Fingolimod for the treatment of acute optic neuritis: Design of a phase II study (ADONIS)

P 570

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CONCLUSIONS

- **Effective therapies reducing visual impairment resulting from acute demyelinating optic neuritis (ADON) are an important unmet medical need**
- **The ADONIS (Fingolimod in Acute Demyelinating Optic NeuritIS) study will investigate the effects of fingolimod in ADON both on an anatomical and clinical level and will advance the knowledge about structural and functional changes following the first episode of ADON**
- **In addition, given that patients with ADON are at increased risk of developing multiple sclerosis (MS), the study will explore the effects of fingolimod on radiographic/clinical conversion of ADON to MS**

INTRODUCTION

- ADON is a condition of the optic nerve characterized by inflammation, demyelination and retinal nerve fibre layer (RNFL) loss which may cause temporary or permanent loss of vision (**Table 1**)
- Approximately 20% of MS patients present with ADON as a clinically isolated syndrome (CIS).[1] After presenting with ADON as a CIS, 45–78%[2-5] of patients develop clinically definite MS (CDMS) by the most conservative criteria[6] **(Figure 1)**. The Optic Neuritis Treatment Trial demonstrated that the most potent predictor of future CDMS risk in ADON patients is the baseline magnetic resonance imaging (MRI) scan[3]
- To date, patients with ADON may be treated with high-dose corticosteroids depending upon their degree of visual loss and baseline MRI status.[3] Corticosteroids tend to hasten visual recovery in patients destined to improve but there is no approved therapy available to mitigate the development of permanent visual sequelae. A treatment with the ability to reduce the influx of autoreactive lymphocytes into the inflamed optic nerve and limit axonal loss might be effective in preserving anatomical structures and visual function in ADON
- Once daily fingolimod (FTY720; Gilenya®, Novartis Pharma AG), is a sphingosine 1-phosphate receptor (S1PR) modulator approved for the treatment of relapsing MS[a]
- In MS, modulation of S1PRs on lymphocytes by fingolimod rapidly retains circulating lymphocytes in the lymph nodes, thereby reducing the recirculation of autoreactive lymphocytes and preventing their infiltration into the CNS. Preclinical data also support a potential effect of fingolimod on remyelination.[7,8] The mechanism of action of fingolimod in MS allows the hypothesis, that it could be effective in mitigating RNFL thinning and permanent loss of visual function in ADON patients[9,10]

[a]The approved indication may vary from country to country. In the EU, fingolimod is approved for treatment of patients with highly active relapsing-remitting MS. In the United States, it is approved for the treatment of patients with relapsing forms of MS

OBJECTIVE

- To present the design and endpoints of the phase II ADONIS study, which evaluates the efficacy and safety of oral fingolimod versus placebo in preventing RNFL loss in patients with a first episode of ADON receiving symptomatic steroid treatment

METHODS

Study Design

- ADONIS is a 48-week, multi-centre, randomised, double-blind, parallel-group, partially placebo-controlled study comparing structural changes in the retina and evolution of visual function after 18 weeks of treatment with either fingolimod 0.5 mg daily or placebo and further 30 weeks of treatment with fingolimod 0.5 mg daily in all patients (NCT01757691) (**Figure 2**)
- The primary and the key secondary objectives are presented in **Table 2**
- An interim analysis is planned to address the uncertainties of assumptions for RNFL thinning by a one-time blinded sample-size re-estimation when a minimum of 70 patients have completed their Week 18 assessment

Patients

- Eligible participants are male and female patients aged 18–50 years, suffering from unilateral suspected ADON as a probable first clinical manifestation of an underlying demyelinating disease; additional key inclusion and exclusion criteria are presented in **Table 3**

Study assessments

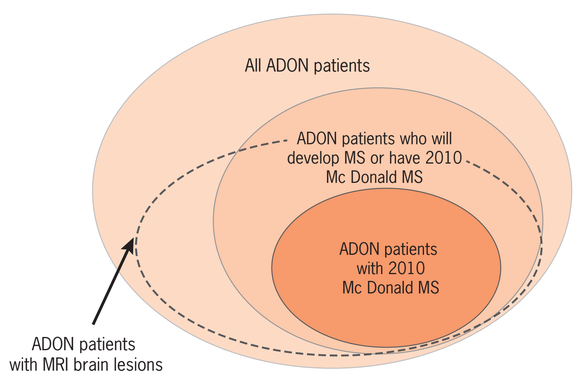
- Primary efficacy assessments will include RNFL thickness, ganglion cell/inner plexiform layer thickness, average macular thickness (optical coherence tomography [OCT] measurements; **Figure 3**) and key secondary efficacy assessments will include visual acuity (Sloan letter charts at different contrast levels), vision-based quality of life (25-item National Eye Institute Visual Functioning Questionnaire),[11] and conversion to either 2005 McDonald MS[12] or 2010 McDonald MS[13] or to CDMS[6]
- Safety assessments will include physical and neurological examination, examination of vital signs, laboratory analyses (haematology, clinical chemistry, urinalysis, pregnancy testing), and first dose monitoring

Table 1. Typical signs and symptoms of ADON[14,15]

- Acute to subacute onset: progressive over a few days to 2 weeks
- 18–50 years of age
- Periocular pain (90%), especially with eye movement - preceding or coinciding with visual loss
- Unilateral loss of visual acuity of variable severity
- Reduced contrast and color vision (out of proportion to loss of visual acuity; red desaturation)
- Exacerbation of symptoms with increased body temperature (Uhthoff's phenomenon)
- Phosphenes, Pulfrich's effect
- Ipsilateral relative afferent pupillary defect
- No visible swelling of optic nerve head in most patients (65%)
- Visual field defect consistent with an optic neuropathy
- Increased VEP latency
- Rarely deterioration in vision when corticosteroids are withdrawn
- Spontaneous visual improvement in >90% starting within 2–3 weeks regardless of treatment
- Variable degree of optic disc pallor and atrophy of the optic nerve after 4–6 weeks

ADON, acute demyelinating optic neuritis; VEP, visual evoked potentials

Figure 1. Relationship between ADON and MS

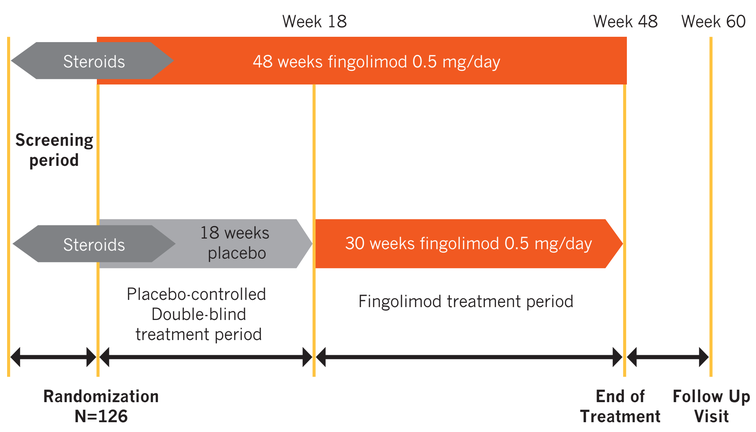


Note: Not all patients with ADON will develop MS – the risk is higher in patients with abnormal brain MRI at time of ADON

For illustrative purposes only. Proportions shown are not representative of actual incidence

ADON, acute demyelinating optic neuritis; MRI, magnetic resonance imaging; MS, multiple sclerosis

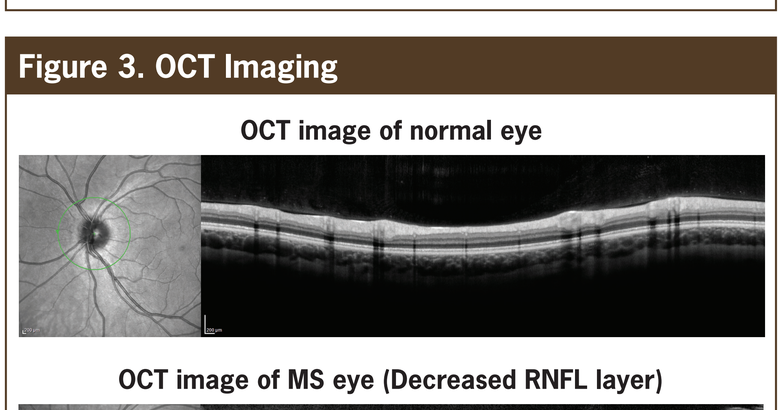
Figure 2. Design of ADONIS study



Note: Patients with a first episode of ADON will be randomised **shortly** after disease onset

ADONIS, **A**cute **D**emyelinatin **O**ptic **N**eurit**IS**

Figure 3. OCT Imaging



Courtesy of Dr. A.J. Green, University of California, San Francisco

MS, multiple sclerosis; OCT, optical coherence tomography; RNFL, retinal nerve fibre layer

Statistical analysis

- With 60 randomised patients per treatment group, the study has 80% power to detect an absolute treatment difference of 6.75 µm in fellow-eye-controlled thinning of RNFL, using a two-sided student's t-test at the 0.05 significance level

Patient enrolment

- The study plans to recruit patients in approximately 45 to 60 centres worldwide **(Figure 4).** Patient enrolment started in August 2013
- The study is expected to be completed in 2016

Table 2. Primary and key secondary objectives

Primary objective	Key secondary objective
• To evaluate efficacy of fingolimod 0.5 mg/day in reducing the mean RNFL thinning versus placebo after 18 weeks in patients with suspected ADON, all of whom will receive standard steroid treatment	• To compare the effect of immediate versus delayed treatment with fingolimod 0.5 mg/day in patients with suspected ADON who are receiving standard treatment with steroids on the following outcomes: – Low-contrast visual acuity of the affected eye assessed at Week 48 – Vision-based quality of life assessed at Week 18 and 48 – The proportion of patients converting to either 2005 McDonald MS[12] or 2010 McDonald MS[13] between the assessment at the screening visit and Week 18 and 48 • To evaluate the tolerability and safety of fingolimod in patients with ADON

ADON, acute demyelinating optic neuritis; MS, multiple sclerosis; RNFL, retinal nerve fibre layer

Table 3. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Male and female patients aged between 18 and 50 years • Clinical signs and symptoms of unilateral ADON (loss of vision, pain on movement, impairment of colour vision) • The qualifying ADON must be the first clinical episode of a probable demyelinating disease • Able to undergo treatment with IVMP • Received first IVMP dose prior to Visit 2	• Patients with history of any unexplained eye or neurological symptomatology lasting longer than 48 hours and indicative of a demyelinating disorder • Patients with bilateral optic neuritis • Concurrent functionally or clinically relevant disturbances of the eye not affected by ADON • Functionally or clinically relevant comorbidity of either eye • High clinical likelihood of a form of optic neuritis other than ADON • Uncontrolled diabetes mellitus

Note: In addition, other exclusion criteria related to the safety profile of the study drug apply

ADON, acute demyelinating optic neuritis; IVMP, intravenous methyl prednisolone

Figure 4. Participating countries

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