Sponsor

Novartis

Generic Drug Name

NIM811

Therapeutic Area of Trial

Hepatitis C

Approved Indication

Investigational.

Study Number

CNIM811B2202

Title

A randomized, adaptive-design dose finding study to assess the antiviral efficacy and safety of NIM811 administered in combination with Standard of Care (SOC) in relapsed HCV-1 infected patients.

Phase of Development

II

Study Start/End Dates

08 Sep 2009 to 27 Apr 2011

Study Design/Methodology

This was a randomized, adaptive-design study in patients with chronic hepatitis C genotype 1 (HCV-1) who had relapsed after treatment with long-acting interferon and ribavirin The primary objective was to identify a dose of NIM811+ standard of care (SOC) with a good safety profile and well tolerated, and which provided a clinically meaningful effect in viral load reduction as compared to SOC alone.
In this study the safety and efficacy profile of NIM811 combined with SOC for 4 weeks was evaluated.
Patients were randomized to a 1:1:1:1:1 ratio to receive NIM811 100 mg bid, 200 mg bid, 400 mg bid, 600 mg bid or placebo.
Once patients were randomized they received the first dose of NIM811 or placebo at the study clinic along with SOC. Patients were instructed to self administer study medication and were provided with the necessary materials for at home administration. Patients returned to the study clinic on a pre-defined schedule for routine safety assessments, review of study drug self-administration and re-supply of study medication. NIM811 or Placebo was administered on a dai-

ly bid basis for 4 weeks (patient self administration). SOC consisted of weekly PEG IFNα2a at 180 µg once per week and twice daily weight based ribavirin (1000 mg/day for patients weighing < 75 kg; 1200 mg/day for patients weighing ≥ 75 kg).
Weekly clinic visits occured during the first 5 weeks, monthly up to Week 41, and bi-monthly up to Week 49. Rapid Virologic Response (RVR) was assessed at Week 5 of NIM811/Placebo + SOC administration and Early Virologic Response (EVR) was assessed at Week 13. If there was a > 2 log decline in HCV RNA or HCV RNA was negative at Week 13, patients were continuing on SOC treatment alone, as per standard management, for up to a total of 48 weeks. If there was a > 2 log decline in HCV RNA at week 13, the patients were discontinuing treatment and subsequently, they withdrawn from the study. Patients and investigators were only informed of the 'blinded' HCV RNA results at week 13. Patients returned to the study clinic in Week 53 for safety assessement, in Week 61 for safety and SVR12 assessments and finally in Week 73 for safety, SVR24 and end of study assessments.

Centres

15 centers in 7 countries: Australia (2), Germany (1), Italy (1), Spain (3), Switzerland (1), Taiwan (2), United States (5).

Publication

None

Objectives

Primary objective(s)

To evaluate the safety and tolerability of NIM811 dosed daily for 4 weeks in combination with SOC.
To identify a dose of NIM811 which is safe and tolerated and produces in combination with SOC a clinically meaningful improvement over SOC dual therapy in antiviral response.

Secondary objective(s)

To assess the percentage of patients achieving rapid virologic response (RVR) in patients treated with NIM811 in combination with SOC.
To explore the pharmacokinetics and pharmacodynamics of NIM811 given in combination with SOC in patients with chronic hepatitis C genotype-1.
To evaluate the effect of NIM811 given in combination with SOC in patients with chronic hepatitis C on sustained virologic response at 24 weeks after the cessation of treatment (SVR24).
To evaluate the effect of NIM811 given in combination with SOC in patients with chronic hepatitis C genotype 1 on sustained virologic response 12 weeks after the cessation of treatment (SVR12).
To evaluate the positive and negative predictive value of RVR and EVR for SVR24 rate in patients treated with NIM811 in combination with SOC.

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

NIM811 100 mg/ml was provided as an oral solution at the doses of 100 mg bid, 200 mg bid, 400 mg bid and 600 mg bid. NIM811 was administered as 2 daily doses separated by 12 hours.

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

PEG IFNα2a was administered by subcutaneous injections. PEG IFNα2a was supplied as a sterile solution in pre-filled syringes at 180 µg once per week and twice daily weight based ribavirin (1000 mg/day for patients weighing < 75 kg; 1200 mg/day for patients weighing ≥ 75 kg). Ribavirin was supplied as commercially available capsules or tablets at 1000 mg/day or 1200 mg/day dose (1000 mg/day for patients weighing < 75 kg; 1200 mg/day for patients weighing ≥ 75 kg) divided between 12 hours.

Criteria for Evaluation

Efficacy assessments

Efficacy assessments included HCV viral load and platelet count. HCV RNA samples were collected at screening (visit 1), baseline (visit 2), and randomization (visit 3). For the treatment period, at Week 2 (visit 4), Week 3 (visit 5), Week 4 (visit 6), and Week 5 (visit 7). For the standard of care only period, HCV RNA samples were collected monthly in Weeks 9, 13, 17, 21, 25, 29, 33, 37, 41, and 49 (visits 8-17). For the follow-up period, HCV RNA samples were collected at week 53, week 61 and 73 (visits 18-20).

Safety and tolerability

Safety assessments included monitoring and recording all AEs, at each visit with their severity, duration and relationship to study drug. Serious adverse events (SAEs) were monitored throughout the study. Safety assessments also included the regular monitoring of clinical chemistries, (including bilirubin, ALT, AST), hematology (including platelets), urinalysis, pregnancy testing in females, ocular assessments, pharmacokinetic assessments, depression scale, FSH (visit 1 males and females, other visits only males), inhibin (males), thyroid function, creatinine clearance, palatability and adverse events monitoring.

Pharmacology

Drug concentration measurements: PK samples for NIM811 and ribavirin levels were taken in all patients at 0 hour (pre-morning dose) and 0.5, 1, 2 and 4 hours post dose on week 3 (Day 15) and week 5 (Day 29).
For any PK sampling scheduled on the same day as PEG IFN injection, PK sample was collected prior to the injection
The PK parameters (AUC0-4, Cmax, Tmax) were determined using non-compartmental methods.

Statistical Methods

Study safety and efficacy parameters were summarized using descriptive statistics. No formal hypothesis testing was conducted. No unplanned analyses were conducted on the data.
The randomized set, consisting of all randomized patients in IVRS. Patients were analyzed in the treatment group they were randomized to. The modified full analysis set, consisting of all randomized patients who received at least one dose of study medication and had at least one post-baseline HCV RNA assessment. Patients were analyzed as actually treated. All evaluations regarding efficacy used the modified full analysis set. The safety set, consisting of all patients who took at least one dose of study drug during the treatment period and had at least one post-baseline laboratory or adverse event assessment during that period. The statement that a patient had no AEs also constituted a safety assessment. Patients were analyzed according to the treatment they actually received. The safety population was used in the analysis of all safety variables.

The primary analysis variable is HCV viral load at Week 5 (RVR) and platelet count at Week 5.
HCV RNA levels/Platelet counts were measured at every visit. Absolute and change from baseline values were summarized. In addition, HCV RNA levels/Platelet counts were analyzed with an analysis of covariance by week with treatment and baseline HCV RNA level/platelet count and country (if possible) as covariates. Least squares means and treatment group differences together with their 95% confidence intervals were computed.
Baseline was defined as latest non-missing pre-dose assessment (which means up to Visit 3 assessment).
Least squares means of HCV RNA levels and the mean change from baseline were displayed graphically over time for each treatment group.
A listing for HCV RNA levels, changes from baseline in HCV RNA levels, doses of study medication, Ribavirin and PEG IFN over time was presented.
Supportive analyses (EVR, SVR12, SVR24 and end-of-treatment assessments) were analyzed to assess the robustness of the results of the RVR analysis. These analyses were conducted to confirm the outcome of the RVR analysis with respect to long term outcome and accounting for early withdrawals.
Secondary Virological response was assessed at the following time points:

RVR at Week 5, defined as a ≥2 log decline in HCV RNA from baseline or undetectable (less than limit of detection, LoD).

EVR, defined as HCV RNA undetectable (less than limit of detection, LoD) at Week 13.

End of treatment response (ETR), defined as HCV RNA undetectable (less than limit of detection, LoD) at the end of treatment. The last HCV RNA assessment before or on the max((last NIM date +1, last RBV dose +1, last PEG-INF dose +8) was used to determine the ETR.

Sustained virological response, defined as HCV RNA undetectable (less than limit of detection, LoD) 12 weeks after end of treatment (SVR12), Week 61.

Sustained virological response, defined as HCV RNA undetectable (less than limit of detection, LoD) 24 weeks after end of treatment (SVR24), Week 73.

Study Population: Inclusion/Exclusion Criteria and Demographics

Main inclusion criteria:

- Chronic Hepatitis C infection Genotype 1 with documented histology and biochemical results consistent with compensated chronic hepatitis C.
- HCV-RNA was ≥ 4 x 10^5 IU/mL at screening.
- Male and female patients from 18 to and including 69 years of age.
- Recipient of prior long acting interferon (either as PegIntron, Pegasys or albumin-interferon alpha-2b) and ribavirin (either ribavirin or the ribavirin pro-drug, viramidine) treatment for at least 12 weeks, with documented negative serum HCV RNA on treatment, who subsequently became serum HCV RNA positive after stopping treatment (“relapser”). Patients were off all treatment for at least 3 months. Appropriate documentation of viral load was provided in the patient’s source documentation for verification of relapse status.
- Platelets counts > 150,000 / mm^3 .

Main exclusion criteria:

- Contraindication to either pegylated interferon or ribavirin.
- Pregnant or breastfeeding females.
- Hepatic decompensation.
- Evidence of cirrhosis by any means available in clinical use in the local clinical setting, for example transient elastography or liver biopsy, or any other licensed test for detection of cirrhosis.

Number of Subjects

Patient disposition (Randomized set)

	NIM 100 mg + SOC N=12		NIM 200 mg + SOC N=14		NIM 400 mg + SOC N=11		NIM 600 mg + SOC N=12		Placebo + SOC N=10		Total N=59	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Disposition												
Randomized	12	100	14	100	11	100	12	100	10	100	59	100
Completed study	8	66.7	9	64.3	3	27.3	4	33.3	9	90.0	33	55.9
Discontinued study	4	33.3	5	35.7	8	72.7	8	66.7	1	10.0	26	44.1
during NIM treatment	0	0.0	0	0.0	1	9.1	1	8.3	0	0.0	2	3.4
Primary reason for premature study discontinuation												
Adverse Event(s)	0	0.0	0	0.0	1	9.1	3	25.0	0	0.0	4	6.8
Death	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Lost to follow-up	1	8.3	0	0.0	0	0.0	1	8.3	0	0.0	2	3.4
Protocol deviation	0	0.0	2	14.3	2	18.2	0	0.0	0	0.0	4	6.8
Subject withdrew consent	1	8.3	0	0.0	1	9.1	0	0.0	1	10.0	3	5.1
Subject's condition no longer requires study drug	0	0.0	1	7.1	0	0.0	0	0.0	0	0.0	1	1.7
Unsatisfactory therapeutic effect	2	16.7	2	14.3	4	36.4	4	33.3	0	0.0	12	20.3
Primary reason for premature study discontinuation during NIM treatment												
Adverse Event(s)	0	0.0	0	0.0	0	0.0	1	8.3	0	0.0	1	1.7
Protocol deviation	0	0.0	0	0.0	1	9.1	0	0.0	0	0.0	1	1.7

Demographic and Background Characteristics

Demographics, by treatment (Randomized set)

		NIM 100 mg + SOC N=12	NIM 200 mg + SOC N=14	NIM 400 mg + SOC N=11	NIM 600 mg + SOC N=12	Placebo + SOC N=10	Total N=59
Age (years)	n	12	14	11	12	10	59
	Mean	55.5	50.5	48.5	49.9	51.5	51.2
	SD	6.57	6.82	9.20	5.81	8.18	7.47

	Median	54.0	49.5	48.0	50.5	52.5	51.0
	Min - Max	47- 65	37- 65	36- 62	39- 57	41- 61	36- 65
Age group - n (%)	18 to <45	0 (0.0)	2 (14.3)	4 (36.4)	3 (25.0)	3 (30.0)	12 (20.3)
	45 to ≤65	12 (100.0)	12 (85.7)	7 (63.6)	9 (75.0)	7 (70.0)	47 (79.7)
	>65 to ≤69	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0	0 (0.0)
	>69	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sex - n (%)	Male	5 (41.7)	8 (57.1)	8 (72.7)	8 (66.7)	6 (60.0)	35 (59.3)
	Female	7 (58.3)	6 (42.9)	3 (27.3)	4 (33.3)	4 (40.0)	24 (40.7)
Race - n (%)	Caucasian	5 (41.7)	10 (71.4)	6 (54.5)	9 (75.0)	5 (50.0)	35 (59.3)
	Black	0 (0.0)	1 (7.1)	2 (18.2)	0 (0.0)	1 (10.0)	4 (6.8)
	Asian	7 (58.3)	3 (21.4)	0 (0.0)	3 (25.0)	4 (40.0)	17 (28.8)
	Other	0 (0.0)	0 (0.0)	3 (27.3)	0 (0.0)	0 (0.0)	3 (5.1)
Weight (kg)	n	12	14	11	12	10	59
	Mean	64.4	78.4	82.4	81.9	76.7	76.7
	SD	6.42	15.65	8.55	10.69	9.76	12.48
	Median	65.5	83.0	85.3	81.2	75.0	76.0
	Min - Max	55- 75	49- 108	69- 93	66- 103	66- 94	49- 108
BMI (kg/m^2)	n	12	14	11	12	10	59
	Mean	24.1	27.4	28.8	28.8	26.7	27.1
	SD	2.14	3.61	3.80	4.16	2.79	3.71
	Median	23.6	27.8	27.9	28.3	26.1	27.1
	Min - Max	21.2- 29.3	22.2- 34.0	23.9- 35.6	21.4- 36.2	23.6- 32.6	21.2- 36.2
BMI - n (%)	<30	12 (100.0)	11 (78.6)	8 (72.7)	8 (66.7)	8 (80.0)	47 (79.7)
	≥30	0 (0.0)	3 (21.4)	3 (27.3)	4 (33.3)	2 (20.0)	12 (20.3)

Baseline disease characteristics - HCV virus load, by treatment (Randomized set)

		NIM 100 mg + SOC N=12	**NIM 200 m + SOC N=14**	**NIM 400 mg + SOC N=11**	**NIM 60 mg + SOC N=12**	**Placebo + SOC N 10**	**Total N=59**
HCV RNA (log 10)	n	12	14	11	12	10	59
	Mean	6.67	6.59	6.87	6.74	6.61	6.69
	SD	0.586	0.584	0.423	0.428	0.512	0.508
	Median	6.88	6.79	6.85	6.82	6.55	6.81
	Min - Max	5.5-7.4	5.7-7.3	6.3-7.6	6.1-7.4	5.9-7.3	5.5-7.6
HCV RNA n (%)	≤ 4 log	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	≤ 5 log	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	≤ 6 log	2 (16.7)	4 (28.6)	0 (0.0)	0 (0.0)	2 (20.0)	8 (13.6)
	> 6 log	10 (83.3)	10 (71.4)	11 (100.0)	12 (100.0)	8 (80.0)	51 (86.4)
HCV genotype n (%)	1	0 (0.0)	3 (21.4)	0 (0.0)	1 (8.3)	1 (10.0)	5 (8.5)
	1a	3 (25.0)	4 (28.6)	4 (36.4)	5 (41.7)	3 (30.0)	19 (32.2)
	1b	9 (75.0)	7 (50.0)	7 (63.6)	6 (50.0)	6 (60.0)	35 (59.3)
	unable to	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

genotype

BMI = Body mass index (= weight [kg] / height [m]^2)

Primary and secondary Objective Results

Number and percentage of patients with RVR, EVR, SVR12 and SVR24 (Modified full analysis set)

	NIM 100 mg + SOC N=12 n / N	NIM 200 mg + SOC N=12 n / N	NIM 400 mg + SOC N=10 n / N	NIM 600 mg + SOC N=12 n / N	Placebo + SOC N=10 n / N
RVR	8 / 12 (66.7)	10 / 12 (83.3)	6 / 9 (66.7)	6 / 11 (54.5)	8 / 10 (80.0)
EVR	4 / 12 (33.3)	5 / 11 (45.5)	2 / 8 (25.0)	4 / 11 (36.4)	3 / 10 (30.0)
SVR12	3 / 12 (25.0)	5 / 12 (41.7)	2 / 10 (20.0)	5 / 12 (41.7)	6 / 10 (60.0)
SVR24	2 / 12 (16.7)	5 / 12 (41.7)	1 / 10 (10.0)	4 / 12 (33.3)	5 / 10 (50.0)
Viral breakthrough	2 / 12 (16.7)	0 / 12 (0.0)	0 / 10 (0.0)	1 / 11 (9.1)	0 / 10 (0.0)
Viral relapse	6 / 9 (66.7)	5 / 9 (55.6)	3 / 5 (60.0)	1 / 6 (16.7)	4 / 9 (44.4)

N = patients with HCV RNA assessment at visit

Viral breakthrough was defined as on-treatment increase of HCV RNA level by 1 log10 or more above nadir (lowest level during treatment) confirmed by a second consecutive measurement or HCV RNA becoming detectable (≥10 IU/mL) on drug confirmed by a second measurement after being undetectable (<10 IU/mL).

Viral relapse was defined as detectable (≥10 IU/mL) HCV RNA during follow-up after patients achieved non detectable HCV RNA (<10 IU/mL) at the end of standard treatment.

Safety Results

Adverse Events by System Organ Class

	NIM 100 mg + SOC N=12		NIM 200 mg + SOC N=14		NIM 400 mg + SOC N=10		NIM 600 mg + SOC N=12		Total NIM + SOC N=48		Placebo + SOC N=10	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects with any AE(s)	12	(100.0)	14	(100.0)	10	(100.0)	12	(100.0)	48	(100.0)	10	(100.0)
Primary system organ class												
Blood and lymphatic system disorders	5	(41.7)	7	(50.0)	5	(50.0)	5	(41.7)	22	(45.8)	4	(40.0)
Cardiac disorders	0	(0.0)	2	(14.3)	1	(10.0)	2	(16.7)	5	(10.4)	2	(20.0)
Ear and labyrinth disorders	1	(8.3)	0	(0.0)	1	(10.0)	1	(8.3)	3	(6.3)	1	(10.0)
Endocrine disorders	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(10.0)
Eye disorders	3	(25.0)	4	(28.6)	3	(30.0)	6	(50.0)	16	(33.3)	3	(30.0)
Gastrointestinal disorders	9	(75.0)	11	(78.6)	7	(70.0)	9	(75.0)	36	(75.0)	9	(90.0)
General disorders and administration site conditions	10	(83.3)	11	(78.6)	6	(60.0)	9	(75.0)	36	(75.0)	10	(100.0)
Hepatobiliary disorders	1	(8.3)	0	(0.0)	1	(10.0)	0	(0.0)	2	(4.2)	1	(10.0)
Immune system disorders	1	(8.3)	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.1)	0	(0.0)
Infections and infestations	5	(41.7)	4	(28.6)	5	(50.0)	5	(41.7)	19	(39.6)	6	(60.0)
Injury, poisoning and procedural complications	1	(8.3)	3	(21.4)	1	(10.0)	0	(0.0)	5	(10.4)	0	(0.0)
Investigations	2	(16.7)	5	(35.7)	2	(20.0)	4	(33.3)	13	(27.1)	1	(10.0)
Metabolism and nutrition disorders	3	(25.0)	3	(21.4)	3	(30.0)	2	(16.7)	11	(22.9)	4	(40.0)
Musculoskeletal and connective tissue disorders	5	(41.7)	7	(50.0)	4	(40.0)	6	(50.0)	22	(45.8)	7	(70.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(10.0)
Nervous system disorders	9	(75.0)	8	(57.1)	2	(20.0)	9	(75.0)	28	(58.3)	10	(100.0)
Psychiatric disorders	5	(41.7)	8	(57.1)	3	(30.0)	6	(50.0)	22	(45.8)	7	(70.0)
Renal and urinary disorders	2	(16.7)	1	(7.1)	0	(0.0)	2	(16.7)	5	(10.4)	1	(10.0)
Respiratory, thoracic and mediastinal disorders	6	(50.0)	6	(42.9)	6	(60.0)	5	(41.7)	23	(47.9)	4	(40.0)

Skin and subcutaneous tissue disorders	6	(50.0)	9	(64.3)	1	(10.0)	5	(41.7)	21	(43.8)	5	(50.0)
Vascular disorders	1	(8.3)	2	(14.3)	2	(20.0)	1	(8.3)	6	(12.5)	2	(20.0)

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

10 Most frequent AEs (in Total NIM treated patients) by preferred term and treatment - n (%) of patients (Safety set)

	NIM 100 mg + SOC N=12		NIM 200 mg + SOC N=14		NIM 400 mg + SOC N=10		NIM 600 mg + SOC N=12		Total NIM + SOC N=48		Placebo + SOC N=10	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects with any AE(s)	12	(100.0)	14	(100.0)	10	(100.0)	12	(100.0)	48	(100.0)	10	(100.0)
Preferred term												
Fatigue	5	(41.7)	8	(57.1)	2	(20.0)	9	(75.0)	24	(50.0)	6	(60.0)
Headache	8	(66.7)	6	(42.9)	2	(20.0)	6	(50.0)	22	(45.8)	8	(80.0)
Nausea	2	(16.7)	5	(35.7)	3	(30.0)	6	(50.0)	16	(33.3)	6	(60.0)
Cough	2	(16.7)	3	(21.4)	6	(60.0)	4	(33.3)	15	(31.3)	2	(20.0)
Depression	2	(16.7)	4	(28.6)	1	(10.0)	4	(33.3)	11	(22.9)	1	(10.0)
Insomnia	2	(16.7)	5	(35.7)	1	(10.0)	3	(25.0)	11	(22.9)	5	(50.0)
Myalgia	2	(16.7)	6	(42.9)	2	(20.0)	1	(8.3)	11	(22.9)	4	(40.0)
Anaemia	3	(25.0)	4	(28.6)	2	(20.0)	1	(8.3)	10	(20.8)	4	(40.0)
Arthralgia	3	(25.0)	3	(21.4)	2	(20.0)	2	(16.7)	10	(20.8)	2	(20.0)
Decreased appetite	2	(16.7)	2	(14.3)	3	(30.0)	2	(16.7)	9	(18.8)	3	(30.0)

Preferred terms are sorted in descending order of frequency in the total column.

Serious Adverse Events and Deaths

Deaths, other serious adverse events and adverse events leading to discontinuation of study drug by treatment - n (%) of patients (Safety set)

	NIM 100 mg + SOC N=12 n (%)	NIM 200 mg + SOC N=14 n (%)	NIM 400 mg + SOC N=10 n (%)	NIM 600 mg + SOC N=12 n (%)	Total NIM + SOC N=48 n (%)	Placebo + SOC N=10
Patients with any AE(s)	12 (100.0)	14 (100.0)	10 (100.0)	12 (100.0)	48 (100.0)	10 (100.0)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
SAE(s)	0 (0.0)	0 (0.0)	3 (30.0)	1 (8.3)	4 (8.3)	2 (20.0)
Discontinued due to AE(s)	0 (0.0)	0 (0.0)	1 (10.0)	3 (25.0)	4 (8.3)	0 (0.0)
Study drug interrupted/ modified due to AE(s)	5 (41.7)	6 (42.9)	4 (40.0)	4 (33.3)	19 (39.6)	4 (40.0)

Other Relevant Findings

Arithmetic mean +/- SD pharmacokinetic parameters of NIM811 following 100 mg bid, 200 mg bid, 400 mg bid or 600 mg bid with SOC; Days 15 and 29 data

NIM PK Parame-ter	NIM 100 mg + SOC		NIM 200 mg + SOC		NIM 400 mg + SOC		NIM 600 mg + SOC	
	Day 15 (n=9)	Day 29 (n=9)	Day 15 (n=12)	Day 29 (n=11)	Day 15 (n=10)	Day 29 (n=7)	Day 15 (n=7)	Day 29 (n=7)
AUC0-4 (ng*h/mL)	2259 ± 493	2571 ± 789	3124 ± 1112	3306 ± 1201	5052 ± 582	6013 ± 1016	5820 ± 971	6480 ± 1391
Cmax (ng/mL)	809 ± 176	915 ± 335	1298 ± 362	1405 ± 350	1631 ± 321	1993 ± 350	2116 ± 603	2153 ± 456
Tmax (h[1])	1 (1-4)	1 (1-2)	1 (0.5-2)	1 (1-2)	2 (1-4)	2 (1-2)	1 (1-2)	1 (1-2)

[1] Represents Median (Range) values

Date of Clinical Trial Report

13 September 2011

Date Inclusion on Novartis Clinical Trial Results Database

7 May 2012

Date of Latest Update

7 May 2012