FTY720 (Fingolimod) backgrounder

What is FTY720?
- FTY720 (fingolimod) is being investigated as a potential once-daily oral therapy for relapsing-remitting forms of multiple sclerosis (MS)\(^1,2\).
- FTY720 leads a new class of compounds – sphingosine 1-phosphate receptor (S1PR) modulators, which targets MS via effects on the immune system and evidence from animal models indicates that it may also have actions in the central nervous system (CNS)\(^3,4\).

How does FTY720 work?
- FTY720 interacts with S1PRs found on lymphocytes (a sub-group of white blood cells) and cells in the CNS.
- Modulation of S1PRs on lymphocytes by FTY720 retains circulating lymphocytes in the lymph nodes, thereby reducing the recirculation of autoreactive lymphocytes and preventing their infiltration into the CNS\(^3,4\).
- In addition, S1P receptors are expressed on cells in the CNS and these are known to play a role in the MS pathology. In vitro and animal experiments indicate that FTY720 may also interact with the MS disease process through these receptors within the CNS.

What is the regulatory review status of FTY720?
- Approval is being sought for the 0.5 mg dose, as clinical study results indicate this dose has the most favorable benefit to risk profile of doses tested in MS.
- In February 2010, FTY720 was granted priority review status by the FDA. The review period has been extended to September 2010.
- FTY720 is also under review by the EMA in the EU as well as other health authorities worldwide. The regulatory file was submitted in December 2009.

How effective is FTY720?
- In phase II FTY720 was investigated in a six-month placebo controlled trial, followed by an ongoing extension. In phase III, FTY720 was studied versus an approved first-line therapy over one year and also versus placebo over two years, both studies are now in their extension phase.
- FTY720 has demonstrated superior efficacy to an approved first-line therapy - intramuscular (IM) interferon β-1a - and placebo, with benefits extending across clinical and MRI measures and across all studies in relapsing MS\(^1,2,5-7\).
- FTY720 significantly reduced MRI measures of inflammatory brain lesion activity, tissue damage or brain atrophy compared with the approved therapy IM interferon β-1a and placebo\(^1,2\).

- Results from the pivotal phase III TRANSFORMS study, published in The New England Journal of Medicine (NEJM), showed that FTY720 had superior efficacy at one year vs. an approved first-line therapy, in patients with relapsing-remitting MS (RRMS)\(^1\).
  - Relapse rate at one year was 52% lower in patients taking FTY720 0.5 mg than on IM interferon β-1a (p<0.001)\(^1\).
  - Reductions in the rate of brain atrophy over one year were significantly greater with FTY720 0.5 mg than with IM interferon β-1a\(^1\).

TRANSFORMS: Fingolimod 0.5 mg reduced ARR by 52% compared with the approved first-line therapy interferon β-1a

ARR = Annualized relapse rate
Results from the pivotal phase III FREEDOMS study, published in The New England Journal of Medicine (NEJM), showed that FTY720 had superior efficacy over two years vs. placebo in patients with RRMS\(^2\).

- Patients on FTY720 0.5 mg had 30% lower risk of disability progression, confirmed after three months and a 37% lower risk of disability progression, confirmed after six months\(^2\).
- FTY720 0.5 mg significantly reduced the rate of brain atrophy compared with placebo throughout the 2 year study, indicating a consistent and sustained beneficial effect\(^2\).

**What is the safety profile of FTY720?**

- Large-scale studies in MS have ensured that the safety profile of FTY720 is well-characterized and demonstrate that it is generally well tolerated\(^1,2,5-7\).
- In the TRANSFORMS and FREEDOMS studies the most commonly reported adverse events for both FTY720 and control groups were nasopharyngitis, headache and fatigue. FTY720-related adverse events included transient, dose-related, generally asymptomatic heart rate reduction and infrequent transient AV conduction block at treatment initiation, mild (1-3 mm Hg) blood pressure increase, macular edema (more common with 1.25 mg than the 0.5 mg target dose), and asymptomatic, reversible elevation of liver enzymes.
- The rates of infections overall, including serious infections, were comparable among treatment groups, although a slight increase in lung infections (primarily bronchitis) was seen in patients treated with FTY720. The number of malignancies reported across the two studies was small with comparable rates between the FTY720 and control groups\(^1,2\).

**How was FTY720 investigated?**

- Studies of FTY720 in patients with MS provide data from more than 3000 patients, including more than 100 patients receiving their sixth year of therapy. The phase III clinical program consists of trials referred to as TRANSFORMS, FREEDOMS, FREEDOMS II and INFORMS.
- Please refer to the TRANSFORMS and FREEDOMS backgrounder for additional information on these studies.

**References:**