
Antineoplastic Agents
Antiviral Agents
Anti-Infective Agents
Immunologic Factors
Physiological Effects of Drugs