

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Supplementary Appendix

Contents

ENESTnd Investigators – Page 2

Data Monitoring Board Members – Page 6

Supplementary Methods – Page 7

Supplementary Tables – Page 9

Supplementary Figure – Page 14

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Supplementary Methods

Other secondary end points

Other secondary end points included rate of MMR and CCyR over time; time to and duration of MMR and CCyR; rate of BCR-ABL/ABL ratio of $\leq 0.01\%$ and $\leq 0.0032\%$ by international scale at 12 months; event-free survival (EFS; event defined as loss of CHR, loss of PCyR, loss of CCyR, progression to AP/blast crisis [BC], or death from any cause during treatment); PFS (defined as progression to AP/BC or death from any cause during treatment); progression to AP/BC (defined as progression to AP/BC or CML-related death); OS; safety; dose intensity; and pharmacokinetics.

Statistical Analysis

The primary analysis was performed on the intent-to-treat (ITT) population when the last patient completed 12 cycles of therapy (1 cycle=28 days). Patients who left the study early or those without sufficient data for any other reason were included in the ITT analysis as nonresponders. Patients with atypical transcripts at baseline were also considered nonresponders. Two primary comparisons were made by using a step-down procedure: nilotinib 400 mg BID was compared with imatinib first, and then nilotinib 300 mg BID was compared with imatinib. A 2-sided Cochran–Mantel–Haenszel (CMH) test stratified by Sokal risk group was used at a 5% level to test statistical significance of response rates. All time-to-event comparisons were presented as Kaplan–Meier curves and compared using the log-rank test stratified by Sokal risk group.

All patients who received at least 1 dose of study drug were included in the safety analysis. Safety assessments were based mainly on the frequency of adverse events (AEs), the number of patients with notably abnormal laboratory values, and the number of patients with notably abnormal electro- and echocardiogram data. Patients were monitored and centrally evaluated for QT interval prolongation and left ventricular ejection fraction (LVEF).

The sample-size calculation for this study was based on a 15% (55% vs 40%) increase in MMR rate for the nilotinib arms vs imatinib. The study had 90% power to detect such a difference (at the 5% significance level based on stratified CMH test).

Ethics and Study Management

This study was conducted in accordance with the Declaration of Helsinki and the protocol was reviewed by the ethics committee or review board at each participating institution. All patients were required to give written informed consent. This study was registered at www.clinicaltrials.gov as #NCT00471497. Novartis employees were blinded from treatment information until database lock.

Supplementary Table 1. Patient Disposition (ITT Population).

Disposition/Reason	Nilotinib 300 mg BID N=282	Nilotinib 400 mg BID N=281	Imatinib 400 mg QD N=283
	n (%)	n (%)	n (%)
All randomization patients	282 (100)	281 (100)	283 (100)
Randomized but not treated	3 (1)	3 (1)	4 (1)
Still on study	268 (95)	271 (96)	274 (97)
Still on treatment	236 (84)	230 (82)	224 (79)
Discontinued	46 (16)	51 (18)	59 (21)
Discontinuation reason			
Adverse event(s)	13 (5)	26 (9)	21 (7)
Abnormal laboratory value(s)	6 (2)	5 (2)	3 (1)
Abnormal test procedure result(s)	0 (0)	1 (<1)	1 (<1)
Subject's condition no longer requires study drug	1 (<1)	0 (0)	0 (0)
Subject withdrew consent	6 (2)	5 (2)	3 (1)
Lost to follow-up	2 (<1)	2 (<1)	1 (<1)
Death	2 (<1)	0 (0)	0 (0)
Disease progression	2 (<1)	2 (<1)	10 (4)
Protocol deviation	4 (1)	5 (2)	4 (1)
Suboptimal response/treatment failure	10 (4)	5 (2)	16 (6)

Supplementary Table 2. BCR-ABL Ratio (IS) Categories at 12 Months (ITT Population).

	Nilotinib 300 mg BID N=282 n (%)	Nilotinib 400 mg BID N=281 n (%)	Imatinib 400 mg QD N=283 n (%)
BCR-ABL ratio categories			
≤0.0032%	12 (4.3)	13 (4.6)	1 (0.4)
>0.0032 - ≤0.01%	21 (7.4)	11 (3.9)	10 (3.5)
>0.01 - ≤0.1%	91 (32.3)	96 (34.2)	52 (18.4)
>0.1 - ≤1%	95 (33.7)	89 (31.7)	95 (33.6)
>1 - ≤10%	20 (7.1)	27 (9.6)	61 (21.6)
>10%	3 (1.1)	4 (1.4)	16 (5.7)
Atypical transcripts at baseline	5 (1.8)	1 (0.4)	2 (0.7)
Missing and/or discontinued	35 (12.4)	40 (14.2)	46 (16.3)
Ongoing	2 (0.7)	1 (0.4)	0
Discontinued due to PD/death	4 (1.4)	2 (0.7)	8 (2.8)
Discontinued due to other reason	29 (10.3)	37 (13.2)	38 (13.4)
PD, progressive disease			

Supplementary Table 3. BCR-ABL Ratio (IS) for Patients With Available Molecular Analysis at 15 and 18 Months of Therapy.

	Nilotinib 300 mg BID N=282 n (%)	Nilotinib 400 mg BID N=281 n (%)	Imatinib 400 mg QD N=283 n (%)
At 15 months			
Number observed	154	155	145
≤0.0032%	11 (7.1)	15 (9.7)	7 (4.8)
≤0.01%	22 (14.3)	31 (20.0)	13 (9.0)
≤0.1%	87 (56.5)	88 (56.8)	48 (33.1)
≤1%	145 (94.2)	142 (91.6)	116 (80.0)
≤10%	153 (99.4)	155 (100)	137 (94.5)
At 18 months			
Number observed	83	78	89
≤0.0032%	11 (13.3)	9 (11.5)	2 (2.2)
≤0.01%	20 (24.1)	17 (21.8)	6 (6.7)
≤0.1%	50 (60.2)	44 (56.4)	23 (25.8)
≤1%	79 (95.2)	73 (93.6)	76 (85.4)
≤10%	83 (100)	78 (100)	85 (95.5)

Supplementary Table 4. Best Cytogenetic Response by 12 Months (ITT Population).

	Nilotinib 300 mg BID N=282 n (%)	Nilotinib 400 mg BID N=281 n (%)	Imatinib 400 mg QD N=283 n (%)
Major cytogenetic response (MCyR)	238 (84.4)	227 (80.8)	219 (77.4)
Complete (CCyR)	226 (80.1)	219 (77.9)	184 (65.0)
Partial (PCyR)	12 (4.3)	8 (2.8)	35 (12.4)
Minor	3 (1.1)	2 (0.7)	7 (2.5)
Minimal	3 (1.1)	4 (1.4)	7 (2.5)
None	0	3 (1.1)	9 (3.2)
Ph- at baseline	0	0	1 (0.4)
Missing	38 (13.5)	45 (16.0)	40 (14.1)
Ongoing	35 (12.4)	40 (14.2)	35 (12.4)
Discontinued due to PD/death	0	0	0
Discontinued due to other reason	3 (1.1)	5 (1.8)	5 (1.8)

Ph-, Philadelphia Chromosome negative; PD, progressive disease

Supplementary Table 5. Number (%) of Patients With Serious Adverse Events Suspected to Be Related to Study Drug by System Organ Class and Treatment (Safety Population).

	All Grades			CTC Grade 3 or 4		
	Nilotinib 300 mg BID N=279 n (%)	Nilotinib 400 mg BID N=277 n (%)	Imatinib 400 mg QD N=280 n (%)	Nilotinib 300 mg BID N=279 n (%)	Nilotinib 400 mg BID N=277 n (%)	Imatinib 400 mg QD N=280 n (%)
Any system organ class	11 (3.9)	24 (8.7)	13 (4.6)	7 (2.5)	22 (7.9)	11 (3.9)
Blood and lymphatic system disorders	6 (2.2)	10 (3.6)	4 (1.4)	6 (2.2)	10 (3.6)	4 (1.4)
Cardiac disorders	3 (1.1)	1 (0.4)	0	0	0	0
Congenital, familial, and genetic disorders	0	0	1 (0.4)	0	0	1 (0.4)
Ear and labyrinth disorders	1 (0.4)	0	0	0	0	0
Endocrine disorders	0	1 (0.4)	0	0	1 (0.4)	0
Gastrointestinal disorders	1 (0.4)	5 (1.8)	2 (0.7)	1 (0.4)	4 (1.4)	1 (0.4)
General disorders and administration site conditions	1 (0.4)	1 (0.4)	1 (0.4)	0	1 (0.4)	0
Hepatobiliary disorders	0	4 (1.4)	1 (0.4)	0	2 (0.7)	1 (0.4)
Infections and infestations	0	1 (0.4)	1 (0.4)	0	0	1 (0.4)
Investigations	0	3 (1.1)	0	0	2 (0.7)	0
Metabolism and nutrition disorders	1 (0.4)	0	1 (0.4)	0	0	1 (0.4)
Musculoskeletal and connective tissue disorders	0	1 (0.4)	1 (0.4)	0	1 (0.4)	1 (0.4)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	0	1 (0.4)	1 (0.4)	0	1 (0.4)	1 (0.4)
Nervous system disorders	0	1 (0.4)	1 (0.4)	0	1 (0.4)	0
Reproductive system and breast disorders	0	0	1 (0.4)	0	0	1 (0.4)
Respiratory, thoracic, and mediastinal disorders	0	3 (1.1)	0	0	2 (0.7)	0

Figure 1. Kaplan-Meier Estimate of Time to AP/BC (ITT Population).

