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| Sponsor<br><br>Novartis |
| Generic Drug Name<br><br>TCH346 |
| Therapeutic Area of Trial<br><br>Amyotrophic Lateral Sclerosis |
| Approved Indication<br><br>Investigational; not yet approved |
| Study Number<br><br>CTCH346A2211E1 |
| Title<br><br>A long-term extension to a randomized, double-blind, placebo-controlled, stratified, parallel-group, multicenter, dose-ranging study evaluating four oral doses of TCH346 (1.0, 2.5, 7.5 and 15 mg) administered once daily in patients with Amyotrophic Lateral Sclerosis |
| Phase of Development<br><br>IIb |
| Study Start/End Dates<br><br>29-Nov-2004 - 11-Feb-2005 |
| Study Design/Methodology<br><br>This study was designed as a 2 part extension to the core study TCH346A2211. During the first part, patients continued their blinded treatment assignment from the core study for [variable duration up to a maximum of 44 weeks]. Following analyses of the core study and dose selection, patients entered the second part of the extension which included open label administration of the selected dose for [variable duration up to a maximum of 12 weeks due to study early termination]. However, analyses of the core study did not identify an efficacious dose of TCH346 and the extension study was prematurely discontinued by the sponsor. |
| Centres<br><br>42 centers globally: Belgium (1), Canada (6), France (3), Germany (3), Ireland (1) Italy (2), Netherlands (2), Switzerland (2), United Kingdom (2), USA (20) |
| Publication |

Objectives

Primary outcome/objective:

To determine the long-term safety and tolerability of the most clinically effective dose of TCH346 in patients with Amyotrophic Lateral Sclerosis (ALS).

Secondary outcome/objectives:

To determine the long-term efficacy of TCH346 based on clinical functionality (Amyotrophic Lateral Sclerosis Functional Rating Scale [ALSRFS] slope of progression) and survival.

To characterize the long-term pharmacokinetic/pharmacodynamic (PK/PD) relationship of TCH346 in ALS patients.

Test Product (s), Dose(s), and Mode(s) of Administration

TCH346 was provided for oral administration as 1.0 mg tablets, 2.5 mg tablets and 7.5 mg tablets once daily.

Reference Product(s), Dose(s), and Mode(s) of Administration

Placebo was administered in the same manner as TCH346.

Criteria for Evaluation

Efficacy: As in the core study, efficacy variables were 1) the rate of functional decline in ALS patients as defined by the slope of the Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R), 2) a survival assessment of the time to death, tracheostomy, intubation with artificial ventilation or 23-hr non-invasive ventilation (NPPV) for 7 consecutive days, whichever of these events occurred first; 3) assessments of pulmonary function by spirometry (FVC, forced vital capacity) and manual muscle strength. Since muscle strength measurements, respiratory function tests and neurocognitive evaluations failed to show any trend in terms of slowing down the ALS disease progress in the core study, they were not further analyzed in the extension study

Safety: Safety variables were adverse events (AEs), serious adverse events (SAEs), vital signs, ECG and routine laboratory evaluations.

Pharmacology: plasma concentrations of TCH346 and its metabolites were planned to be measured in all study participants at all study visits, at study completion or at the time of premature discontinuation from the study.

Statistical Methods

Because the study was prematurely discontinued, statistical analyses was revised to the rate of functional decline in ALS patients as defined by the slope of the ALSFRS-R ), based on the main linear mixed effects model, with imputation of a 0 score at the date of death for the core + extension study; Kaplan-Meier estimates for the time from start of study drug treatment to survival endpoint (death, tracheotomy, intubations with artificial ventilation or NPPV for 7 consecutive days), and safety analyses of adverse events, serious adverse events, vital signs, ECG and laboratory evaluations. Due to the early termination of study no pharmacology analysis were conducted.

Demographic data was presented on the extension study population, defined as all patients who

entered the extension study on treatment. For efficacy and safety analyses, data from the extension study was integrated with data from the core study. Intent-to-treat (ITT) and Safety populations of the extension were identical with the corresponding treatment groups of the core study.

Study Population: Inclusion/Exclusion Criteria and Demographics

This study recruited males and females aged 21-80 years, inclusive suffering from clinical diagnosis of laboratory supported probable, probable or definite ALS (conforming to WFN E1 Escoral Revisited; Revised Criteria for the Diagnosis of Amyotrophic Lateral Sclerosis with ALS onset of symptoms for no more than 3.0 years at the study start. Patients could have been riluzole naïve or have been on a stable dose of riluzole (50 mg b.i.d) at study start. A vital capacity equal to or no more than 70% of the theoretical value (% predicted value) was required. Patients were excluded from the study with clinically significant sensory abnormalities, dementia, other neurologic diseases, uncompensated medical illness and or psychiatric illness, know or suspected chronic infectious disease including HIV, hepatitis B or C, and or clinically significant ECG abnormalities.

Number of Subjects

| **Total number of patients studied** | **TCH346 1.0 mg N=72** | **TCH346 2.5 mg N=68** | **TCH346 7.5 mg N=71** | **TCH346 15 mg N=67** | **Placebo N=72** | **Total N=350** |
|---|---|---|---|---|---|---|
| | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| Completed study treatment | 0 | 0 | 0 | 0 | 0 | 0 |
| Discontinued study treatment | 72 (100) | 68 (100) | 71 (100) | 67 (100) | 72 (100) | 350 (100) |
| Patient withdrew consent | 0 | 0 | 0 | 2 (3.0) | 0 | 2 (0.6) |
| Lost to follow-up | 0 | 0 | 1 (1.4) | 1 (1.5) | 0 | 2 (0.6) |
| Administrative problems | 70 (97.2) | 65 (95.6) | 68 (95.8) | 61 (91.0) | 69 (95.8) | 333 (95.1) |
| Death | 2 (2.8) | 3 (4.4) | 2 (2.8) | 3 (4.5) | 3 (4.2) | 13 (3.7) |

Study was prematurely discontinued based on the results of the core trial.

Demographic and Background Characteristics

| **Total number of patients studied** | **TCH346 1.0 mg N=72** | **TCH346 2.5 mg N=68** | **TCH346 7.5 mg N=71** | **TCH346 15 mg N=67** | **Placebo N=72** | **Total N=350** |
|---|---|---|---|---|---|---|
| Age (years) | | | | | | |
| Mean (SD) | 57.1 (10.3) | 56.8 (11.7) | 54.1 (11.8) | 55.2 (11.9) | 56.0 (12.0) | 55.8 (11.5) |
| Median | 56.5 | 59.0 | 55.0 | 56.0 | 57.0 | 56.0 |
| Min,max | (32,79) | (25,78) | (20,77) | (26,76) | (33,78) | (20,79) |
| Sex [n (%)] | | | | | | |
| • Male | 46 (63.9) | 43 (63.2) | 41 (57.7) | 45 (67.2) | 49 (68.1) | 224 (64.0) |
| • Female | 26 (36.1) | 25 (36.8) | 30 (42.3) | 22 (32.8) | 23 (31.9) | 126 (36.0) |
| Race [n (%)] | | | | | | |
| Caucasian | 66 (91.7) | 66 (97.0) | 69 (97.2) | 65 (97.0) | 69 (95.8) | 335 (95.7) |
| Black | 2 ( 2.8) | 1 (1.5) | 0 | 0 | 0 | 3 (0.9) |
| Oriental | 0 | 0 | 0 | 0 | 2 (2.8) | 2 (0.6) |
| Other | 4 ( 5.6) | 1 (1.5) | 2 (2.8) | 2 (3.0) | 1 (1.4) | 10 (2.5) |

Efficacy Result(s)

Rate of functional decline in ALS patients as defined by the slope of the ALSFRS-R

Linear mixed effects model estimates for the slope after start of study treatment (ITT population)

| Treatment | n | Mean of slopes during run-in | Linear mixed effect estimate for slope during DB-treatment | Percent change in slope in relation to placebo | p-value |
|---|---|---|---|---|---|
| Placebo | 108 | -0.771 | -1.227 | - | n.a. |
| TCH346 1.0 mg | 107 | -0.898 | -1.432 | -16.7% | 0.3976 |
| TCH346 2.5 mg | 113 | -0.706 | -1.384 | -12.8% | 0.5162 |
| TCH346 7.5 mg | 110 | -0.798 | -1.259 | - 2.6% | 0.8947 |
| TCH346 15 mg | 105 | -0.913 | -1.590 | -29.5% | 0.1372 |

The estimates for the slopes and the corresponding p-values for the difference to placebo are based on the main linear mixed effects model.

A positive percent change corresponds to a reduced functional decline (positive effect). The unit is points per month.

DB = double-blind treatment.

Survival assessment of the time to death, tracheostomy, intubation with artificial ventilation or 23-hr non-invasive ventilation (NPPV) for 7 consecutive days

Time to death, tracheostomy, intubation with artificial ventilation or 23-hour non-invasive ventilation (NPPV) as well as death alone (ITT population)

| **Treatment** | **N** | **Endpoint reached n (%)** | **Log rank test p-value*** |
|---|---|---|---|
| **Death, tracheostomy, intubation with artificial ventilation or 23-hour NPPV** | | | |
| Placebo | 108 | 11 (10.2) | n.a. |
| TCH346 1.0 mg | 107 | 12 (11.2) | 0.8507 |
| TCH346 2.5 mg | 113 | 11 (9.7) | 0.7730 |
| TCH346 7.5 mg | 110 | 14 (12.7) | 0.4807 |
| TCH346 15 mg | 105 | 16 (15.2) | 0.1968 |
| **Death** | | | |
| Placebo | 108 | 9 (8.3) | n.a. |
| TCH346 1.0 mg | 107 | 11 (10.3) | 0.6674 |
| TCH346 2.5 mg | 113 | 11 (9.7) | 0.5992 |
| TCH346 7.5 mg | 110 | 14 (12.7) | 0.3290 |
| TCH346 15 mg | 105 | 16 (15.2) | 0.1229 |

* p-values are based on the pairwise log-rank tests versus placebo on the time to survival endpoint.

The ITT population does not include all randomized patients. Patients who died without efficacy assessment or study medication are not included.

Safety Results

Adverse Events by System Organ Class

| | TCH346 1.0 mq n(%) | TCH346 2.5 mq n(%) | TCH346 7.5 mq n(%) | TCH346 15 mq n(%) | TCH346 ALL n(%) | Placebo n(%) |
|---|---|---|---|---|---|---|
| Patients studied | | | | | | |
| Total no patients | 108 | 113 | 112 | 108 | 441 | 110 |
| Total no with adverse events | 95 (880) | 95 (84 1) | 101 (90.2\ | 97 (89 8) | 388 (880 | 95 (864) |
| Svstem orqan class | | | | | | |
| Gastrointestinal Disorders | 44 (407) | 44 (389) | 44 (39 3) | 44 (40.7) | 176 (39 9 | 45 (409) |
| Infections and infestations | 35 (324) | 43 (38.1) | 27 (24 1) | 39 (36.1) | 144 (327 | 41 (37 3) |
| Respiratory, thoracic and mediastinal disorder | 27 (250) | 28 (24 8) | 41 (366) | 31 (287) | 127 (288 | 28 (255) |
| Musculoskeletal and connective tissue disorders | 33 (306) | 28 (24 8) | 36 (32 1) | 17 (15.7) | 114(259 | 27 (245) |
| Nervous system disorders | 25 (23.1) | 26 (23.0) | 24 (214) | 26 (24.1) | 101 (229 | 29 (264) |
| General disorders and administration site conditions | 20 (185) | 26 (230) | 28 (250) | 22 (204) | 96 (218) | 25 (227) |
| Psychiatric disorders | 19 (17 6) | 20 (177) | 25 (223) | 28 (259) | 92 (209) | 20(182) |
| Injury, poisoning and procedural complications | 22 (204) | 19 (16.8) | 22 (19 6) | 17 (15.7) | 80 (18.1) | 22 (200) |
| Skin and subcutaneous tissue disorders | 19 (17 6) | 17 (150) | 15 (134) | 15 (139) | 66 (150) | 14 (127) |
| Investigations | 12 (11.1) | 12 (10.6) | 11 .8) | 11 (10.2) | 46 (104) | 9 @.2) |

10 Most Frequently Reported AEs Overall by Preferred Term n (%)

| Preferred term | TCH346 1.0 mg N=108 | TCH346 2.5 mg N=113 | TCH346 7.5 mg N=112 | TCH346 15 mg N=108 | TCH346 ALL N=441 | Placebo N=110 |
|---|---|---|---|---|---|---|
| | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| Any AE | 95 (88.0) | 95 (84.1) | 101 (90.2) | 97 (89.8) | 388 (88.8 | 95 (86.4) |
| Constipation | 12 (11.1) | 14 (12.4) | 14 (12.5) | 14 (13.0) | 54 (12.2) | 12 (10.9) |
| Dysphagia | 16 (14.8) | 13 (11.5) | 12 (10.7) | 11 (10.2) | 52 (11.8) | 8 (7.3) |
| Fall | 12 (11.1) | 9 (8.0) | 13 (11.6) | 9 (8.3) | 43 (9.8) | 13 (11.8) |
| Respiratory failure | 8 (7.4) | 8 (7.1 | 16 (14.3) | 11 (10.2) | 43 (9.8) | 16 (14.5) |
| Depression | 6 (5.6) | 7 (6.2) | 11 (9.8) | 14 (13.0) | 38 (8.6) | 8 (7.3) |
| Nasopharyngitis | 13 (12.0) | 9 (8.0) | 8 (7.1) | 8 (7.4) | 38 (8.6) | 13 (11.8) |
| Headache | 10 (9.3) | 9 (8.0) | 5 (4.5) | 7 (6.5) | 31 (7.0) | 9 (8.2) |
| Diarrhea | 7 (6.5) | 9 (8.0) | 6 (5.4) | 8 (7.4) | 30 (6.8) | 11 (10.0) |
| Nausea | 6 (5.6) | 8 (7.1) | 10 (8.9) | 6 (5.6) | 30 (6.8) | 10 (9.1) |
| Asthenia | 9 (8.3) | 7 (6.2) | 6 (5.4) | 6 (5.6) | 28 (6.3) | 4 (3.6) |

Serious Adverse Events and Deaths

Number (%) of patients who died, had SAEs or other significant AEs (Safety population)

| | TCH346 1.0 mg N=108 | TCH346 2.5 mg N=113 | TCH346 7.5 mg N=112 | TCH346 15 mg N=108 | Placebo N=110 |
|---|---|---|---|---|---|
| | n (%) | n (%) | n (%) | n (%) | n (%) |
| Patients with serious AEs: | | | | | |
| Death | 12 (11.1) | 11 (9.7) | 15 (13.4) | 17 (15.7) | 10 (9.1) |
| SAE | 37 (34.3) | 33 (29.2) | 35 (31.3) | 35 (32.4) | 30 (27.3) |
| Patients with other significant AEs: | | | | | |
| Discontinuations due to AEs | 15 (13.9) | 16 (14.2) | 18 (16.1) | 23 (21.3) | 16 (14.5) |
| Clinically significant AEs* | 2 (1.9) | 2 (1.8) | 2 (1.8) | 1 (0.9) | 2 (1.8) |

Counts are not mutually exclusive; patients may have events which fall into more than one category.

Other Relevant Findings

Date of Clinical Trial Report
25-Sept-2006

Date Inclusion on Novartis Clinical Trial Results Database

Date of Latest Update