Teriflunomide and alemtuzumab are not approved for the treatment of MS and should not be used in MS patients outside of a controlled clinical trial.

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If you have a specific research request or proposal, please contact Genzyme Medical Information at 1-800-745-4447, option 2, Monday - Friday, 8:00 AM - 6:00 PM EST, or contact a Genzyme Medical Science Liaison.

FOR HEALTH CARE PROFESSIONAL INFORMATION ONLY
As a Sanofi company, Genzyme is dedicated to making a distinct positive impact in the lives of patients with multiple sclerosis (MS) and their families. We are committed to becoming a true partner to the MS community by developing innovative therapies to address this community’s unmet needs.

We strive to deliver scientific advancements that will significantly impact the future of MS therapy. That means understanding the diverse needs of patients with MS in order to develop targeted solutions for individuals at various stages of the disease.

Over the past decade, we have developed 2 novel, targeted approaches to the treatment of patients with relapsing forms of MS (RMS): teriflunomide, an investigational once-daily oral immunomodulatory agent, and alemtuzumab, an investigational humanized monoclonal antibody.

The Genzyme MS development program includes extensive clinical trials involving over 4000 patients. Alemtuzumab and teriflunomide may offer alternative treatment options for patients across the relapsing MS spectrum.

**Genzyme MS Clinical Trials Development Program**

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<tr>
<th>Teriflunomide</th>
<th>DESIGN</th>
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<th>STATUS</th>
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<td>CDMS</td>
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**Teriflunomide**

An investigational oral immunomodulatory agent

**Teriflunomide Mechanism of Action**

- The effect of teriflunomide in MS may arise from its ability to selectively and reversibly inhibit the de novo pyrimidine synthesis pathway, thus blocking the activation and proliferation of stimulated T and B lymphocytes in the periphery<sup>12</sup>
- Resting lymphocytes have a much lower requirement for pyrimidines, which is fulfilled through a separate salvage pathway that recycles available molecules back to pyrimidines. The pyrimidine salvage pathway does not appear to be affected by teriflunomide, so basic homeostatic cell functions of resting lymphocytes are preserved and normal immune surveillance is maintained<sup>13</sup>

The exact mechanism by which teriflunomide exerts its therapeutic effect in MS is not fully understood, but may include reduced number of activated lymphocytes in CNS. Studies suggest that teriflunomide diminishes the number of stimulated lymphocytes in the periphery available to migrate into the CNS, limiting “over-activation” of immune responses that can contribute to new MS disease activity.<sup>12,13</sup>

**Alemtuzumab**

An investigational humanized monoclonal antibody

**Alemtuzumab Mechanism of Action**

- As alemtuzumab binds to CD52, it causes lysis of T and B lymphocytes involved in the pathogenesis of MS. Other immune cells are depleted only minimally and transiently<sup>14</sup>
- Decreased levels of circulating lymphocytes may cause a reduction in the inflammatory processes that are associated with MS<sup>15</sup>

The mechanism by which alemtuzumab exerts its therapeutic effects in MS is unknown, but may involve immunomodulation through the depletion and repopulation of lymphocytes. Studies suggest that alemtuzumab’s clinical efficacy may involve reconditioning the immune system through depletion of autoreactive lymphocytes and enhancing regulatory T cells during repopulation.<sup>15</sup>

Teriflunomide is an investigational agent and has not been approved by any regulatory agency worldwide. Alemtuzumab is not approved for treatment of MS and should not be used in MS patients outside of a regulated formal clinical trial.

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P: POC, proof-of-concept; CDMS: clinically definite MS; CIS: clinically isolated syndrome; RRMS: relapsing-remitting MS; IFNβ: interferon beta; GA: glatiramer acetate.

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Teriflunomide Research in MS1-8

**Teriflunomide Proof-of-concept Study**

Safety and Efficacy of Teriflunomide (HMR1726) in Multiple Sclerosis With Relapses (NCT01487096)

**Study design:** Phase II, randomized, double-blind, placebo-controlled, parallel-group study comparing 2 once-daily dose levels of teriflunomide with placebo

**Objective:** To evaluate the efficacy and safety of teriflunomide in reducing the number of unique active lesions in patients with RMS

**Study population:** 179 patients 18 to 65 years of age with CDMS with at least 2 documented relapses as defined by the Poser criteria and:
- Clinical disease severity between 0 and 6 inclusively according to the expanded disability status scale (EDSS)
- Screening magnetic resonance imaging (MRI) scan fulfilling the criteria for a diagnosis of MS
- At least 2 clinical relapses in the 3 years prior to screening with at least 1 relapse in the last year

**Study duration:** 36 weeks per patient plus optional extension

**Primary end points:**
- Number of unique active lesions per MRI scan
- Number of participants with adverse events

**Status:** Completed

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**TEMSON2**

Study of Teriflunomide in Reducing the Frequency of Relapses and Accumulation of Disability in Patients With Multiple Sclerosis (NCT00134563)

**Study design:** Phase III, randomized, double-blind, placebo-controlled, parallel-group study comparing 2 once-daily dose levels of teriflunomide with placebo

**Objective:** To evaluate the efficacy of teriflunomide in reducing relapse frequency and physical disability progression in patients with RMS

**Study population:** 1088 patients 18 to 55 years of age with CDMS with a score of 0 to 5.5 on the EDSS

**Study duration:** 108 weeks per patient plus optional extension

**Primary end point:** Time to failure defined as the first occurrence of a relapse or permanent study drug discontinuation for any cause, whichever comes first

**Status:** Completed. Extension phase is ongoing

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**TOWER4**

An Efficacy Study of Teriflunomide in Patients With Relapsing Multiple Sclerosis (NCT00751881)

**Study design:** Phase III, randomized, double-blind, placebo-controlled, parallel-group, multinational study comparing 2 once-daily dose levels of teriflunomide with placebo

**Objective:** To evaluate the efficacy of teriflunomide in reducing relapse frequency and physical disability progression in patients with RMS

**Study population:** 1110 patients 18 to 55 years of age with a score of 0 to 5.5 on the EDSS, no relapses in the 60 days before randomization, but either:
- 1 relapse in the previous year
- 2 or more relapses in the previous 2 years

**Study duration:** 111 weeks

**Primary end point:** Annualized relapse rate (ARR)

**Status:** Completed. Extension phase is ongoing
Teriflunomide 7 mg

IFNß + Teriflunomide 7 mg

Teriflunomide 14 mg

IFNß + Placebo

Teriflunomide Adjunctive Therapy Trials

Teriflunomide Added to IFNß

Phase III Study With Teriflunomide Versus Placebo in Patients With First Clinical Symptom of Multiple Sclerosis (NCT00622700)

Study design: Phase III, randomized, double-blind, placebo-controlled, parallel-group, multinational study comparing 2 once-daily dose levels of teriflunomide with placebo

Objective: To evaluate the efficacy of early intervention with teriflunomide in preventing or delaying conversion to CDMS in patients presenting with a first clinical episode consistent with MS

Study population: 780 patients 18 to 55 years of age with a first, well-defined neurologic event consistent with demyelination, and who had:
- An onset of MS symptoms within 90 days of randomization
- An MRI scan with 2 or more T2 lesions at least 3 mm in diameter, characteristic of MS

Study duration: 108 weeks per patient plus optional extension

Primary end point: Conversion to CDMS as defined by the occurrence of a relapse

Status: Enrolling

Study design: Phase II, randomized, double-blind, placebo-controlled, parallel-group study comparing 2 once-daily dose levels of teriflunomide with placebo as adjunctive therapy to IFNß

Objective: To evaluate the safety and tolerability of teriflunomide compared with placebo in patients with definite MS who were on a stable dose of IFNß for at least 26 weeks prior to the screening visit and:
- Who had no onset of MS relapse in the preceding 60 days prior to randomization
- Who were clinically stable for 4 weeks prior to randomization

Study duration: 24 weeks per patient plus optional extension

Primary end point: Number of patients with adverse events

Status: Completed

Study population: 116 patients 18 to 55 years of age, with definite MS who were on a stable dose of IFNß for at least 26 weeks prior to the screening visit and:
- Who had an onset of MS relapse in the preceding 60 days prior to randomization
- Who were clinically stable for 4 weeks prior to randomization

Study duration: 24 weeks per patient plus optional extension

Primary end point: Number of patients with adverse events

Status: Completed

TOPIC5

Efficacy and Safety of Teriflunomide in Patients With Relapsing Multiple Sclerosis and Treated With Interferon-beta (NCT01252355)

Study design: Phase III, randomized, double-blind, placebo-controlled, parallel-group, multinational study comparing 2 once-daily dose levels of teriflunomide with placebo in patients with RMS being treated with IFNß

Objective: To evaluate the efficacy of teriflunomide in comparison to placebo in reducing relapse frequency in patients with RMS who are being treated with IFNß

Study population: 1455 patients 18 to 55 years of age with RMS who have been treated with a stable dose of IFNß for at least 6 months prior to randomization and have displayed disease activity in the 12 months prior to randomization and after the first 3 months of IFNß treatment

Study duration: 48 to 152 weeks per patient plus optional 1-year extension

Primary end point: ARR

Status: Enrolling

Teriflunomide is an investigational agent and has not been approved by any regulatory agency worldwide.

Teriflunomide Added to Glatiramer Acetate

Pilot Study of Teriflunomide as Adjunctive Therapy to Glatiramer Acetate in Subjects With Multiple Sclerosis (NCT00475865)

Study design: Phase II, randomized, double-blind, placebo-controlled, parallel-group study comparing 2 once-daily dose levels of teriflunomide with placebo as adjunctive therapy

Objective: To evaluate the safety and tolerability of teriflunomide compared with placebo in patients with definite MS who were currently on a stable dose of glatiramer acetate

Study population: 123 patients 18 to 55 years of age, with definite MS with a score of 0 to 5.5 on the EDSS who were on a stable dose of glatiramer acetate for at least 26 weeks prior to the screening visit and:
- Who had an onset of MS relapse in the preceding 60 days prior to randomization
- Who were clinically stable for 4 weeks prior to randomization

Study duration: 24 weeks per patient plus optional extension

Primary end point: Number of patients with adverse events

Status: Completed

Study population: 123 patients 18 to 55 years of age, with definite MS with a score of 0 to 5.5 on the EDSS who were on a stable dose of glatiramer acetate for at least 26 weeks prior to the screening visit and:
- Who had an onset of MS relapse in the preceding 60 days prior to randomization
- Who were clinically stable for 4 weeks prior to randomization

Study duration: 24 weeks per patient plus optional extension

Primary end point: Number of patients with adverse events

Status: Completed

Study population: 116 patients 18 to 55 years of age, with definite MS who were on a stable dose of IFNß for at least 26 weeks prior to the screening visit and:
- Who had an onset of MS relapse in the preceding 60 days prior to randomization
- Who were clinically stable for 4 weeks prior to randomization

Study duration: 24 weeks per patient plus optional extension

Primary end point: Number of patients with adverse events

Status: Completed

Teriflunomide is an investigational agent and has not been approved by any regulatory agency worldwide.

Source: Adapted from ClinicalTrials.gov (accessed March 21, 2012)
ALEMTUZUMAB

**CARE-MS**

**CARE-MS** I (CAMMS323)$^{10}$

**Study design:** Phase II, randomized, active comparator-controlled, rater-blinded safety and efficacy study comparing 12 and 24 mg dose levels of annual alemtuzumab with 44 mcg 3-times-weekly subcutaneous IFNß-1a (N=840). Alemtuzumab was given intravenously in 2 or 3 brief (3- to 5-day) annual cycles.

- **Objective:** To confirm the findings from CAMMS223 and to further define the safety profile of alemtuzumab therapy for RRMS
- **Study population:** Treatment-naïve patients aged 18 to 50 years with active* RRMS, EDSS ≤3, disease duration ≤3 years
- **Study duration:** 3 years (plus extended follow-up)
- **Primary end points:**
  - Time to sustained accumulation of disability (SAD) by EDSS
  - Rate of relapse
- **Status:** Completed. Patients were eligible for long-term follow-up under the CARE-MS$^{SM}$ Extension Study

$^*$ ≥2 MS attacks in prior 2 years with ≥1 within 12 months of screening; the presence of a gadolinium-enhancing lesion on screening

**CARE-MS$^{SM}$ II (CAMMS324)$^{11}$

**Study design:** Phase III, randomized, active comparator-controlled, rater-blinded safety and efficacy study comparing 12 and 24 mg dose levels of annual alemtuzumab with 44 mcg 3-times-weekly subcutaneous IFNß-1a (N=840). Alemtuzumab was given intravenously in 2 brief (3- to 5-day) annual cycles.

- **Objective:** To extend the findings from CAMMS223 in patients who have relapsed on therapy and to further evaluate the safety profile of alemtuzumab therapy for RRMS
- **Study population:** Patients aged 18 to 55 years with active* RRMS who relapsed† while using disease-modifying treatment; EDSS ≤5, disease duration ≤10 years
- **Study duration:** 2 years
- **Primary end points:**
  - Time to SAD
  - Rate of relapse
- **Status:** Completed. Patients were eligible for long-term follow-up under the CARE-MS$^{SM}$ Extension Study

$^*$ ≥2 MS attacks in prior 2 years with ≥1 within 12 months of screening

$^†$ ≤1 MS attack while receiving treatment with interferon beta or glatiramer acetate after being on therapy for at least 6 months

**An Extension Protocol for Multiple Sclerosis Patients Who Participated in Genzyme-Sponsored Studies of Alemtuzumab (NCT00930553)**

- **Objective:** To examine:
  - Long-term safety and efficacy of alemtuzumab in patients with MS
  - Safety and efficacy of as-needed alemtuzumab retreatment
  - Safety and efficacy of alemtuzumab in patients who received subcutaneous IFNß-1a in a CARE-MS$^{SM}$ trial
- **Study population:** Patients completing participation in CAMMS223, CARE-MS$^{SM}$ I, or CARE-MS$^{SM}$ II (N=1320)
- **Study duration:** 3 years
- **Primary end points:**
  - Time to SAD
  - Rate of relapse
- **Status:** Ongoing

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As a Sanofi company, Genzyme benefits from the research and resources of one of the world’s largest pharmaceutical companies with a shared commitment to improving the lives of patients. Together, we are working to deliver scientific advancements that will positively impact the lives and outlook of people living with MS. Through innovation, transparency, and access, we have built our MS business unit on core principles that guide us toward our goal of expanding the possibilities of life with MS.

References: