**Supplementary Materials**

**Coinvestigators appendix:** ONWARD trial principal investigators, by country.

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**Supplementary Table e-1 Protocol Amendments**

|  |  |  |  |
| --- | --- | --- | --- |
| **Amendment** | **Date** | **Region** | **Rationale** |
| Amendment 1 | 28 April 2008 | USA | Address two potential safety issues identified by the sponsor early in the conduct of the trial   * Ensure administration of blinded study medication occurred only when hematological status was known to the investigator * Elimination of the cladribine high-dose add-on treatment group due to safety signal (abnormal laboratory hematology). This resulted in a change in the randomization schema, number of patients and planned population analyses |
| Amendment 2 | 20 May 2008 | Italy, Spain and Russia | Same as Amendment 1 with additional formulations of interferon beta included in the definition of investigational medicinal products, based on European regulations |
| Amendment 3 | 18 March 2009 | USA | Inclusion of a 96-week extension to the study (open-label cladribine or safety follow-up (interferon beta only), in order to provide/explore long-term safety data for cladribine as an add-on to interferon-beta therapy. |
| Amendment 4 | 10 April 2009 | Italy, Spain and Russia | Same as Amendment 3 but with investigational medicinal product definitions appropriate to the regions of Italy, Spain and Russia (USA definition differs from rest of world) |
| Amendment 5 | 30 August 2011 | Global | Discontinuation of all use of cladribine, based on the Sponsor’s decision to discontinue efforts for global registration of Cladribine Tablets, and to follow patients for safety and efficacy in the extension period for a maximum of 48 weeks while they continued treatment with interferon-beta. |

**Supplementary Table e-2** Selected exclusion criteria

|  |  |
| --- | --- |
| Original protocol | Amended protocol |
| Presence of infectious or immune-compromising diseases | Unchanged |
| Previous treatment with immunosuppressive or cytotoxic therapies at any time | Unchanged |
| Treatment with cytokine-based therapy or plasmapheresis within 3 months of baseline | Unchanged |
| Treatment with adrenocorticotropic hormone within 28 days of baseline | Unchanged |
| Pregnancy | Unchanged |
| Breastfeeding | Unchanged |
| Attempting conception | Unchanged |
| Refusal to use contraception during study (males and females) | Amended to include use of contraception for 6 months after the last dose of study medication in females |
| Prior or current malignancies | Amended to exclude basal cell skin cancer |
| Treatment with oral or parenteral corticosteroids within 28 days of baseline | Treatment with oral or parenteral corticosteroids within 30 days of screening |
| Treatment with intravenous immunoglobulin therapy within 3 months of baseline | Treatment with intravenous immunoglobulin therapy within 30 days of screening |
|  | History or evidence of tuberculosis |

**Supplementary Table e-3**. Adverse events reported by at least 2 patients in any group over the double‑blind period: original protocol population

|  |  |  |  |
| --- | --- | --- | --- |
| Preferred terma | Cladribine  5.25 mg/kg +  IFN-β  (*n =* 17) | Cladribine  3.5 mg/kg +  IFN-β  (*n =* 16) | Placebo + IFN-β (*n =* 9) |
| Lymphopenia | 7 (41.2) | 4 (25.0) | 0 |
| Nausea | 3 (17.6) | 5 (31.3) | 1 (11.1) |
| Diarrhea | 3 (17.6) | 2 (12.5) | 0 |
| Gastroesophageal reflux disease | 0 | 2 (12.5) | 0 |
| Abdominal pain | 3 (17.6) | 0 | 0 |
| Constipation | 2 (11.8) | 0 | 1 (11.1) |
| Influenza like illness | 2 (11.8) | 2 (12.5) | 1 (11.1) |
| Fatigue | 3 (17.6) | 1 (6.3) | 1 (11.1) |
| Pain | 3 (17.6) | 0 | 0 |
| Urinary tract infection | 3 (17.6) | 4 (25.0) | 1 (11.1) |
| Bronchitis | 0 | 3 (18.8) | 1 (11.1) |
| Nasopharyngitis | 2 (11.8) | 2 (12.5) | 3 (33.3) |
| Gastroenteritis, viral | 1 (5.9) | 2 (12.5) | 0 |
| Upper respiratory tract infection | 5 (29.4) | 1 (6.3) | 1 (11.1) |
| Tooth infection | 2 (11.8) | 0 | 0 |
| Contusion | 2 (11.8) | 2 (12.5) | 1 (11.1) |
| Fall | 0 | 0 | 2 (22.2) |
| WBC count decreased | 0 | 5 (31.3) | 0 |
| Lymphocyte count decreased | 4 (23.5) | 3 (18.8) | 0 |
| CD4+ lymphocytes decreased | 2 (11.8) | 2 (12.5) | 0 |
| Neutrophil count decreased | 0 | 2 (12.5) | 0 |
| Back pain | 2 (11.8) | 3 (18.8) | 0 |
| Pain in extremity | 1 (5.9) | 1 (6.3) | 2 (22.2) |
| Myalgia | 3 (17.6) | 0 | 0 |
| Musculoskeletal pain | 2 (11.8) | 0 | 0 |
| Headache | 3 (17.6) | 5 (31.3) | 2 (22.2) |
| Migraine | 2 (11.8) | 1 (6.3) | 1 (11.1) |
| Anxiety | 1 (5.9) | 2 (12.5) | 0 |
| Insomnia | 4 (23.5) | 0 | 0 |
| Pharyngolaryngeal pain | 2 (11.8) | 2 (12.5) | 0 |
| Productive cough | 0 | 2 (12.5) | 0 |
| Sinus congestion | 0 | 2 (12.5) | 0 |
| Upper respiratory tract congestion | 2 (11.8) | 0 | 0 |
| Dermal cyst | 3 (17.6) | 0 | 0 |

Data shown as *n* (%).

aPreferred term from the MedDRA.

*WBC, white blood cell; IFN, interferon; MedDRA, Medical Dictionary for Regulatory Activities.*

**Supplementary Table e-4**. CTCAE Grade 3 or 4 hematological or liver toxicities over the double-blind period: original protocol population

|  |  |  |  |
| --- | --- | --- | --- |
| CTCAE Grade 3 or 4 toxicity | Cladribine  5.25 mg/kg + IFN-β (n=17)  *n* (%) | Cladribine 3.5 mg/kg + IFN-β (*n =* 16)  *n* (%) | Placebo +  IFN-β (*n =* 9) *n* (%) |
| Lymphocytes | 15 (88.2) | 12 (75.0) | 0 |
| CD4 cells | 16 (94.1) | 11 (68.8) | 0 |
| Neutrophils | 4 (23.5) | 5 (31.3) | 0 |
| White blood cells | 3 (17.6) | 4 (25.0) | 0 |
| Hemoglobin | 0 | 0 | 0 |
| Alanine transaminase | 0 | 0 | 0 |
| Aspartate transaminase | 0 | 0 | 0 |
| Platelets | 0 | 0 | 0 |
| Bilirubin | 0 | 0 | 0 |

*CTCAE, Common Terminology Criteria for Adverse Events*

*CTCAE Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living*

*CTCAE Grade 4: Life-threatening consequences; urgent intervention indicated*

**Supplementary Table e-5** Outcomes of pregnancies during the double-blind period: amended protocol populationa

|  |  |  |
| --- | --- | --- |
| Pregnancy | Randomized treatment group | Pregnancy outcome |
| Patient | Cladribine 3.5 mg/kg added to IFN-β | Spontaneous abortion |
| Patient | Placebo added to IFN-β | Elected induced abortion |
| Patient | Placebo added to IFN-β | Spontaneous abortion |
| Patient | Placebo added to IFN-β | Healthy child |
| Partner of patient | Cladribine 3.5 mg/kg added to IFN-β | Healthy child |
| Partner of patient | Cladribine 3.5 mg/kg added to IFN-β | Unknown |

aNo patient or partner of a patient became pregnant in the original protocol population during the study or in the amended protocol population during the open-label extension period.

*IFN, interferon.*

**Supplementary Table e-6**: MRI endpoints for the double-blind period of the amended protocol ITT population

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Cladribine 3.5mg/kg + IFN-β (n=124) | Placebo + IFN-β (n=48) | Relative risk (95%CI)1 | P value |
|  |  |  |  |  |
| N (missing) | 121 (3) | 48 (0) |  |  |
| Total number of new Gd+ T1 lesions, mean (SD) | 0.25 (1.46) | 1.27 (3.39) | 0.10 (0.03, 0.37) | <0.0012 |
| Total number of new T2 lesions, mean (SD) | 2.05 (4.91) | 3.65 (6.83) | 0.54 (0.27, 1.10) | 0.0903 |
| Total number of combined unique lesions, mean (SD) | 2.12 (4.95) | 3.96 (7.38) | 0.41 (0.21, 0.81) | 0.0114 |

1Relative risk and associated 95% CI were estimated using a Negative Binomial model with fixed effects for treatment group and IFN-β treatment, baseline T1 Gd+ lesions as a covariate, and log of number of scans as an off-set variable.

2p-value based on Wald Chi-square test from analysis of total number of new T1 Gd+ lesions using a Negative Binomial model with fixed effects for treatment group and IFN-β treatment, baseline T1 Gd-enhanced lesions as a covariate, and log of number of scans as an off-set variable.

3p-value based on Wald Chi-square test from analysis of total number of active T2 lesions using a Negative Binomial model with fixed effects for treatment group and IFN-beta treatment with the log of number of scans as an off-set variable.

4p-value based on Wald Chi-square test from analysis of total number of combined unique lesions using a Negative Binomial model with fixed effects for treatment group and IFN-beta treatment, baseline T1 Gd-enhanced lesions as a covariate, and log of number of scans as an off-set variable.

*Gd+, gadolinium-enhancing; IFN, interferon.*

*Gd, Gadolinium*

**Supplementary information: Patients classified as SPMS and RRMS: overall ITT population**

The ONWARD study was a Phase II safety study, in which cladribine was administered as an add-on therapy to patients with relapses while receiving interferon-beta (IFN-β). Thus, the analyses compared placebo + IFN-β versus cladribine + IFN-β to assess the treatment effect of Cladribine Tablets. In the placebo and cladribine 3.5 mg/kg subgroups, a total of 197 Secondary Progressive Multiple Sclerosis (SPMS) or RRMS patients, all of whom had had superimposed relapses in the previous year, were randomized in the ONWARD study: 26 were SPMS patients and 171 were RRMS patients. The distribution of patients by treatment groups is presented in Supplementary Table e-7, together with demographic and clinical characteristics at baseline for both the SPMS and the RRMS subgroups.

Despite some differences observed at baseline in the demographics of the ONWARD study between the two subgroups, it should be noted that there were no meaningful differences. It should also be noted that the SPMS subgroup contained only a very small number of patients. Disease duration of the patients in this study was relatively long compared to the typical RRMS studies because the inclusion criteria required previous experience with a DMD for all patients, and allowed entry of SPMS patients. With regard to clinical activity, in the RRMS subgroup, there was no clinical difference in relapses in the prior 12 months between the SPMS and RRMS subgroups. Mean EDSS at baseline was higher in the SPMS subgroup compared to the RRMS subgroup. The SPMS placebo and cladribine 3.5 mg/kg groups had a lower mean number of T1 Gd+ lesions in the placebo group (0.1) compared to the cladribine 3.5 mg/kg group (1.5). In contrast, in the RRMS group, placebo and cladribine 3.5 mg/kg groups had similar mean numbers of T1 Gd+ lesions. Baseline numbers of T2 lesions and T2 lesion volume were balanced in all treatments groups in both the SPMS and RRMS subgroups.

The treatment effect of Cladribine Tablets during the ONWARD study on key outcomes were also analyzed in both the SPMS and the RRMS subgroups (see Supplementary Table e-8). In both RRMS and SPMS patients, the cladribine 3.5 mg/kg group demonstrated a reduction in the ARR compared with placebo. This effect reached nominal statistical significance in both SPMS and RRMS subgroups. In the SPMS subgroup, the relative risk ratio for relapse reduction in the cladribine 3.5 mg/kg over the placebo group was 0.11 with a wide 95% CI (0.01 to 0.94). The relative risk ratio in the cladribine 3.5 mg/kg over the placebo group in the RRMS subgroup was 0.50 with a 95% CI ranging from 0.30 to 0.84. With respect to time to 3-month or 6-month confirmed EDSS progression, no treatment effect was observed in either of the SPMS or RRMS subgroups, which is consistent with the overall study data and as expected given the low number of patients in the study.

Regarding MRI outcomes, cladribine led to a reduction in both T1 Gd+ lesions and mean number of active T2 lesions in both RRMS and SPMS patient subgroups, compared to placebo.

In summary, cladribine 3.5 mg/kg was associated with a reduction of ARR, T1 Gd+ and active T2 lesions when compared to placebo in both RRMS and relapsing SPMS patients in the ONWARD study.

In conclusion, while there were limitations in the analysis of SPMS and RRMS subgroups due to the very low number of SPMS patients, the available data suggests that cladribine 3.5 mg/kg administered with IFN-β showed evidence of efficacy in both subgroups in the ONWARD study.

**Supplementary Table e-7** Demographics and clinical characteristics at ONWARD baseline for patients classified as SPMS and RRMS (overall ITT population)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | SPMS Patients  N=26a | | RRMS Patients  N=171a | |
|  | Placebo + IFN-β  N=9 | Cladribine 3.5 mg/kg + IFN-β  N=17 | Placebo + IFN-β  N=48 | Cladribine 3.5 mg/kg + IFN-β  N=123 |
| Age, years | | | | |
| Mean  Standard  deviation | 39.9  10.1 | 41.1  11.3 | 40.2  10.0 | 38.1  10.0 |
| Female, n (%) | 5 (55.6) | 10 (58.8) | 37 (77.1) | 84 (68.3) |
| Region, n (%) |  |  |  |  |
| Americas | 0 | 1 (5.9) | 23 (47.9) | 57 (46.3) |
| Eastern Europe | 0 | 0 | 0 | 0 |
| Western Europe | 2 (22.2) | 6 (35.3) | 15 (31.3) | 31 (25.2) |
| ROW | 0 | 0 | 0 | 0 |
| Russia | 7 (77.8) | 10 (58.8) | 10 (20.8) | 35 (28.5) |
| Australia | 0 | 0 | 0 | 0 |
| Disease Duration, years | | | | |
| Mean | 8.63 | 8.22 | 8.18 | 6.50 |
| Standard  deviation | 5.15 | 5.85 | 6.50 | 4.85 |
| Prior use of DMD at any time in the patient's history, n (%) | | | | |
|  | 9 (100.0) | 17 (100.0) | 48 (100.0) | 123 (100.0) |
| Relapses in prior 12 months categories, n (%) | | | | |
| 0 | 0 | 0 | 1 (2.1) | 0 |
| 1 | 8 (88.9) | 10 (58.8) | 28 (58.3) | 96 (78.0) |
| 2 | 1 (11.1) | 6 (35.3) | 16 (33.3) | 24 (19.5) |
| ≥3 | 0 | 1 (5.9) | 3 (6.3) | 3 (2.4) |
| EDSS at Baseline | | | | |
| Mean | 4.39 | 4.18 | 2.80 | 2.69 |
| Standard deviation | 0.42 | 1.33 | 1.11 | 1.09 |
| Number of T1 Gd+ lesions at baseline | | | | |
| Mean | 0.1 | 1.5 | 1.0 | 0.9 |
| Standard deviation | 0.3 | 4.8 | 3.1 | 3.6 |
| Number of T2 lesions at baseline | | | | |
| Mean | 37.8 | 38.3 | 32.5 | 32.7 |
| Standard deviation | 26.7 | 28.8 | 19.2 | 21.6 |
| T2 lesion volume, cm3 | | | | |
| Mean | 10.15 | 12.46 | 13.58 | 10.33 |
| Standard deviation | 8.60 | 14.33 | 16.54 | 10.73 |

DMD=disease modifying drug, EDSS=expanded disability status scale, Gd+=gadolinium-enhanced,

aOverall N of placebo and 3.5 mg/kg cladribine groups, excluding 5.2.5 mg/kg cladribine group.

**Supplementary Table e-8** Key clinical and MRI outcomes during the ONWARD study for patients classified as SPMS and RRMS (overall ITT population)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | SPMS Patients  N=26a | | RRMS Patients  N=171a | |
|  | Placebo + IFN-β  N=9 | Cladribine 3.5 mg/kg + IFN-β  N=17 | Placebo + IFN-β  N=48 | Cladribine 3.5 mg/kg + IFN-β  N=123 |
| Qualifying relapse rate (annualized, adjusted) | 0.30 | 0.03 | 0.31 | 0.15 |
| 95% CI  Relative risk ratiob  95% CI | (0.13, 0.73)  NA  NA | (0.00, 0.24)  0.11  (0.01, 0.94) | (0.21, 0.45)  NA  NA | (0.11, 0.22)  0.50  (0.30, 0.84) |
| Time to 3-Month Confirmed EDSS-Progression | | | | |
| Hazard Ratioc | NA | 1.1 | NA | 1.05 |
| 95% CI | NA | (0.28, 4.42) | NA | (0.41, 2.69) |
| Time to 6-Month Confirmed EDSS-Progression | | | | |
| Hazard Ratioc | NA | 0.78 | NA | 1.38 |
| 95% CI | NA | (0.13, 4.67) | NA | (0.45, 4.19) |
| Mean number of new T1 Gd+ lesions per patient per scan | | | | |
| Mean | 0.67 | 0.13 | 0.29 | 0.05 |
| Standard deviation | 2.00 | 0.55 | 0.64 | 0.31 |
| Mean number of active T2 lesions per patient per scan | | | | |
| Mean | 0.59 | 0.29 | 1.31 | 0.58 |
| Standard deviation | 1.66 | 0.52 | 2.36 | 1.40 |

CI=confidence interval, EDSS=expanded disability status scale; Gd+=gadolinium-enhanced

aOverall N of placebo and 3.5 mg/kg cladribine groups, excluding 5.2.5 mg/kg cladribine group.

bRelative risk and associated 95% CI were estimated using a Poisson regression model with fixed effects for

treatment group and with the log of time on Study as the offset variable.

cHazard Ratio (HR) and associated 95% CI were from a Cox proportional hazard model.

**Supplementary Figure e-1.** Study Design Under Protocol Amendments 1 and 2 (Double-Blind Period) and Under Protocol Amendments 3 and 4 (Extension Period)



**Supplementary Figure e-2** Lymphocyte counts and change from baseline in the double-blind period – Safety population (randomized under amended protocol).

