SYNOPSIS

Name of company: sanofi-aventis **Name of finished product:** HP184 **Name of active substance(s):** HP184	**TABULAR FORMAT** **REFERRING TO PART OF THE DOSSIER:** NA **Volume:** NA **Page:** NA	**(For National Authority Use only)**
Title of the study: A PHASE II, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO ASSESS THE EFFICACY AND SAFETY OF HP184 AT 100, 200 AND 400 MG DOSES ADMINISTERED ORALLY ONCE DAILY FOR 24 WEEKS IN ADULT SUBJECTS WITH CHRONIC SPINAL CORD INJURY (CSCI)		
Investigator(s): [redacted]		
Study center(s): 39 study centers, including US, Germany, United Kingdom, Australia, New Zealand, and India.		
Publications (reference): None.		
Study period: Date first subject enrolled: 13 October 2004	Date last subject completed: 31 December 2004	
Phase of development: Exploratory (Phase II)		
Objectives: The primary objective was to evaluate the effect of HP184 as compared to placebo on total motor score of American Spinal Injury Association (ASIA) manual motor test at Week 24 in CSCI subjects. The secondary objectives were to determine safety and tolerability of HP184 when administered for 24 weeks in CSCI subjects as well as the effect of HP184 on a set of motor and sensory neurological exams and reported patient outcomes.		
Methodology: A multicenter, randomized, double-blind, placebo-controlled study in 18 to 65-year-old male and female subjects with CSCI. Subjects were randomly assigned to 1 of the 4 treatment groups and received placebo, 100 mg, 200 mg, or 400 mg HP184 once a day (QD) for 24 weeks.		
Number of subjects: Planned: 240 (60 per dose group) Treated: 261 Pharmacokinetics (PK) population: 262	Randomized: 262 Efficacy population (ITT population): 256 Safety population: 261	
Diagnosis and criteria for inclusion: Male and female subjects aged 18 to 65 years with spinal cord injury (SCI) that is incomplete (traumatic) and chronic (defined as 18 months or more post SCI). CSCI was to be categorized in classes C1 or D2 in the ASIA impairment scale. The level of the SCI was to be between C4 and T10 (neurological).		
Investigational product: HP184 Dose: 100, 200, or 400 mg film coated tablet QD Batch number(s): [redacted]	Administration: Per os (orally) over 24 weeks	
Duration of observation: 26 weeks		
Reference therapy: Placebo Dose: Matching 100 mg and 200 mg film coated tablets Batch number(s): [redacted]	Administration: Per os (orally) over 24 weeks	

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Criteria for evaluation:

Primary variable - Efficacy:
The primary variable was mean change-from-baseline in total ASIA motor score at Week 24.

Secondary variables – Efficacy, safety, pharmacokinetics:
Efficacy: Secondary efficacy endpoints were responders as defined by an improvement of 6 points or more in total ASIA motor score (key secondary variable) and changes from baseline to Week 24 for the following efficacy scales: WISCI (WISCI score and time to walk 10 meters - defined as key secondary variable); neopraxis gait assessment (including gait velocity, step length for right and left legs, and duration of double support); Modified Ashworth spasticity scale; University of Alabama at Birmingham Motor Recovery Index (UABMRI), testing voluntary movement in additional muscle groups not included in ASIA sensory examination; ASIA sensory examination; SCIM; and PRO (including ISCIS, EQ-5D, and Glasgow Coma Scale questionnaire).

Safety: Adverse events (AEs) and Treatment-emergent adverse events (TEAEs) reported by the subject or noted by the investigator, physical examination, vital signs, 12-lead electrocardiogram (ECG), and standard hematology, serum chemistry, and urinalysis.

Pharmacokinetics: HP184 and HP183 (a metabolite of HP184) concentrations in plasma were measured using a validated LC/MS/MS method (Lower limit of quantitation: 0.1 ng/mL).

Statistical methods:

Primary variable - Efficacy: The primary efficacy analysis was the comparison of HP184 dose groups versus placebo with regard to the mean change-from-baseline to Week 24 in total ASIA motor score using an analysis of covariance (ANCOVA) model with terms for baseline, treatment, country, and time since injury in months.

Secondary variables – Efficacy, safety, pharmacokinetics: For the key secondary variables the following were done.

Efficacy: A supportive analysis of the primary efficacy endpoint using a logistic regression model with the categorized response rate based on $\geq$6 point change-from-baseline in total ASIA motor score at Week 24 was done. For WISCI, change from baseline to Week 24 was assessed using the ANCOVA model with terms of baseline WISCI, treatment, country, and the time since injury in months as covariates. Change-from-baseline in WISC time to walk 10 meters was analyzed using an ANCOVA model with terms for baseline, treatment, country (pooled centers), time since injury in months, baseline WISCI score, and change in total ASIA motor score.

Safety: Safety and tolerability of HP184 was evaluated from the review of individual values and descriptive statistics. TEAEs were listed and summarized by treatment group, Medical Dictionary for Regulatory Activities (MedDRA) body system, and preferred term. Potentially clinically abnormal (predefined change abnormal, PCA) laboratory parameters, vital signs, and ECG parameters were assessed.

Pharmacokinetics: Graphical presentation per dose group of the individual HP184 and HP183 plasma concentrations over time (actual time). In addition, descriptive statistics per dose group on plasma concentrations as a function of nominal time intervals (half-hourly or hourly) were reported. This analysis was performed disregarding the week of visit as steady-state was reached after four weeks of administration.

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Summary:

Subject baseline characteristics: A total of 262 patients were randomized into the double-blind phase of the trial. One patient randomized to placebo treatment group was not exposed to study medication. The 261 patients that received study drug were treated at 39 centers in the US, Europe, South Africa, Australia, and India. Of the 261 randomized and treated, 5 had no post-baseline ASIA assessment score and were thus excluded from the primary (intent-to-treat) ITT analysis.

In general, there were no apparent differences prior to treatment administration in the demographics and baseline disease characteristics among the four treatment groups.

Demographics: Of the 261 subjects who participated in the study and received investigational product, 31 (11.9%) were females and 230 (88.1%) were males. The mean (±SD) age for all subjects was 40.3 ± 11.91 years. The overall age range for the study was 18 to 72 years (waivers were obtained for 3 subjects aged >65 years). The majority of the subjects were either white (114/261, 43.7%), or Asian (118/261, 45.2%).

Baseline disease characteristics: The mean placebo baseline total ASIA score was 65.3 compared with a combined mean HP184 score of 66.1 (66.3 in the 100 mg, 69.0 in the 200 mg and 62.8 in the 400 mg dose). Baseline mean time to walk 10 meters was skewed by one subject with an extreme baseline value (3603.0); the placebo group means baseline values (and standard deviations) with and without this subject are respectively 113.9 (412.76) seconds and 63.3 (63.58) seconds. Otherwise treatment groups were comparable regarding mean time to walk 10 meters upon exclusion of this extreme value.

Protocol violations: No subject had a major protocol violation during the study. Five subjects had no post-baseline ASIA motor score and were excluded from the ITT population and the efficacy analyses. All 5 subjects were included in the safety analyses. There were no randomization or dosing irregularities during the study. Overall, the percentage of subjects with any protocol violation was similar between the active treatment and placebo groups. The most common protocol violation overall was <70% investigational product compliance.

Changes in the conduct of the study or planned analyses: Two protocol amendments were issued prior to subjects being enrolled in the study: Amendment No. 1, dated 15 July 2004, and Amendment No. 2, dated 26 August 2004.

The following changes were made to the planned analyses prior to the blind being broken: the primary endpoint (change from baseline to Week 24 in total ASIA motor score) was analyzed using an ANCOVA model; a key secondary endpoint was revised to be the response rate as defined by a change from baseline to Week 24 of $\geq$6 points in total ASIA motor score; another key secondary endpoint was revised to be the change from baseline in the time to complete the 10 meter walk as evaluated by the WISCI test; WISCI scores were analyzed as continuous data using the ANCOVA model similar to the primary endpoint.

Efficacy results: The ITT primary efficacy analysis failed to show any statistically significant differences for the primary endpoint, change from baseline in total ASIA motor score, for the combined HP184 treatment group compared with placebo. In addition, there was no statistically significant treatment effect between individual HP184 doses and placebo. Results for subgroup analyses were similar to those seen in the primary analysis. Similarly, no significant findings were observed for the secondary endpoint, response rate, between HP184 and placebo.

No statistically significant differences between HP184 and placebo were shown in analyses of most other secondary efficacy variables. For the MRI secondary efficacy endpoint, however, subjects treated with HP184 100 mg doses showed significant improvement compared with those treated with placebo.

Pharmacokinetic results: After the 100, 200, and 400 mg repeated oral doses, maximal mean (SD, standard deviation) HP184 concentrations were 287 (241) ng/mL, 941 (418) ng/mL, and 1738 (1381) ng/mL, respectively. The metabolite HP183 maximal mean (SD) concentrations reached 91.3 (72.3) ng/mL, 297 (180) ng/mL, and 401 (262) ng/mL, respectively.

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Safety results: Overall, 85.4% (223 of 261 [172 subjects in HP184 treatment groups; 51 placebo group subjects]) of subjects experienced TEAEs during the study.

For the categories any TEAEs, any treatment-related TEAEs, and incidence of withdrawal from study due to AE, the rates were similar or only slightly higher for HP184 compared to placebo, for details see Table 1. With respect to withdrawals due to AEs, the highest rate occurred in the HP184 400 mg treatment group (10/65, 15.4%), the lowest rate occurred in the HP184 100 mg treatment group (1/65, 1.5%). The majority of TEAEs reported by subjects in all treatment groups were either mild or moderate in severity.

There were 13 subjects who experienced serious TEAEs in this study (3.1% [2/65] from the placebo group and 5.6% [11/196] from the HP184 group), for details see Table 2. Only 2 of the 13 subjects (1 subject in the HP184 200 mg group [reporting chest pain] and 1 subject in the HP184 400 mg group [reporting miscarriage of partner]) experienced serious TEAEs that were considered to be possibly related to the investigational product. There was 1 death reported in the HP184 100 mg group (sudden death) in a 34-year-old-male patient without other significant disease who complained of sudden onset excruciating headache and died on the way to hospital. No autopsy was performed. According to the investigator this sudden death may be possibly related to autonomic dysreflexia or cerebral hemorrhage. The death was considered not related to the investigational product.

The most common TEAEs in subjects receiving HP184 were nervous system disorders, followed by gastrointestinal disorders, see Table 3. The most commonly reported TEAEs (by decreasing incidence) in subjects receiving HP184 were dizziness, nausea, urinary tract infection, headache, constipation, fatigue, and somnolence, for details see Table 4. Slightly higher rates of treatment-related dizziness and nausea were reported in subjects receiving HP184 200 mg and 400 mg, and a slightly higher rate of headache was reported in subjects receiving HP184 200 mg.

Table 1 - Number (%) of subjects with at least 1 event during the study – all treated subjects

	Placebo (N=65)	HP184 100 mg (N=65)	HP184 200 mg (N=66)	HP184 400 mg (N=65)	Total HP184 subjects (N=196)
Any TEAEs	51 (78.5)	59 (90.8)	58 (87.9)	55 (84.6)	172 (87.8)
Any treatment-related AEs	33 (50.8)	34 (52.3)	42 (63.6)	40 (61.5)	116 (59.2)
Any serious TEAEs	2 (3.1)	6 (9.2)	3 (4.5)	2 (3.1)	11 (5.6)
All deaths	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	1 (0.5)
Permanent withdrawals from study due to AE	4 (6.1)	1 (1.5)	6 (9.1)	10 (15.4)	17 (8.7)

For hematology parameters, the number of PCA values was higher in the HP184 group compared to the placebo group, these PCA values were for hemoglobin, red blood cells, and neutrophil decrease. For clinical chemistry parameters in the HP184 treatment groups, laboratory PCA values were most frequently increased alkaline phosphatase, serum gamma-glutamyltransferase (SGGT), serum glutamic-oxaloacetic transaminase (SGOT), and serum glutamic-pyruvic transaminase (SGPT), with overall rates of occurrence being predominantly higher in the HP184 treatment group compared with the placebo group. A higher number of PCA values was noted in the HP184 200 mg and 400 mg dose groups for alkaline phosphatase, SGGT, SGOT, and SGPT

compared to HP184 100 mg dose group and placebo.

For vital signs, decreases in systolic and diastolic blood pressure were the most frequent PCAs observed, with overall occurrence rates being predominantly higher in the HP184 treatment groups (particularly in the 400 mg group) compared with placebo.

Overall, no clinically relevant or dose-related trends were observed for the ECG PCAs. One subject had a QTc value >500 msec.

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Table 2 - Serious treatment-emergent adverse events (serious TEAEs) reported during the study – safety population

Site/ Subject Number	Treatment	Gender /Age	Preferred term	Intensity/ treatment-related	Onset date	Duration (days)	Outcome
1	Placebo	Male/30	Viral infection	Severe/No	21 Dec 2004	5	Rec, no seq
2	Placebo	Male/51	Obstructive, incisional hernia	Severe/No	21 Aug 2005	11	Rec, no seq
			Paralytic ileus	Mild/No	05 Sep 2005	2	Rec, no seq
3	HP184 100 mg	Male/51	Staphylococcal bacteremia	Moderate/No	29 Apr 2005	21	Rec, seq
4	HP184 100 mg	Male/22	Urinary tract infection	Mild/No	07 Aug 2005	12	Rec, no seq
5	HP184 100 mg	Male/41	Pneumonia	Severe/No	19 Feb 2005	12	Rec, no seq
6	HP184 100 mg	Male/34	Sudden death	Severe/No	10 Oct 2005	1	Died
7	HP184 100 mg	Male/59	Hyperreflexia	Moderate/No	30 May 2005	1	Rec, no seq
			Hyperreflexia	Mild/No	31 May 2005	6	Rec, no seq
8	HP184 100 mg	Male/39	Orchitis	Severe/No	04 Jul 2005	13	Rec, no seq
9	HP184 200 mg	Male/33	Staphylococcal infection	Mild/No	30 Oct 2005	5	Rec, no seq
10	HP184 200 mg	Male/54	Intervertebral disc protrusion	Moderate/No	28 Jun 2005	Ongoing	Ongoing at time of AE report
11	HP184 200 mg	Male/28	Chest pain	Moderate/Yes	28 Nov 2005	5	Rec, no seq
			Abdominal pain	Moderate/Yes	28 Nov 2005	5	Rec, no seq
12	HP184 400 mg	Male/49	Hyperreflexia	Moderate/No	09 May 2005	16	Rec, no seq
13	HP184 400 mg	Male/33	Pregnancy of partner	Moderate/No	04 Jul 2005	15	Rec, seq
			Miscarriage of partner	Moderate/Yes	17 Jul 2005	2	Rec, no seq

Rec, no seq=recovery without sequelae; Rec, seq=recovery with sequelae

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Table 3 - TEAEs occurring in ≥5% of subjects in any treatment group – safety population

System organ class	Placebo (N=65) n (%)	HP184 100 mg (N=65) n (%)	HP184 200 mg (N=66) n (%)	HP184 400 mg (N=65) n (%)	Total HP184 subjects (N=196) n (%)
No. of subjects with TEAEs	**51 (78.5)**	**59 (90.8)**	**58 (87.9)**	**55 (84.6)**	**172 (87.8)**
Blood and lymphatic system disorders	0 (0.0)	4 (6.2)	2 (3.0)	2 (3.1)	8 (4.1)
Cardiac disorders	4 (6.2)	4 (6.2)	6 (9.1)	1 (1.5)	11 (5.6)
Gastrointestinal disorders	20 (30.8)	24 (36.9)	32 (48.5)	25 (38.5)	81 (41.3)
General disorders and administration site conditions	14 (21.5)	18 (27.7)	21 (31.8)	21 (32.3)	60 (30.6)
Infections and infestations	22 (33.8)	21 (32.3)	22 (33.3)	17 (26.2)	60 (30.6)
Injury, poisoning, and procedural complications	5 (7.7)	5 (7.7)	18 (27.3)	6 (9.2)	29 (14.8)
Investigations	15 (23.1)	15 (23.1)	12 (18.2)	15 (23.1)	42 (21.4)
Metabolism and nutrition disorders	5 (7.7)	3 (4.6)	4 (6.1)	2 (3.1)	9 (4.6)
Musculoskeletal and connective tissue disorders	18 (27.7)	20 (30.8)	24 (36.4)	14 (21.5)	58 (29.6)
Nervous system disorders	27 (41.5)	25 (38.5)	35 (53.0)	35 (53.8)	95 (48.5)
Psychiatric disorders	3 (4.6)	9 (13.8)	5 (7.6)	1 (1.5)	15 (7.7)
Renal and urinary disorders	6 (9.2)	8 (12.3)	9 (13.6)	2 (3.1)	`19 (9.7)
Respiratory, thoracic, and mediastinal disorders	2 (3.1)	3 (4.6)	6 (9.1)	5 (7.7)	14 (7.1)
Skin and subcutaneous tissue disorders	9 (13.8)	6 (9.2)	12 (18.2)	12 (18.5)	30 (15.3)

Table 4 - Subjects with TEAEs by decreasing incidence (≥5% HP184 subjects overall) – safety population

Adverse event	Placebo (N=65) n (%)	HP184 100 mg (N=65) n (%)	HP184 200 mg (N=66) n (%)	HP184 400 mg (N=65) n (%)	Total HP184 subjects (N=196) n (%)
Dizziness	9 (13.8)	9 (13.8)	13 (19.7)	13 (20.0)	35 (17.9)
Nausea	3 (4.6)	3 (4.6)	14 (21.2)	13 (20.0)	30 (15.3)
Urinary tract infection	11 (16.9)	11 (16.9)	9 (13.6)	8 (12.3)	28 (14.3)
Headache	7 (10.8)	7 (10.8)	14 (21.2)	4 (6.2)	25 (12.8)
Constipation	4 (6.2)	5 (7.7)	10 (15.2)	7 (10.8)	22 (11.2)
Fatigue	4 (6.2)	5 (7.7)	9 (13.6)	8 (12.3)	22 (11.2)
Somnolence	4 (6.2)	6 (9.2)	7 (10.6)	6 (9.2)	19 (9.7)
Pyrexia	5 (7.7)	6 (9.2)	5 (7.6)	6 (9.2)	17 (8.7)
Diarrhea	7 (10.8)	2 (3.1)	6 (9.1)	6 (9.2)	14 (7.1)
Muscle spasms	4 (6.2)	7 (10.8)	5 (7.6)	1 (1.5)	13 (6.6)
Upper respiratory tract infections	1 (1.5)	4 (6.2)	4 (6.1)	4 (6.2)	12 (6.1)
Muscle spasticity	7 (10.8)	2 (3.1)	7 (10.6)	1 (1.5)	10 (5.1)
Myalgia	1 (1.5)	4 (6.2)	5 (7.6)	1 (1.5)	10 (5.1)

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Conclusions: [redacted]

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