2 SYNOPSIS

Name of Sponsor/Company: Teva Pharmaceutical Industries, Ltd., POB 8077, Sapir Industrial Zone, Kiryat Nordau, Netanya 42504, Israel	**Protocol No.:** ALS-TAL-201
Name of Active Ingredients: talampanel (AMPA Antagonist)	
Study Title: A Multinational, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Assess the Efficacy, Tolerability and Safety of Talampanel in Subjects with Amyotrophic Lateral Sclerosis (ALS)	
Study Principal Investigator [redacted] France [redacted] USA	
Study Site Investigators and Respective Study Sites N/A to an abbreviated report.	
Publication Based on Study Results N/A	
Study Dates September 29, 2008 – April 8, 2010	**Clinical Phase:** II
Objectives: The study objective was to assess the efficacy, tolerability and safety of talampanel in subjects with amyotrophic lateral sclerosis (ALS). The primary objective was to compare the rate of functional decline of subjects with ALS as measured by the Revised ALS Functional Rating Scale (ALSFRS-R) score, between the 50mg three times daily (tid) talampanel group and placebo. The secondary objective was to compare the time from baseline to either death, tracheostomy or permanent assisted ventilation, between the 50mg tid talampanel group and placebo.	

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Methodology: The study was a multinational, multicenter, randomized, double-blind, placebo-controlled, parallel group, Phase II study in subjects diagnosed with ALS. Subjects who were found eligible to participate in the study were randomized in a 2:1:2 ratio into one of three treatment groups: 50mg talampanel tid (150mg daily), 25mg talampanel tid (75mg daily) or Placebo for treatment duration of up to one year, followed by an open-label phase. The primary objectives of the study were to compare 50mg talampanel tid to placebo for efficacy (assessed by change from baseline in ALSFR-R), tolerability and safety. Scheduled study visits were conducted in clinic at study weeks: screening (-4 to -1), baseline, end of first escalation period (4-6), 12, 26, 40 and 52/ET. Telephone call visits to assess ALSFRS-R and record any changes in AEs and concomitant medications were conducted at study weeks: 8, 17, 22, 31, 36, 44 and 48.	
Number of Subjects (total and for each treatment): 559 subjects; 220 on talampanel 50mg tid, 112 on talampanel 25mg and 227 on placebo	

Name of Sponsor/Company: Teva Pharmaceutical Industries, Ltd., POB 8077, Sapir Industrial Zone, Kiryat Nordau, Netanya 42504, Israel	**Protocol No.:** ALS-TAL-201

Diagnosis and Main Criteria for Inclusion:
Eligible subjects were males and females with definite, probable or probable laboratory-supported familial or sporadic ALS according to the World Federation of Neurology revised El Escorial criteria who have experienced their first ALS symptoms within 3 years inclusive prior to the screening visit. The sum of the 3 respiratory items from the ALSFRS-R had to total at least 10 points at the screening and baseline visits. Subjects taking riluzole had to be on a stable dose for at least 8 weeks prior to the screening visit. Participants had to be able to take oral medication at time of screening and baseline visits. Subjects were of age 18-80 and women of child- bearing potential had to practice a medically accepted birth control method. Subjects had to have a Slow VC score equal to or greater than 70% of the predicted value for gender, height and age at the screening and baseline visits. Subjects had to be willing and able to give written informed consent prior to performing any study procedures. The following criteria excluded subjects from the study:
The use of mechanical ventilation for any part of the day or night or Bilevel Positive Airway Pressure (BiPap) for any part of the day prior to the screening visit or baseline. Feeding tube present at time of screening or baseline. Patients whose mean QTc value was above 450msec. Patients with ECG signs of Brugada syndrome and/ or complete or incomplete RBBB during screening and/ or baseline visits. Patients with clinical signs and symptoms of dementia. Known HIV positive. History of known sensitivity or intolerability to benzodiazepines. Subjects who participated in any other investigational drug trial and used any other investigational drug within 12 weeks prior to screening. Females who were pregnant or nursing at the time of screening or who would not practice medically acceptable methods of contraception. Addiction to a drug or substance within the past year prior to screening. Subjects unable at time of the screening and baseline visits to comply with the planned schedule of study visits and study procedures. Any clinically significant or unstable medical or surgical condition in the investigator's opinion, placed the subject at undue risk by participating in the study.

Subjects having used within the specified time prior to screening any of the following: (i) Talampanel (any previous use), (ii) Mecasermin (rhIGF-1) (within 4 weeks prior to screening), (iii) Chronic use of minocycline (14 consecutive days or more within 4 weeks prior to screening), (iv) Chronic use of lithium carbonate within 4 weeks prior to screening, (v) Use of more than 600mg/day coenzyme Q10 (within 4 weeks prior to screening), (vi) Any marketed drug (within 12 weeks prior to screening) if its use was not clearly indicated for any underlying medical condition other than ALS (symptomatic drugs for ALS and supplements allowed), (vii) Any drugs which induce or inhibit talampanel metabolism within 2 weeks prior to screening, (viii) Substrates of CYP2C8 within 2 weeks prior to screening, with the exception of amiodarone and chloroquine that could not be taken within 4 months prior to screening.

Test product, dose and mode of administration:
Talampanel 12.5mg, 25mg capsules and placebo were of identical appearance [redacted]

Duration of Treatment: Total treatment duration of 1 year in the placebo controlled double blind phase.

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Criteria for Evaluation:

Efficacy Measures:

Primary Endpoint:

The primary end-point of this study was the change from baseline to each visit in ALSFRS-R score. Under linear deterioration in time assumption, the primary analysis aimed at slope comparison between the 50mg tid talampanel group and the placebo group. However, due to the rejection of linearity, the pre-defined alternative analysis was employed, and the primary analysis was a comparison of the change from baseline at Week 52 between these two groups, using mixed-effect repeated measures model with categorical time.

Secondary Endpoints:

The secondary end-point of this study was the time from baseline to the first occurrence of either death, tracheostomy or permanent assisted ventilation.

[redacted]

Safety Evaluations:

Tolerability and safety evaluations included adverse events (AEs), a chest X-ray, clinical laboratory tests, vital signs, weight, physical examinations and ECG measurements.

SUMMARY-RESULTS

Subject Disposition:

559 subjects participated in the study, 220 in the talampanel 50mg tid group , 112 in the talampanel 25mg tid group and 227 in the placebo group. The study was conducted in seven EU countries (Belgium, France, Germany, Hungary, Italy, Netherlands and Spain) and in Canada, USA and Israel.
388 (69.4%) subjects completed the study according to protocol: 149 (67.7%) in the 50mg talampanel group, 77 (68.8%) in the 25mg talampanel group and 162 (71.4%) in the placebo group.
Overall 171 (30.6%) subjects prematurely terminated from the study with comparable incidence across treatment groups: 71 (32.2%) in the 50mg talampanel group, 35 (31.2%) in the 25mg talampanel group and 65 (28.6%) in the placebo group.

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Efficacy Results:
The study did not meet its primary efficacy endpoint. According to the hierarchy principle set for the study, no other formal statistical analyses of the secondary efficacy endpoints was performed.

Safety Results:
The safety profile of talampanel in this study was similar to that previously described in earlier studies with the drug. The moderate escalation scheme led to the desired tolerance with most subjects achieving maximal daily doses of 5-6 capsules and upholding them as their modal doses.
No specific laboratory, vital sign or ECG safety signal was detected. Reports of deaths were not more prevalent in talampanel-treated subjects, nor were SAEs or severe AEs.
59 subjects (10.6%) terminated due to AEs. The proportion of subjects terminating due to AEs was dose-related; the highest proportion was in the 50mg tid talampanel group (35 subjects, 15.9%), followed by the 25mg tid talampanel group (11 subjects, 9.8%). The lowest incidence of termination due to AE was in the placebo group (13 subjects, 5.7%). The foremost AEs leading to early termination were dizziness and fatigue.
50 subjects (8.9%) died during the study; distribution of deaths was similar among treatment groups: 19 (8.6%) in the 50mg talampanel group, 9 (8%) in the 25mg talampanel group and 22 (9.7 %) in the placebo group. Subject consent withdrawal showed no specific trend: 10 (4.5%) in the 50mg talampanel group, 10 (8.9%) in the 25mg talampanel group and 17 (7.5%) in the placebo group. Based on previous experience with talampanel, five grouped AEs were pre-defined as AEs of interest: dizziness, somnolence, asthenia, ataxia and fall. Contrary to pre-study assessment, fall did not display a drug relationship: general incidence of fall as well as incidence of severe fall were comparable between treatment groups.
The other four AEs of interest seem to comprise a safety signal:

- Incidence of all of these grouped AEs were higher in talampanel treated subjects than in placebo-administered ones. These AEs were among the common AEs in both talampanel groups and among the common AEs of the 50mg tid group.
- These AEs were among the most common AEs leading to early termination of talampanel treated subjects
  These AEs were among the AEs most commonly reported as severe by talampanel treated subjects.
- Dizziness was also among the SAEs with higher incidence in the 50mg tid group than placebo.

None of the AEs of interest resulted in death.

SUMMARY AND CONCLUSION:
Due to the lack of efficacy, the Sponsor decided to stop development of talampanel for the treatment of amyotrophic lateral sclerosis. The safety profile of talampanel, as shown in this study and previous studies revealed no safety signal that should preclude development of talampanel for other indications.

1 SYNOPSIS

Name of Sponsor/Company:	**Individual Study Table referring to of the Dossier**	**(For National Authority Use Only)**
Teva Pharmaceutical Industries Ltd.		
Code Name of Finished Product:		
Not applicable.	**Protocol No.: ALS-TAL-201-OL**	
Name of Active Ingredients:		
Talampanel		

Study Title: A Multinational, Multicenter, Open Label Phase to Assess Tolerability and Safety of Talampanel 50 mg TID in Subjects with Amyotrophic Lateral Sclerosis (ALS) **ALS-TAL-201-OL is an open label extension of the ALS-TAL-201 study.**

Study Principal Investigators:

[redacted] France

[redacted] USA

Publication Based on Study Results: Not Applicable

Study Period for ALS-TAL-201-OL: May 2009 – 8 April 2010	**Clinical Phase:** II

Test Product, Doses, Mode of Administration: Talampanel, oral dose starting at 25 mg 3 times daily (TID) and escalated over 2 to 6 weeks to 50 mg TID at the investigator's discretion.

Objectives: The primary objective of this study was to provide talampanel treatment to all subjects who completed the double blind placebo-controlled phase of study ALS-TAL-201 (if the investigator and subject considered it to be in the subject's interest to continue to receive talampanel 50 mg TID). The study also enabled the exploration of long-term safety and tolerability of talampanel 50 mg TID.

Methodology: This was the open-label extension of the double-blind, placebo-controlled ALS-TAL-201 study. The main study protocol ALS-TAL-201 was amended in May 2009 (Global amendment #2) which allowed initiation of the open-label extension phase (ALS-TAL-201-OL). For eligible subjects, the first study visit for ALS-TAL-201-OL was conducted at the termination visit (Week 52) of study ALS-TAL-201; this visit served as the study/baseline visit of ALS-TAL-201-OL.

To maintain the blind of study ALS-TAL-201, all subjects eligible for ALS-TAL-201-OL underwent a dose reduction to 3 capsules per day (one 25 mg capsule TID for a total of 75 mg talampanel daily) followed by escalation over 2 to 6 weeks to talampanel 50 mg TID (two 25 mg capsule TID for a total

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Talampanel		

of 150 mg talampanel daily). At the end of the dose escalation, samples for assessment of talampanel plasma levels were obtained. Subjects exceeding talampanel plasma level of 1200 ng/mL reduced talampanel to 25 mg TID. Subjects exceeding a talampanel plasma level of 1200 ng/mL while on 25 mg TID were withdrawn from the study.

Study visits were conducted at the end of open label escalation period, at Week 26, and every 26 weeks thereafter. Telephone calls were conducted every 4 weeks throughout the study.

Diagnosis and Main Criteria for Inclusion: Subjects were males and females between 18 and 80 years of age with definite, probable, or probable laboratory-supported familial or sporadic ALS according to the World Federation of Neurology revised El Escorial criteria who met all of the inclusion and none of exclusion criteria for study ALS-TAL-201. In addition, subjects must have received double-blind study medication through at least Week 52 and performed the termination visit of Protocol ALS-TAL-201 in order to enter the open-label extension.

Inclusion Criteria

Subjects must meet all the inclusion criteria to be eligible:

1) Subjects must have completed 52 weeks of treatment of the double blind placebo-controlled phase of ALS-TAL-201.
2) Women must be postmenopausal, surgically sterile, or using adequate birth control methods.
3) Subjects must be willing and able to give written informed consent prior to performing any open-label study procedures. If the subject is unable to write, he/she may give oral consent or if not possible visual consent (such as head nodding) in the presence of at least one witness as provided in local country legislation.

Duration of Treatment: It was planned that treatment in the open label extension would continue until one of the following occurred: lack of efficacy of talampanel in treatment of ALS subjects as determined by the final data analysis of the double blind placebo-controlled study ALS-TAL-201 data; issuance of a marketing authorization for talampanel in the indication of treatment of ALS; halt of the development of talampanel in ALS by Teva; or the study stops by Teva for other reasons. As the ALS-TAL-201 data did not demonstrate efficacy, this open-label extension study was terminated by the Sponsor.

Criteria for Evaluation: Telephone calls to assess the revised ALS Functional Rating Scale (ALSFRS-R) and record any changes in adverse events (AEs), ventilation and gastrostomy status, and concomitant medications were made every 4 weeks throughout the study.

At clinic visits, the following were assessed/performed: Revised ALS Functional Rating Scale (ALSFRS-R); slow VC; physical examination; laboratory tests including hematology, blood chemistry, pregnancy testing, urinalysis and the lithium carbonate; ECGs; vital signs and weight; ventilation and gastrostomy status; concomitant medications, the nature, frequency, and severity of AEs and compliance.

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Not applicable.		
Name of Active Ingredients:		
Talampanel		

Statistical Methods: Demographic characteristics and AEs are summarized descriptively. Other safety assessments and findings for the open-label extension phase are not summarized in this synopsis report.

RESULTS: Results are summarized for all subjects pooled together, regardless of the actual dose of talampanel received (75 mg or 150 mg total daily dose).

Subject Disposition: Five-hundred fifty-nine (559) subjects participated in study ALS-TAL-201 (220 in the talampanel 50mg tid group, 112 in the talampanel 25mg tid group and 227 in the placebo group), and 388 subjects completed that study (226 in the talampanel-treated groups and 162 in the placebo group). The original intent for the ALS-TAL-201-OL study data was to demonstrate long-term safety of talampanel. As such, all talampanel-treated subjects who had at least one dose of study medication in Study ALS-TAL-201 and/or the ALS-TAL-201-OL extension study were included in the ALS-TAL-201-OL data set. This included subjects who received talampanel in ALS-TAL-201 and withdrew from the study before entering ALS-TAL-201-OL; subjects who received talampanel in ALS-TAL-201 and ALS-TAL-201-OL; and subjects who received placebo treatment in the ALS-TAL-201 study and talampanel in ALS-TAL-201-OL. Together, the dataset includes 475 subjects.

Upon notification that the study was being terminated by the Sponsor, many subjects refused to return for a final visit. As such, the reason for early termination for the majority of subjects enrolled in ALS-TAL-201-OL was due to Sponsor termination of the study. Details for subjects who withdrew from the study due to death, AE or SAE are provided below under Safety Results.

Demographic Characteristics:

	Total (N=475)
Age (years)	
Mean (SD)	55.9 (11.9)
Median (Range)	57.1 (20.0-80.8)
Sex, n (%)	
Female	164 (34.5)
Male	311 (65.5)
Height (cm), n (%)	
Mean (SD)	170.2 (9.6)
Median (Range)	170.0 (145.0-196.0)
Weight (kg), n (%)	
Mean (SD)	73.7 (14.0)
Median (Range)	73.0 (44.0-120.0)
BMI (kg/m^2), n (%)	
Mean (SD)	25.4 (4.1)
Median (Range)	25.0 (17.1-42.9)

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Talampanel		

Safety Results:

Dizziness, fall, fatigue and somnolence were the most frequently reported AEs (i.e., reported in >20% of subjects, see table below) and were the AEs most frequently considered related to treatment with talampanel.

Adverse Events Reported by at Least 5% of Subjects that Received at least One Dose of Talampanel:

System Organ Class Preferred Term	**Total (N=475)** **n (%)**
Subjects Reporting Any AE	437 (92)
Ear and Labyrinth Disorders	
Vertigo	27 (5.7)
General Disorders and Administration Site Conditions	
Fatigue	102 (21.5)
Asthenia	46 (9.7)
Oedema Peripheral	26 (5.5)
Gait disturbance	24 (5.1)
Gastrointestinal Disorders	
Nausea	49 (10.3)
Constipation	41 (8.6)
Salivary hypersecretion	33 (6.9)
Diarrhea	32 (6.7)
Dysphagia	24 (5.1)
Infections and Infestations	
Nasopharyngitis	43 (9.1)
Bronchitis	26 (5.5)
Injury, Poisoning, and Procedural Complications	
Fall	119 (25.1)
Musculoskeletal and Connective Tissue Disoders	
Muscular weakness	42 (8.8)
Muscle spasms	34 (7.2)
Back pain	24 (5.1)
Metabolism and Nutrition Disorders	
Decreased appetite	24 (5.1)
Nervous System Disorders	
Dizziness	253 (53.3)
Somnolence	98 (20.6)
Headache	45 (9.5)
Balance disorder	34 (7.2)
Psychiatric Disorders	
Depression	54 (11.4)

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Not applicable.		
Name of Active Ingredients:		
Talampanel		

Anxiety	34 (7.2)
Insomnia	27 (5.7)
Respiratory, Thoracic and Mediastinal Disorders	
Respiratory failure	37 (7.8)
Dyspnoea	27 (5.7)
Cough	25 (5.3)

As previously noted, the open-label population included subjects who received talampanel in ALS-TAL-201 and withdrew from the study before entering ALS-TAL-201-OL; subjects who received talampanel in ALS-TAL-201 and ALS-TAL-201-OL; and subjects who received placebo treatment in the ALS-TAL-201 study and talampanel in ALS-TAL-201-OL. As such, safety data reported for the core double blind study may also be captured in the open-label data set.

In the ASL-TAL-201-OL dataset, it was reported that 39 subjects experienced an AE that resulted in death. Respiratory failure or acute respiratory failure accounted for 23 deaths. Three (3) deaths were considered to have a reasonable possibility of being due to talampanel; these were 2 subjects who died due to sudden death (narratives provided in the core double blind study report) and 1 subject who died as a result of respiratory failure due to ALS (verbatim term).

One hundred five (105) subjects experienced serious adverse events (SAEs) during or after treatment. Nine (9) subjects experienced SAEs that were considered reasonably attributable to talampanel; the SAEs were dizziness (3 subjects), fall and sudden death (2 subjects each) and dyspnoea, urinary retention, loss of consciousness, hyponatremia, brain lesion, tremor, and visual disturbance (1 subject each; subjects could have experienced more than 1 SAE). Narratives were provided in the core double blind study report for all related SAEs except for 1 subject with fall and brain lesion and 1 subject with sudden death. SAEs experienced by more than one subject are listed in the table below.

Seventy (70) subjects (14.7%) experienced an AE which led to premature withdrawal. Dizziness and fatigue were the leading causes of premature withdrawal, being cited by 19 and 12 subjects, respectively, as a reason for discontinuation of study medication.

Serious Adverse Events Reported by more than 1 Subject, Subjects that Received at least One Dose of Talampanel:

System Organ Class Preferred Term	**Total (N=475)** **n (%)**
Subjects Reporting Any SAE	105 (22.1)
Cardiac Disorders	
Acute coronary syndrome	2 (0.4)
General Disorders and Administration Site Conditions	
Sudden death	2 (0.4)
Gastrointestinal Disorders	
Dysphagia	4 (0.8)
Infections and Infestations	
Postoperative wound infection	3 (0.6)

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Name of Active Ingredients:		
Talampanel		

Respiratory tract infection	3 (0.6)
Bronchitis	4 (0.8)
Pneumonia	10 (2.1)
Injury, Poisoning, and Procedural Complications	
Femur fracture	4 (0.8)
Fall	6 (1.3)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	
Breast cancer	2 (0.4)
Nervous System Disorders	
Loss of consciousness	2 (0.4)
Syncope	2 (0.4)
Amyotrophic lateral sclerosis	3 (0.6)
Dizziness	3 (0.6)
Psychiatric Disorders	
Suicide attempt	4 (0.8)
Respiratory, Thoracic and Mediastinal Disorders	
Dyspnoea	9 (1.9)
Respiratory distress	2 (0.4)
Pneumonia aspiration	3 (0.6)
Pulmonary embolism	6 (1.3)
Acute respiratory failure	3 (0.6)
Respiratory failure	24 (5.1)
Lung disorder	5 (1.1)
Surgical and Medical Disorders	
Tracheostomy	3 (0.6)
Vascular Disorders	
Deep vein thrombosis	4 (0.8)

Overall Conclusions and Discussion:
Due to the lack of efficacy in the core double blind ALS-TAL-201 study, the Sponsor has decided to halt development of talampanel for ALS and terminate the open-label extension of the ALS-TAL-201 study. However, no safety signal of concern has been detected that may prevent continuing the development of talampanel for other indications.

Date of the report: May 2011