Sponsor

Novartis

Generic Drug Name

nilotinib (AMN107) / sonidegib (LDE225)

Trial Indication

Treatment of chronic myeloid leukemia.

Protocol Number

CAMN107Y2101

Core Protocol: 24-Jan-2013

Protocol Title

A single-arm dose-finding phase Ib multicenter study of the oral smoothened antagonist LDE225 in combination with nilotinib in chronic or accelerated phase of chronic myeloid leukemia patients who have failed prior therapy with other BCR-ABL tyrosine-kinase inhibitors

Clinical Trial Phase

Phase Ib

Study Start/End Dates

First patient first visit: 05-Jan-2012
Last patient completed: 05-Feb-2014

Study Design/Methodology

Single arm, open label, dose finding study to determine the safety and tolerability of combined treatment with nilotinib (at a planned dose level of 400 mg bid which is the approved second line CML recommended dose) and LDE225 and to obtain first insights into the efficacy of this new drug combination in Ph+ CML. The study comprised a dose escalation phase in which the maximum tolerated dose (MTD) and/or the recommended Phase II dose (RP2D) of LDE225 in combination with nilotinib was planned to be identified, and a dose expansion phase where additional patients were planned to be enrolled to further evaluate safety and tolerability of the combination. Patients were planned to be in the dose escalation or dose expansion phase for up to 12 cycles. The study core phase includes the dose escalation and dose expansion phases.

After the completion of the first 12 cycles (i.e. the core phase), patients who were still benefitting from the drug combination had the option to transition into an extension phase where safety of nilotinib (400 mg bid) and LDE225 combination was further evaluated.

Patients in the extension phase remained on treatment until progression of disease, unacceptable toxicity or if the patient discontinued for other reasons, whichever came first.

Centers

Patients were enrolled across 5 countries at 7 study centers as follows: Canada (1 center), France (1 center), Germany (2 centers), Italy (1 center) and Spain (2 centers).

Publication

None.

Objectives:

Primary objective: to determine the maximum tolerated dose (MTD) and/or recommended Phase II dose (RP2D) of nilotinib and LDE225 when administered in combination.

Secondary objective: to assess the safety and tolerability profile of the nilotinib + LDE225 combination (including extension phase), to assess the pharmacokinetic characteristics of nilotinib and LDE225 administered in combination, to determine kinetics of molecular response, to determine cytogenetic response rates

Test Product s, Doses, and Mode of Administration

Patients received two nilotinib 200 mg capsules for oral use twice daily to receive a nilotinib daily dose of 800 mg. In addition, patients received either LDE225 100 mg or 200 mg capsules for oral use once daily to receive a LDE225 daily dose of either 400 mg or 600 mg or 800 mg.

Statistical Methods

The primary objective of the dose escalation part was to determine the MTD and/or RP2D of LDE225 when administered in combination with nilotinib. The corresponding primary analysis method was an adaptive Bayesian logistic regression model guided by the escalation with overdose control (EWOC) principle. Historical information regarding the dose-toxicity curves of LDE225 and nilotinib was summarized in a prior distribution. This obtained prior distribution was then updated after each cohort of patients with the dose limiting toxicity (DLT) data from the current trial.

The primary variable was the frequency of DLTs associated with continuous daily administration of LDE225 in combination with nilotinib during the first two cycles of treatment in the dose escalation phase (up to 56 days following the first dose of study treatment). DLTs were listed using the dose determining set (DDS). The primary objective was addressed by reporting the posterior distributions of the DLT rate after each dose escalation teleconference.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria

- Patients were male or female, ≥ 18 years of age, with WHO Performance Status of ≤ 2, with Philadelphia chromosome positive CML in documented chronic or accelerated phase with resistance or intolerance or suboptimal response to at least one prior BCR-ABL targeting TKI therapy (imatinib, dasatinib, bosutinib or ponatinib).

- Patients must have been receiving nilotinib for at least 56 days prior study start without any emerging signs of intolerance and/or resistance to nilotinib as assessed by the Investigator and to be for at least 14 days prior study start on a nilotinib dose of 400 mg bid.

Exclusion criteria

- Patients could not have prior intolerance or resistance to nilotinib or an impaired cardiac function.

Participant Flow Table

Patient disposition (FAS)

Disposition Reason	LDE 400 mg qd + AMN 400 mg bid N=4 n (%)	LDE 600 mg qd + AMN 400 mg bid N=7 n (%)	All patients N=11 n (%)
Patients treated			
Treatment ongoing	0	0	0
End of treatment	4 (100.0)	7 (100.0)	11 (100.0)
Primary reason for end of treatment			
Adverse Event(s)	1 (25.0)	4 (57.1)	5 (45.5)
Subject withdrew consent	0	1 (14.3)	1 (9.1)
Administrative problems*	1 (25.0)	0	1 (9.1)
Treatment duration completed as per protocol	2 (50.0)	2 (28.6)	4 (36.4)
Primary reason for study evaluation completion			
Follow-up phase completed as per protocol	4 (100.0)	7 (100.0)	11 (100.0)

Baseline Characteristics

Demographic summary by treatment group (FAS)

Characteristics	LDE 400 mg qd + AMN 400 mg bid N=4	LDE 600 mg qd + AMN 400 mg bid N=7	All Patients N=11
Age (years)			
n	4	7	11
Mean (SD)	57.8 (8.14)	51.1 (15.37)	53.5 (13.14)
Median (Min, Max)	58.0 (48, 67)	46.0 (34, 76)	53.0 (34, 76)
25-75th percentiles	51.5-64.0	38.0-67.0	44.0-67.0
Age category - n (%)			
<35 years	0	1 (14.3)	1 (9.1)
≥ 35 - <45 years	0	2 (28.6)	2 (18.2)
≥ 45 - <55 years	1 (25.0)	2 (28.6)	3 (27.3)
≥ 55 - <65 years	2 (50.0)	0	2 (18.2)

Characteristics	LDE 400 mg qd + AMN 400 mg bid N=4	LDE 600 mg qd + AMN 400 mg bid N=7	All Patients N=11
≥ 65 years	1 (25.0)	2 (28.6)	3 (27.3)
Sex - n (%)			
Male	4 (100)	5 (71.4)	9 (81.8)
Female	0	2 (28.6)	2 (18.2)
Race - n (%)			
Caucasian	4 (100)	5 (71.4)	9 (81.8)
Missing	0	2 (28.6)	2 (18.2)
Ethnicity - n (%)			
Other	4 (100)	5 (71.4)	9 (81.8)
Missing	0	2 (28.6)	2 (18.2)
Weight (kg) at baseline			
n	4	6	10
Mean (SD)	79.88 (9.059)	85.00 (9.329)	82.95 (9.095)
Median (Min, Max)	80.75 (68.0, 90.0)	85.15 (75.0, 95.0)	80.75 (68.0, 95.0)
25-75th percentiles	74.00-85.75	76.70-93.00	76.70-92.30
Height (cm) at baseline			
n	4	7	11
Mean (SD)	173.50 (4.203)	176.29 (8.420)	175.27 (7.058)
Median (Min, Max)	173.00 (169.0, 179.0)	178.00 (160.0, 187.0)	178.00 (160.0, 187.0)
25-75th percentiles	170.50-176.50	172.00-180.00	172.00-179.00

Summary of Efficacy

Cumulative BCR-ABL ratio categories at Baseline and at Month 3, 6 and 12, by treatment group

Time	BCR-ABL ratio	LDE 400 mg qd + AMN 400 mg bid N=4 n (%)	LDE 600 mg qd + AMN 400 mg bid N=7 n (%)
Baseline	≤ 0.0032% (CMR)	0	1 (14.3)
	≤ 0.1% (MMR)	2 (50.0)	2 (28.6)
Month 3	≤ 0.0032% (CMR)	0	1 (14.3)
	≤ 0.1% (MMR)	3 (75.0)	2 (28.6)
Month 6	≤ 0.0032% (CMR)	0	0

	≤ 0.1% (MMR)	3 (75.0)	1 (14.3)
Month 12	≤ 0.0032% (CMR)	0	0
	≤ 0.1% (MMR)	2 (50.0)	2 (28.6)

Best cytogenetic response at Baseline and by Month 3, 6 and 12, by treatment group

Time	Cytogenetic response	LDE 400 mg qd + AMN 400 mg bid N=4 n (%)	LDE 600 mg qd + AMN 400 mg bid N=7 n (%)
At Baseline	CCyR	3 (75.0)	7 (100.0)
	MCyR	3 (75.0)	7 (100.0)
By Month 3	CCyR	3 (75.0)	5 (71.4)
	MCyR	3 (75.0)	5 (71.4)
By Month 6	CCyR	3 (75.0)	5 (71.4)
	MCyR	3 (75.0)	5 (71.4)
By Month 12	CCyR	3 (75.0)	5 (71.4)
	MCyR	3 (75.0)	5 (71.4)

Summary of Pharmacokinetics

In the LDE 400 + AMN 400 group, nilotinib mean Cmax and AUC0-12h at Cycle 1 Day 1 were 1360 ng/mL and 10500 ng*hr/mL, respectively. The Cmax and AUC0-12h of nilotinib at Cycle 2 Day 1 were comparable to those of Cycle 1 Day 1. Numerically higher Cmax and AUC0-12h were observed for nilotinib in both Cycle 1 Day 1 and Cycle 2 Day 1 in combination with 600 mg LDE225.
For LDE225, the mean Cmax and AUC0-24h following a daily 400 mg dose at Cycle 2 Day 1 were 748 ng/mL and 8570 ng*hr/mL, respectively. The Cmax of LDE225 following a daily 600 mg dose appeared to be increased dose-proportionally. The AUC0-24h of LDE225 appeared to be increased more than dose-proportionally.

Summary of PK parameters for nilotinib

Statistics	AUC0-12h (ng*hr/mL)	Cmax (ng/mL)	Tmax (hr)[#]	Cmin (ng/mL)	CL/F(L/h)
Cycle 1 Day 1 - LDE 400 mg qd + AMN 400 mg bid					
n	4	4	4	4	
Mean (SD)	10500 (682)	1360 (314)	2.50	759 (117)	
Geo-mean (CV%)	10500 (6.39)	1330 (22.4)	[0.00; 6.00]	753 (15.0)	
Cycle 1 Day 1 - LDE 600 mg qd + AMN 400 mg bid					
n	7	7	7	7	
Mean (SD)	14200 (5160)	1850 (622)	1.02	1070 (315)	
Geo-mean (CV%)	13500 (36.2)	1750 (36.0)	[0.00; 4.00]	1030 (28.8)	
Cycle 2 Day 1 - LDE 400 mg qd + AMN 400 mg bid					
n	4	4	4	4	4
Mean (SD)	9510 (4260)	1070 (489)	5.33	838 (181)	47.6 (17.1)
Geo-mean (CV%)	8900 (42.5)	1000 (41.8)	[2.00; 8.92]	823 (22.2)	45.0 (42.5)
Cycle 2 Day 1 - LDE 600 mg qd + AMN 400 mg bid					
n	7	7	7	7	7
Mean (SD)	15700 (8370)	2060 (1120)	2.00	1070 (475)	35.8 (27.7)
Geo-mean (CV%)	13600 (70.2)	1750 (73.4)	[0.00; 9.00]	973 (49.6)	29.5 (70.2)

Summary of PK parameters for LDE225

	AUC0-24h (ng*hr/mL)	Cmax (ng/mL)	Tmax (hr)[#]	Cmin (ng/mL)	CL/F(L/h)
Cycle 2 Day 1 - LDE 400 mg qd + AMN 400 mg bid					
n	3	3	3	3	3
Mean (SD)	8570 (3790)	748 (247)	2.00	576 (217)	53.8 (25.1)
Geo-mean (CV%)	7990 (49.3)	718 (38.0)	[1.08; 9.00]	551 (36.3)	50.1 (49.3)
Cycle 2 Day 1 - LDE 600 mg qd + AMN 400 mg bid					
n	7	7	7	7	7
Mean (SD)	19600 (8010)	1090 (365)	3.92	833 (379)	36.0 (15.6)
Geo-mean	18100 (46.1)	1030 (35.5)	[1.00; 9.00]	756 (52.0)	33.1 (46.1)

(CV%)

Summary of Safety

The Dose-Determining Set (DDS) consisted of 10 patients in 3 cohorts over 2 dose levels in the dose escalation phase. Cohort 1 (LDE225 400 mg qd + AMN 400 mg bid) had four patients of which three patients were evaluable (one patient received LDE225 200 mg throughout the study by error) and no DLTs were observed. The decision was to increase the LDE225 dose to 600 mg qd. Then cohort 2 (LDE225 600 mg qd + AMN 400 mg bid) had four evaluable patients with one patient having a DLT. The decision was to continue with the same LDE225 dose (i.e. 600 mg qd). Finally, cohort 3 had 3 evaluable patients with one patient having a DLT.

In total, two patients experienced one DLT within the first 56 days of study treatment (first 2 cycles).

Incidence of AEs by primary system organ class (Safety set)

	All grades				Grade 3/4			
System organ class	**LDE 200 mg qd + AMN 400 mg bid N=1 n (%)**	**LDE 400 mg qd + AMN 400 mg bid N=3 n (%)**	**LDE 600 mg qd + AMN 400 mg bid N=7 n (%)**	**All Patients N=11 n (%)**	**LDE 200 mg qd + AMN 400 mg bid N=1 n (%)**	**LDE 400 mg qd + AMN 400 mg bid N=3 n (%)**	**LDE 600 mg qd + AMN 400 mg bid N=7 n (%)**	**All Patients N=11 n (%)**
Any system organ class	1 (100)	3 (100)	7 (100)	11 (100)	0	2 (66.7)	3 (42.9)	5 (45.5)
Skin and subcutaneous tissue disorders	1 (100)	3 (100)	7 (100)	11 (100)	0	0	0	0
Investigations	1 (100)	3 (100)	6 (85.7)	10 (90.9)	0	2 (66.7)	3 (42.9)	5 (45.5)
Musculoskeletal and connective tissue disorders	1 (100)	2 (66.7)	6 (85.7)	9 (81.8)	0	0	1 (14.3)	1 (9.1)
Infections and infestations	1 (100)	2 (66.7)	5 (71.4)	8 (72.7)	0	0	2 (28.6)	2 (18.2)
General disorders and administration site conditions	1 (100)	0	6 (85.7)	7 (63.6)	0	0	0	0
Nervous system disorders	1 (100)	0	6 (85.7)	7 (63.6)	0	0	0	0

System organ class	All grades				Grade 3/4			
	LDE 200 mg qd + AMN 400 mg bid N=1 n (%)	LDE 400 mg qd + AMN 400 mg bid N=3 n (%)	LDE 600 mg qd + AMN 400 mg bid N=7 n (%)	All Patients N=11 n (%)	LDE 200 mg qd + AMN 400 mg bid N=1 n (%)	LDE 400 mg qd + AMN 400 mg bid N=3 n (%)	LDE 600 mg qd + AMN 400 mg bid N=7 n (%)	All Patients N=11 n (%)
Gastrointestinal disorders	0	0	6 (85.7)	6 (54.5)	0	0	1 (14.3)	1 (9.1)
Metabolism and nutrition disorders	0	2 (66.7)	4 (57.1)	6 (54.5)	0	0	1 (14.3)	1 (9.1)
Renal and urinary disorders	0	1 (33.3)	3 (42.9)	4 (36.4)	0	0	0	0
Respiratory, thoracic and mediastinal disorders	0	1 (33.3)	3 (42.9)	4 (36.4)	0	0	0	0
Psychiatric disorders	1 (100)	0	2 (28.6)	3 (27.3)	0	0	0	0
Vascular disorders	0	1 (33.3)	2 (28.6)	3 (27.3)	0	0	1 (14.3)	1 (9.1)
Blood and lymphatic system disorders	0	1 (33.3)	1 (14.3)	2 (18.2)	0	0	0	0
Hepatobiliary disorders	1 (100)	1 (33.3)	0	2 (18.2)	0	0	0	0
Injury, poisoning and procedural complications	0	1 (33.3)	1 (14.3)	2 (18.2)	0	0	0	0
Cardiac disorders	0	0	1 (14.3)	1 (9.1)	0	0	0	0
Endocrine disorders	0	1 (33.3)	0	1 (9.1)	0	0	0	0
Eye disorders	0	0	1 (14.3)	1 (9.1)	0	0	0	0

Incidence of AEs by preferred term (at least 10% incidence in overall population) (Safety set)

	All grades	Grade 3/4

Preferred term	LDE 200 mg qd + AMN 400 mg bid N=1 n (%)	LDE 400 mg qd + AMN 400 mg bid N=3 n (%)	LDE 600 mg qd + AMN 400 mg bid N=7 n (%)	All Patients N=11 n (%)	LDE 200 mg qd + AMN 400 mg bid N=1 n (%)	LDE 400 mg qd + AMN 400 mg bid N=3 n (%)	LDE 600 mg qd + AMN 400 mg bid N=7 n (%)	All Patients N=11 n (%)
Any AE	1 (100)	3 (100)	7 (100)	11 (100)	0	2 (66.7)	3 (42.9)	5 (45.5)
Alopecia	1 (100)	3 (100)	4 (57.1)	8 (72.7)	0	0	0	0
Blood creatine phosphokinase increased	1 (100)	3 (100)	3 (42.9)	7 (63.6)	0	2 (66.7)	2 (28.6)	4 (36.4)
Dysgeusia	1 (100)	0	6 (85.7)	7 (63.6)	0	0	0	0
Muscle spasms	0	2 (66.7)	5 (71.4)	7 (63.6)	0	0	0	0
Folliculitis	1 (100)	0	4 (57.1)	5 (45.5)	0	0	1 (14.3)	1 (9.1)
Weight decreased	0	1 (33.3)	3 (42.9)	4 (36.4)	0	0	0	0
Alanine aminotransferase increased	0	0	3 (42.9)	3 (27.3)	0	0	1 (14.3)	1 (9.1)
Amylase increased	0	0	3 (42.9)	3 (27.3)	0	0	0	0
Asthenia	0	0	3 (42.9)	3 (27.3)	0	0	0	0
Blood bilirubin increased	0	1 (33.3)	2 (28.6)	3 (27.3)	0	0	0	0
Constipation	0	0	3 (42.9)	3 (27.3)	0	0	0	0
Fatigue	1 (100)	0	2 (28.6)	3 (27.3)	0	0	0	0
Lipase increased	0	1 (33.3)	2 (28.6)	3 (27.3)	0	1 (33.3)	1 (14.3)	2 (18.2)
Myalgia	1 (100)	0	2 (28.6)	3 (27.3)	0	0	0	0

Preferred term	All grades				Grade 3/4			
	LDE 200 mg qd + AMN 400 mg bid N=1 n (%)	LDE 400 mg qd + AMN 400 mg bid N=3 n (%)	LDE 600 mg qd + AMN 400 mg bid N=7 n (%)	All Patients N=11 n (%)	LDE 200 mg qd + AMN 400 mg bid N=1 n (%)	LDE 400 mg qd + AMN 400 mg bid N=3 n (%)	LDE 600 mg qd + AMN 400 mg bid N=7 n (%)	All Patients N=11 n (%)
Nausea	0	0	3 (42.9)	3 (27.3)	0	0	0	0
Abdominal pain	0	0	2 (28.6)	2 (18.2)	0	0	1 (14.3)	1 (9.1)
Blood bilirubin unconjugated increased	1 (100)	1 (33.3)	0	2 (18.2)	0	0	0	0
Blood chloride increased	0	0	2 (28.6)	2 (18.2)	0	0	0	0
Blood creatinine increased	0	0	2 (28.6)	2 (18.2)	0	0	0	0
Burning sensation	0	0	2 (28.6)	2 (18.2)	0	0	0	0
Headache	1 (100)	0	1 (14.3)	2 (18.2)	0	0	0	0
Hyperglycaemia	0	1 (33.3)	1 (14.3)	2 (18.2)	0	0	0	0
Hypokalaemia	0	1 (33.3)	1 (14.3)	2 (18.2)	0	0	0	0
Hypophosphataemia	0	0	2 (28.6)	2 (18.2)	0	0	1 (14.3)	1 (9.1)
Oropharyngeal pain	0	0	2 (28.6)	2 (18.2)	0	0	0	0
Proteinuria	0	0	2 (28.6)	2 (18.2)	0	0	0	0
Pruritus	0	1 (33.3)	1 (14.3)	2 (18.2)	0	0	0	0
Rash	1 (100)	0	1 (14.3)	2 (18.2)	0	0	0	0
Troponin T increased	0	0	2 (28.6)	2 (18.2)	0	0	0	0

Study treatment-related adverse events by preferred term (at least 10% incidence in overall population) (Safety set)

	All grades				Grade 3/4			
Preferred term	**LDE 200 mg qd + AMN 400 mg bid N=1 n (%)**	**LDE 400 mg qd + AMN 400 mg bid N=3 n (%)**	**LDE 600 mg qd + AMN 400 mg bid N=7 n (%)**	**All Patients N=11 n (%)**	**LDE 200 mg qd + AMN 400 mg bid N=1 n (%)**	**LDE 400 mg qd + AMN 400 mg bid N=3 n (%)**	**LDE 600 mg qd + AMN 400 mg bid N=7 n (%)**	**All Patients N=11 n (%)**
Any AE	1 (100)	3 (100)	7 (100)	11 (100)	0	2 (66.7)	3 (42.9)	5 (45.5)
Alopecia	1 (100)	3 (100)	4 (57.1)	8 (72.7)	0	0	0	0
Blood creatine phosphokinase increased	1 (100)	3 (100)	3 (42.9)	7 (63.6)	0	2 (66.7)	2 (28.6)	4 (36.4)
Dysgeusia	1 (100)	0	6 (85.7)	7 (63.6)	0	0	0	0
Muscle spasms	0	2 (66.7)	5 (71.4)	7 (63.6)	0	0	0	0
Folliculitis	1 (100)	0	4 (57.1)	5 (45.5)	0	0	1 (14.3)	1 (9.1)
Alanine aminotransferase increased	0	0	3 (42.9)	3 (27.3)	0	0	1 (14.3)	1 (9.1)
Asthenia	0	0	3 (42.9)	3 (27.3)	0	0	0	0
Fatigue	1 (100)	0	2 (28.6)	3 (27.3)	0	0	0	0
Lipase increased	0	1 (33.3)	2 (28.6)	3 (27.3)	0	1 (33.3)	1 (14.3)	2 (18.2)
Myalgia	1 (100)	0	2 (28.6)	3 (27.3)	0	0	0	0
Weight decreased	0	1 (33.3)	2 (28.6)	3 (27.3)	0	0	0	0
Amylase increased	0	0	2 (28.6)	2 (18.2)	0	0	0	0
Rash	1 (100)	0	1 (14.3)	2 (18.2)	0	0	0	0

Preferred term	All grades				Grade 3/4			
	LDE 200 mg qd + AMN 400 mg bid N=1 n (%)	LDE 400 mg qd + AMN 400 mg bid N=3 n (%)	LDE 600 mg qd + AMN 400 mg bid N=7 n (%)	All Patients N=11 n (%)	LDE 200 mg qd + AMN 400 mg bid N=1 n (%)	LDE 400 mg qd + AMN 400 mg bid N=3 n (%)	LDE 600 mg qd + AMN 400 mg bid N=7 n (%)	All Patients N=11 n (%)
Troponin T increased	0	0	2 (28.6)	2 (18.2)	0	0	0	0

Serious Adverse Events and Deaths

Deaths, other serious or clinically significant adverse events or related discontinuations (Safety set)

Category	LDE 200 mg qd + AMN 400 mg bid N=1 n (%)		LDE 400 mg qd + AMN 400 mg bid N=3 n (%)		LDE 600 mg qd + AMN 400 mg bid N=7 n (%)		All Patients N=11 n (%)	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Deaths	0	0	0	0	0	0	0	0
Adverse events	1 (100.0)	0	3 (100.0)	2 (66.7)	7 (100.0)	3 (42.9)	11 (100.0)	5 (45.5)
Suspected to be study treatment-related	1 (100.0)	0	3 (100.0)	2 (66.7)	7 (100.0)	3 (42.9)	11 (100.0)	5 (45.5)
Serious adverse events	0	0	1 (33.3)	1 (33.3)	2 (28.6)	2 (28.6)	3 (27.3)	3 (27.3)
Suspected to be study treatment-related	0	0	1 (33.3)	1 (33.3)	1 (14.3)	1 (14.3)	2 (18.2)	2 (18.2)
AEs leading to discontinuation	0	0	1 (33.3)	0	4 (57.1)	1 (14.3)	5 (45.5)	1 (9.1)
Suspected to be study treatment-related	0	0	1 (33.3)	0	4 (57.1)	1 (14.3)	5 (45.5)	1 (9.1)
AEs requiring dose interruption and/or change	0	0	2 (66.7)	1 (33.3)	4 (57.1)	3 (42.9)	6 (54.5)	4 (36.4)
AEs requiring additional therapy	1 (100.0)	0	2 (66.7)	0	7 (100.0)	3 (42.9)	10 (90.9)	3 (27.3)

Conclusion:

- In the LDE 400 + AMN 400 group, one patient who had no MMR at baseline achieved MMR at post-baseline (from 1 month until 9 months) and one patient who had a MMR at baseline achieved CMR at post-baseline (at 2 months only). In the LDE 600 + AMN 400 group, one patient who had no MMR at baseline achieved MMR at post-baseline (at 12 months).
- For nilotinib, the mean Cmax and AUC0-12h at Cycle 2 Day 1 were comparable to those of Cycle 1 Day 1 for both treatment groups of 400 and 600 mg LDE225.
- No deaths were reported in the study.
- One patient in the LDE 400 + AMN 400 group experienced an SAE and two patients in the LDE 600 + AMN 400 group experienced each two SAEs. This included two SAEs of blood CPK increased of grade 4 severity that was suspected to be related to study treatment and a grade 3 SAE of appendicitis which was not suspected to be related to study treatment.
- The SAEs of blood CPK increased were events that could be expected from the safety profile of LDE225.
- Three patients of this study were adjudicated by the LDE225 Adjudication Committee for Muscular Events because they had experienced a blood CPK increase that was 10 times above ULN during treatment. None of these patients met the definition of rhabdomyolysis defined by the adjudication committee. One patient additionally was diagnosed with rhabdomyolysis by the Investigator; however, this event did not meet the definition of rhabdomyolysis of the LDE225 Adjudication committee for muscular events. Increases in blood CPK and rhabdomyolysis are expected side effects of LDE225.
- One patient in the LDE 400 + AMN 400 group and four patients in the LDE 600 + AMN 400 group had suspected AEs related to study treatment that led to discontinuation.
- No major adverse events were seen due to nilotinib.
- The study was early terminated since the potential benefit of adding sonidegib (LDE225) to backbone treatment with nilotinib did not appear to outweigh the additional risks. No evidence of clinical benefit or impact on molecular response was seen with the addition of sonidegib to nilotinib.
- The MTD was not determined, and no combination dose was found to be recommended for Phase II trials with respect to an acceptable risk/benefit ratio for patients with chronic phase CML.

Date of Clinical Trial Report

Final report: Published date – 08-Sep-2014

Date of Initial Inclusion on Novartis Clinical Trial Results website

20-Nov-2014

Date of Latest Update

21-Nov-2014

Reason for Update

Updated Template