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Trial 2008-004551-30, CTRIAL-IE (ICORG) 08-02

A phase II multi-center, open-label, study of Nilotinib at a dose of 300mg twice daily in adult patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia in chronic phase (CML-CP)

Clinical Trial Results:
The final technical support submitted for this trial is the full extent of results available to the sponsor. Due to differences in the reporting of specific data fields in EudraCT, certain details required for validation of trial results in EudraCT are not available to us (e.g. format of breakdown of age groups).

We as sponsor are therefore posting a PDF file of results incl. a justification.

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[redacted]

NILOTINIB

A phase II multi-centre, open-label, study of Nilotinib at a dose of 300mg twice daily in adult patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia in chronic phase (CML-CP)

Protocol Number/Version: CTRIAL-IE 08-02 / V 11
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FINAL TECHNICAL REPORT

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CONFIDENTIAL

Approvals:

Approved By:

[redacted]		9th October 2017
Chief Investigator	Chief Investigator Signature	Date:
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Trial Statistician	Trial Statistician Signature	Date:
[redacted]		09 Oct 2017
Clinical Lead (On behalf of Sponsor)	Signature	Date

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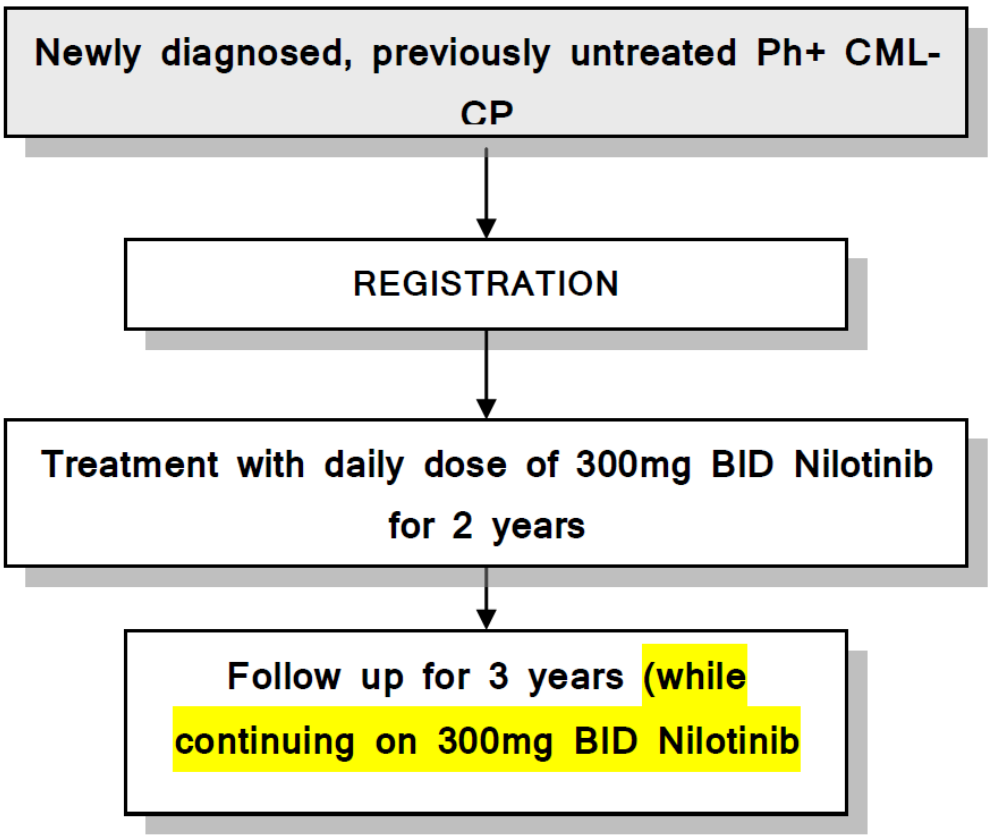
List of Abbreviations

Abbreviation	Definition
BCR-ABL	A fused gene that results from the Philadelphia chromosome
CCyR	Complete Cytogenetic Response
CHR	Complete Haematological Response
CI	Confidence Interval
CML-CP	Chronic Myelogenous leukemia in Chronic Phase
mCyR	Minor Cytogenetic Response
MCyR	Major Cytogenetic Response
MMR	Major Molecular response
PCyR	Partial Cytogenetic Response
Ph+	Philadelphia Chromosome positive
RQ-PCR	Real Time Quantitative Polymerase Chain Reaction

Background and Design

This study is an open-label, phase II, multi-centre study designed to establish whether the treatment of newly diagnosed, previously untreated Philadelphia chromosome-positive CML-CP patients treated with twice daily doses of 300mg of nilotinib is both safe and effective. It is anticipated that this study will provide preliminary evidence of possible superiority of nilotinib to imatinib mesylate, the current standard of care. The primary efficacy endpoint in this study is the **6-month** rate of complete cytogenetic response as detected by metaphase analysis, with molecular response a secondary endpoint. The rationale for using complete cytogenetic response as a primary endpoint is described in detail in Section 2.2.2 of the protocol.

Study Schema



Full details of the background to the trial and its design are presented in the protocol.

Analysis Populations

All enrolled Set: all subjects who provide informed consent and provide demographic and/or baseline screening assessments, regardless of the subject's treatment status in the study. There were 62 patients in this set.

Full Analysis Set (or intent-to-treat population): all patients who received at least one dose of the treatment and had at least one post-baseline efficacy measurement. There were 60 patients in this set (Patient 15 withdrew consent one week after registration; Patient 39 met all Inclusion/Exclusion criteria but did not meet MG level requirements for treatment at Cycle 1 day 1).

Safety Population Set: all patients who receive at least one dose of the treatment. This set is identical to the full analysis set.

Note that the all enrolled set will be used in all the baseline summary tables. Full analysis set will be used for all the efficacy tables and the safety population set will be used in all the safety tables.

Baseline Summaries

Age at registration

Table DEMO_1:
All enrolled set.

Total Subjs	MIS	Mean	SD	Median	Min	Max
62	0	51.6	14.5	53	19	77

Gender

Table DEMO_2:
All enrolled set.

Gender	n	%
Male	34	54.8% (34/62)
Female	28	45.2% (28/62)

Ethnicity

All patients were Caucasian with the following distribution of ethnic origin:

Table DEMO_3:
All enrolled set.

Ethnicity	n	%
Caucasian	4	6.5% (4/62)
English	1	1.6% (1/62)
European	1	1.6% (1/62)
Hispanic/Latino	5	8.1% (5/62)
Irish/Celtic	31	50% (31/62)
Israeli	6	9.7% (6/62)
Mixed Ethnicity	1	1.6% (1/62)
North European	7	11.3% (7/62)
Northern Irish	4	6.5% (4/62)
Russian	1	1.6% (1/62)
Unknown	1	1.6% (1/62)

Vital Signs (Baseline)

Table VITB_1:
All enrolled set.

		Vital Signs (Baseline)					
Test	Total Subjs	MIS	Mean	SD	Median	Min	Max
Weight (kg)	62	2	81.16	17.73	79.80	48.0	134.5
Height (cm)	62	14	167.25	9.53	167.50	151.1	186.0
Heart Rate (beats per minute)	62	2	81.1	14.2	80.5	52	111
Systolic BP (mmHg)	62	2	129.1	15.6	125.0	94	164
Diastolic BP (mmHg)	62	2	73.8	9.9	74.5	51	96

		Vital Signs (Baseline)					
Test	Total Subjs	MIS	Mean	SD	Median	Min	Max
Temperature (°C)	62	5	36.55	0.38	36.60	35.5	37.6

Extramedullary Involvement

Table XMED_1:

All enrolled set.

			Liver/Spleen											
extra-medullary involvement?					Liver (cm below costal margin)					Spleen (cm below costal margin)				
Total Subjs	MIS	Yes (%)	n	MIS	Min	Q1	Median	Q3	Max	Min	Q1	Median	Q3	Max
62	1	31.1% (19/61)	19	2	0	0	0	0	12	1	2	7	10	18

Echocardiogram

Table ECHOB_1:

All enrolled set.

		Echocardiogram (Baseline)					
		normal		significant clinical abnormality		non significant clinical abnormality	
Total Subjs	MIS	n	%	n	%	n	%
62	2	56	93.3%	0		4	6.7%

Electrocardiogram

Table ECGB_1:

All enrolled set.

		Electrocardiogram (Baseline)					
		normal		significant clinical abnormality		non significant clinical abnormality	
Total Subjs	MIS	n	%	n	%	n	%
62	2	52	86.7%	0		8	13.3%

ECOG Performance status

Table ECOGB_1:

All enrolled set.

		ECOG Performance status (Baseline)											
		0		1		2		3		4		5	
Total Subjs	MIS	n	%	n	%	n	%	n	%	n	%	n	%
62	2	43	71.7%	16	26.7%	1	1.7%	0		0		0	

Haematology (baseline)

Table HEMB_1:
All enrolled set.

			Haematology (Baseline)								
								Outside normal range		Clinically Significant	
Test	Total Subjs	MIS	Mean	SD	Median	Min	Max	MIS	%	MIS	%
Haemoglobin (g/dl)	62	1	12.01	1.87	11.90	7.2	16.3	2	66.7% (40/60)	2	3.3% (2/60)
Haematocrit (L/L)	62	1	0.533	1.286	0.376	0.20	10.40	2	68.3% (41/60)	2	0% (0/60)
White Blood Cell Count (x10^9/L)	62	1	66.01	68.59	46.65	6.7	425.0	1	93.4% (57/61)	1	6.6% (4/61)
Platelets (x10^9/L)	62	1	478.1	358.4	372.0	105	1715	1	47.5% (29/61)	1	4.9% (3/61)
Absolute Neutrophil Count (x10^9/L)	62	5	38.45	30.54	31.80	4.1	140.1	4	84.5% (49/58)	4	3.4% (2/58)
Bands (x10^9/L)	62	35	4.17	5.08	3.12	0.0	20.0	35	25.9% (7/27)	35	3.7% (1/27)
Lymphocytes (x10^9/L)	62	5	4.27	3.04	3.40	0.0	15.9	6	57.1% (32/56)	6	1.8% (1/56)
Monocytes (x10^9/L)	62	8	1.96	2.26	1.30	0.0	10.7	9	62.3% (33/53)	9	0% (0/53)
Eosinophils (x10^9/L)	62	14	1.629	3.166	0.830	0.00	18.69	15	66% (31/47)	15	0% (0/47)
Basophils (x10^9/L)	62	12	1.83	2.47	1.09	0.0	15.2	13	85.7% (42/49)	13	0% (0/49)
Promyelocytes (x10^9/L)	62	29	2.04	3.31	0.59	0.0	13.9	30	21.9% (7/32)	30	0% (0/32)
Myleocytes (x10^9/L)	62	20	10.21	15.53	4.00	0.0	56.8	20	54.8% (23/42)	21	0% (0/41)
Metamyelocytes (x10^9/L)	62	23	4.66	5.62	2.69	0.0	28.3	23	71.8% (28/39)	24	0% (0/38)
Blasts (x10^9/L)	62	33	1.36	4.12	0.16	0.0	22.0	34	32.1% (9/28)	34	0% (0/28)

Biochemistry (baseline)

Table CHEB_1:
All enrolled set.

			Biochemistry								
								Outside normal range		Clinically Significant	
Test	Total Subjs	MIS	Mean	SD	Median	Min	Max	MIS	%	MIS	%
AST (U/L)	62	2	27.1	7.6	25.0	15	48	3	6.8% (4/59)	3	0% (0/59)
ALT (U/L)	62	3	29.2	13.5	29.0	7	72	4	15.5% (9/58)	4	0% (0/58)
Lactate Dehydrogenase (U/L)	62	11	699.8	381.2	592.0	203	1951	11	94.1% (48/51)	11	0% (0/51)

			Biochemistry								
								Outside normal range		Clinically Significant	
Test	Total Subjs	MIS	Mean	SD	Median	Min	Max	MIS	%	MIS	%
Serum Albumin (g/L)	62	1	43.9	3.1	44.0	35	50	2	1.7% (1/60)	2	0% (0/60)
Alkaline Phosphatase (U/L)	62	2	78.2	29.4	74.0	1	194	2	10% (6/60)	2	0% (0/60)
Total Bilirubin (umol/L)	62	1	8.0	3.8	7.2	1	22	2	1.7% (1/60)	2	0% (0/60)
Blood Urea Nitrogen (BUN) or Urea (mmol/L)	62	1	7.22	3.45	6.20	3.6	18.2	2	16.7% (10/60)	2	1.7% (1/60)
Calcium (mmol/L)	62	1	2.286	0.115	2.300	2.04	2.58	2	10% (6/60)	2	1.7% (1/60)
Creatinine (umol/L)	62	1	80.0	18.2	78.0	49	135	2	13.3% (8/60)	2	1.7% (1/60)
Magnesium (mmol/L)	62	3	0.852	0.105	0.850	0.45	1.05	3	6.8% (4/59)	3	3.4% (2/59)
Potassium (mmol/L)	62	1	4.14	0.46	4.10	2.9	5.2	2	6.7% (4/60)	2	1.7% (1/60)
Sodium (mmol/L)	62	1	139.5	2.1	140.0	135	144	2	3.3% (2/60)	2	0% (0/60)
Total Protein (g/L)	62	7	73.5	4.3	73.0	63	82	7	3.6% (2/55)	7	0% (0/55)
Phosphorus (mmol/L)	62	1	1.133	0.218	1.110	0.72	1.81	2	11.7% (7/60)	2	0% (0/60)
Uric Acid (mmol/L)	62	32	10.07	53.16	0.36	0.1	291.6	33	31% (9/29)	33	3.4% (1/29)
Glucose (mmol/L)	62	3	5.725	1.824	5.300	4.05	14.15	5	15.8% (9/57)	5	0% (0/57)
Chloride (mmol/L)	62	7	103.0	2.6	103.0	96	108	8	1.9% (1/54)	8	0% (0/54)
Lipase (U/L)	62	3	49.1	48.8	35.0	9	287	4	10.3% (6/58)	4	0% (0/58)
GGT (U/L)	62	4	49.4	40.5	39.0	16	242	5	31.6% (18/57)	5	0% (0/57)
Amylase (U/dL)	62	5	55.2	20.9	54.0	20	119	6	7.1% (4/56)	6	0% (0/56)

Analysis of Primary Outcome Measure

Cytogenetic response was assessed every 3 months by bone marrow aspiration, with evaluation of a minimum of 20 metaphases, until achievement of a complete cytogenetic response (CCyR).

The rate of CCyR at 6 months was the primary endpoint for this study.

Cytogenetic Response (6 month visit)

Cytogenetic response was assessed as the percentage of Ph+ metaphases in the bone marrow and is defined as the following (a review of a minimum of 20 metaphases was required):

- Complete (**CCyR**) – 0% Ph+ metaphases
- Partial (**PCyR**) - 1 to 35% Ph+ metaphases
- Major (**MCyR**) - 0 to 35% Ph+ metaphases
- Minor (**mCyR**) - 36 to 65% Ph+ metaphases
- **Minimal** - 66 to 95% Ph+ metaphases
- **None** - 96 to 100% Ph+ metaphases

Note that a major response (0 to 35% Ph+ metaphases) combines both complete and partial responses.

The following table summarises CCyR at cycle 6.

Table CYTO_1:
Full analysis set.

Was the patient's bone marrow analysed?			Complete Cytogenetic Response (CCyR)		
Total Subjs	MIS	Yes (%)	n	MIS	CCyR (%)
60	4	75% (42/56)	42	8	94.1% (32/34)

Note that 4 patients (missing in the table) did not have the bone marrow analysed at cycle 6:

- Patient 22 was on holiday.
- Patient 24 discontinued study due to grade 3 thrombocytopenia AE.
- Patient 49 discontinued treatment due to an eye disorder (dry eye).
- Patient 52 came off trial due to rectal cancer.

Also, note that, out of the 42 patients who had the bone marrow analysed, 8 of them did not have enough number of metaphases.

As one can see, 32 out of the 34 patients who had the outcome measured at cycle 6, reached CCyR, i.e. 94.1% (95% CI using Wilson method 80.9% to 98.4%). Note that the estimated response rate is much higher than the 54% reported for Imatinib and the originally declared as clinically useful for Nilotinib, 72%. In fact, the estimated response rate is significantly higher than 72% (95% CI excludes 72%). This high success rate is consistent with the results of a previous study were patients were treated with Nilotinib 400mg BID (see Section 2.1.2 of the protocol).

Although there is a high proportion of subjects for whom either bone marrow was not analysed (15, note that patient 22 is included here since, even though this field is missing, the patient was still on study) or not enough metaphases were obtained (8 among those who had bone marrow analysed) at cycle 6, i.e. 23 out of 60 (38%), a high proportion among those with missing values had CCyR at cycle 3 and after cycle 6 (9 out of 23, 39%) or CCyR just at cycle 3 (6 out of 23, 26%) (see table below) which would indicate a likely success outcome at cycle 6 had the outcome been measured at that visit, under the reasonable assumption that the response value would carry forward to the subsequent cycle. Following this assumption (last value carried forward) another subject (patient 1) would have CCyR at cycle 6, two patients (32 and 61) would have PCyR and one patient (47) would have “None” response (see table

below). Patients 27, 35, 36 and 60 either did not have enough number of metaphases or no response was recorded before cycle 6. Using these "imputed" values, the estimated CCyR rate would be 84% (48/57) with a 95% CI using Wilson method of 72.6% to 91.5%.

Due to the small sample size (only 34 patients had the outcome measured) and the high proportion of complete cytogenetic responses (94.1% of patients had CCyR), logistic models, to adjust for potential prognostic factors, were deemed not adequate because the estimated coefficients are likely to be biased.

The following information was recorded for those patients who did not have the outcome measured at 6 months (last column indicates the outcome at prior and posterior cycles):

Patient ID	Bone Marrow Analysed at Cycle 6?	Was the aspirate specimen quality adequate for assessment	If no, specify	Outcome at other visits
1	Yes			**CCyR** at C3 and **PCyR** 18 months later (C21)
2	No			**CCyR** at C3, C15 and C24
5	No			**CCyR** at C3
11	No			**CCyR** at C3 and C15
12	Yes	No	Only 3 metaphases could be analysed, all metaphases were negative for Philadelphia chromosome	**CCyR** at C3 and C9
20	No			**CCyR** at C3
22				**CCyR** at C3, C9 and C21
24				**mCyR** at end of study visit 5.5 months post-baseline.
25	No			**CCyR** at C3 and C24
27	No			Attempts made 3 and 6 months post baseline but not enough number of metaphases
30	No			**CCyR** at C3 and C15
32	Yes	No	Insufficient sample	**PCyR** at C3 and **CCyR** at C24
35	No			Not enough metaphases at C3 and no analysis after that
36	Yes	No	Hypocellular Sample	**CCyR** at C9 and C24
41	No			**CCyR** at C3 and C24
42	Yes	No	Dry Tap	**CCyR** at C3, C9, C15, C18 and C24 (at C12 an impossible value was recorded, 46 Ph+ out of 20

Patient ID	Bone Marrow Analysed at Cycle 6?	Was the aspirate specimen quality adequate for assessment	If no, specify	Outcome at other visits
				metaphases. This value was found after DB lock and has not been queried)
46	No			**CCyR** at C3
47	No			"**None**" at C3 and **CCyR** at C12
48	No			**CCyR** at C3
49				"**Minimal**" after 4 months
51	No			**CCyR** at C3
52				No information at all
56	No			**CCyR** at C3
60	Yes	No	Bone Marrow sample failed to produce sufficient metaphases to perform cytogenetic analysis	**CCyR** at C9 and C12
61	Yes	No		**PCyR** at C3 and C9
62	Yes	Yes		**CCyR** at C3, C9, C12 and C24

Cytogenetic Response (at other cycles)

The following table summarises CCyR at other cycles.

Table CYTO_2:
Full analysis set.

	Was the patient's bone marrow analysed?			Complete Cytogenetic Response (CCyR)			95% CI Wilson method	
Visit	Total Subjs	MIS	Yes (%)	n	MIS	CCyR (%)	LB	UB
Baseline	60	0	100% (60/60)	60	7	0% (0/53)	0%	6.8%
End Cycle 3	60	2	98.3% (57/58)	57	10	74.5% (35/47)	60.5%	84.7%
End Cycle 6	60	4	75% (42/56)	42	8	94.1% (32/34)	80.9%	98.4%
End Cycle 9	60	3	35.1% (20/57)	20	3	100% (17/17)	81.6%	100%
End Cycle 12	60	6	18.5% (10/54)	10	3	85.7% (6/7)	48.7%	97.4%
End Cycle 15	60	10	18% (9/50)	9	2	100% (7/7)	64.6%	100%
End Cycle 18	60	12	10.4% (5/48)	5	3	100% (2/2)	34.2%	100%
End Cycle 21	60	15	2.2% (1/45)	1	0	100% (1/1)	20.7%	100%
End Cycle 24	60	4	57.1% (32/56)	32	9	91.3% (21/23)	73.2%	97.6%

Analysis of Secondary Outcomes

Molecular response

Major molecular response (MMR) is defined as <= 0.1% BCR-ABL/ABL % by international scale as measured by RQ-PCR.

The following table summarises MMR for different months into the treatment period (note that the CRF form where this outcome was recorded was formatted as an event driven rather than visit driven form, and only the date of sample was recorded. The number of months are calculated from the date of registration to the date the sample was collected). Note that patient 52 never had molecular response assessed and therefore has been excluded from this table.

Table MOLE_1:
Full analysis set.

			MMR	95% CI Wilson method	
Visit	**Total Subjs**	**MIS**	**%**	**LB**	**UB**
Month 0	59	15	0% (0/44)	0%	8%
Month 2	45	9	13.9% (5/36)	6.1%	28.7%
Month 3	12	1	45.5% (5/11)	21.3%	72%
Month 4	3	2	0% (0/1)	0%	79.3%
Month 5	46	6	67.5% (27/40)	52%	79.9%
Month 6	10	3	57.1% (4/7)	25%	84.2%
Month 7	3	1	0% (0/2)	0%	65.8%
Month 8	47	6	70.7% (29/41)	55.5%	82.4%
Month 9	11	1	70% (7/10)	39.7%	89.2%
Month 10	10	2	75% (6/8)	40.9%	92.9%
Month 11	37	5	71.9% (23/32)	54.6%	84.4%
Month 12	12	3	88.9% (8/9)	56.5%	98%
Month 13	23	4	78.9% (15/19)	56.7%	91.5%
Month 14	19	3	75% (12/16)	50.5%	89.8%
Month 15	12	5	85.7% (6/7)	48.7%	97.4%
Month 16	28	7	81% (17/21)	60%	92.3%
Month 17	19	5	64.3% (9/14)	38.8%	83.7%
Month 18	7	3	25% (1/4)	4.6%	69.9%
Month 19	29	7	90.9% (20/22)	72.2%	97.5%
Month 20	15	3	83.3% (10/12)	55.2%	95.3%
Month 21	13	4	77.8% (7/9)	45.3%	93.7%
Month 22	26	6	85% (17/20)	64%	94.8%
Month 23	14	6	100% (8/8)	67.6%	100%
Month 24	6	2	75% (3/4)	30.1%	95.4%
Month 25	4	1	100% (3/3)	43.9%	100%
Month 26	5	1	75% (3/4)	30.1%	95.4%
Month 27	1	0	100% (1/1)	20.7%	100%
Month 28	2	0	50% (1/2)	9.5%	90.5%
Month 29	1	0	100% (1/1)	20.7%	100%

			MMR	95% CI Wilson method	
Visit	Total Subjs	MIS	%	LB	UB
Month 30	2	1	100% (1/1)	20.7%	100%
Month 31	1	0	100% (1/1)	20.7%	100%
Month 32	1	0	0% (0/1)	0%	79.3%
Month 34	2	0	50% (1/2)	9.5%	90.5%

Prevalence of BCR-ABL mutations

The following table shows a 2x2 table of the prevalence of BCR-ABL mutations prior to and during therapy with Nilotinib (each patient is allocated to the corresponding cell depending of the “prior to” and “during” therapy BCR-ABL mutation status). Note that for some patients a negative BCR-ABL mutation during therapy could be followed by a positive BCR-ABL mutation, i.e. the corresponding cells in the table count the number of subjects who had at least one episode of negative BCR-ABL mutation during therapy.

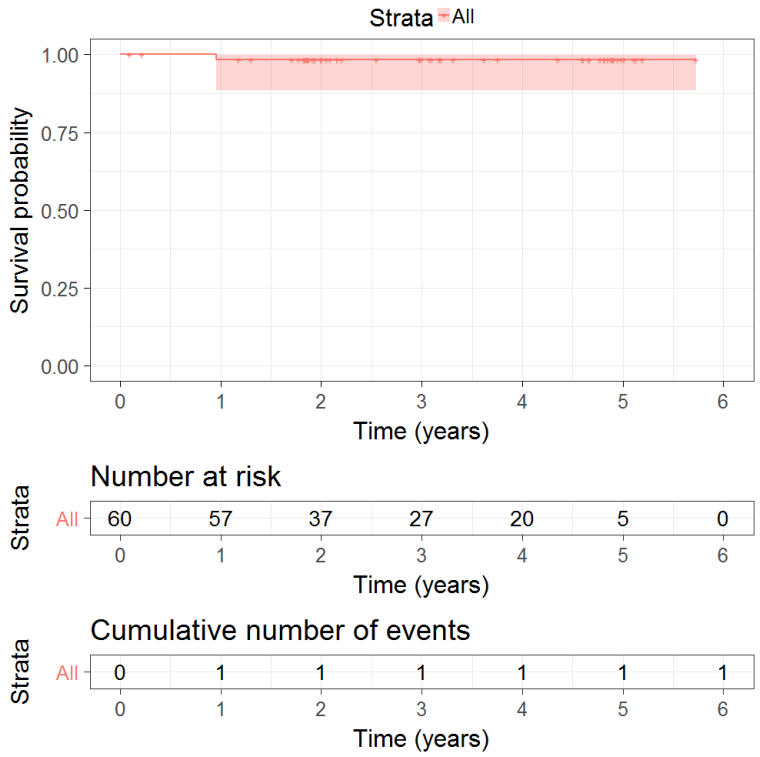
Table BCRMU_1:
Full analysis set.

	BCR-ABL mutations during therapy				McNemar's test
BCR-ABL mutations prior to therapy	Positive	Negative	MIS	Total	p-value
Positive	27	9	0	36	0.004
Negative	0	6	5	11	
MIS	1	6	6	13	
Total	28	21	11	60	

The results of test suggest a significant reduction of the prevalence of BCR-ABL mutations during therapy.

Overall Survival

This section analyses the time from study entry (date of registration) to the date of death.



FIG_OS_1

Note that there is only one reported death in the dataset, for patient 5 with cause of death due to a “Pre-existing neurological condition”.

Event Free Survival

Of additional interest was the analysis of the time from study entry to other events such as loss of Complete Haematological Response (CHR), loss of Partial Cytogenetic Response (PCyR) or loss of CCyR (first occurrence of any of those). Note that loss of CHR only applies to patients who have lost CCyR and/or PCyR.

Two patients were identified as having lost CCyR:

- Patient 1 had CCyR on 04-Mar-2009 (cycle 3) and in an unscheduled visit on 08-Sep-2010 the subject had PCyR (no other measurements were made in between or after).
- Patient 42 had CCyR at the end of cycle 9 and "none" (no response) at the end of cycle 12. Afterwards, at the end of cycle 15, the patient had CCyR again (however note that the “none” response comes from a recorded value of 46 Ph+ out of 20 metaphases. This value was found after DB lock and has not been queried).

However, none of these losses were confirmed by a second cytogenetic analysis a month after (in fact, patient 42 had CCyR measured after 3 months) as required in the protocol. No cases of loss of PCyR were identified in the available dataset either.

Therefore, none of these events have been found in the database.

Safety

Drug Exposure

Table DRUG_1 shows summaries of the number of days of drug treatment per cycle:

Table DRUG_1:
Safety set.

			Number of days of drug treatment				
Visit	Total Subjs	MIS	Mean	SD	Median	Min	Max
Cycle 1	60	0	31.3	13.1	28	7	84
Cycle 2	59	0	29.2	10.5	28	1	82
Cycle 3	58	2	28.4	9.5	28	8	80
Cycle 4	58	2	29.2	7.6	28	17	76
Cycle 5	58	5	27.9	3.7	28	9	35
Cycle 6	57	1	46.6	28.3	28	25	118
Cycle 9	57	1	81.2	15.9	84	30	126
Cycle 12	55	1	84.2	24.4	84	1	160
Cycle 15	52	0	90.4	19.8	84	63	167
Cycle 18	51	0	84.8	17.4	84	48	175
Cycle 21	51	0	82.9	19.9	84	21	126
Cycle 24	56	17	77.7	32.7	85	1	127

Table DRUG_2 shows summaries of the number of days of drug treatment interruption (zero drug administration) per cycle:

Table DRUG_2:
Safety set.

		Number of days of drug treatment interruption				
Visit	Total Subjs	Mean	SD	Median	Min	Max
Cycle 1	21	10	6.7	7	1	27
Cycle 2	8	6.8	5.5	5.5	1	16
Cycle 3	9	10.6	6.5	8	5	24
Cycle 4	5	8.2	4.6	8	2	14
Cycle 5	3	15	5.2	12	12	21
Cycle 6	6	4.7	4.5	4	1	13
Cycle 9	12	14.2	15.1	8.5	1	41
Cycle 12	9	20	25.1	12	1	77
Cycle 15	7	10.9	6.9	13	1	20
Cycle 18	5	18.8	11.6	13	9	35
Cycle 21	5	11.4	7.4	14	1	20
Cycle 24	7	12.1	12.6	14	0	36

Table DRUG_3 shows summaries of the average drug administered per patient per day (mg) averaged over the number of drug days, excluding days of drug interruption:

Table DRUG_3:
Safety set.

		Average drug administered per patient per day (mg)					
Visit	**Total Subjs**	**MIS**	**Mean**	**SD**	**Median**	**Min**	**Max**
Cycle 1	60	0	565.8	74.7	600	250	600
Cycle 2	59	0	550.3	99.1	600	227.9	600
Cycle 3	58	2	578.8	82.8	600	270	865.4
Cycle 4	58	2	575.8	80.7	600	232.7	800
Cycle 5	58	5	594.5	67.5	600	392.6	800
Cycle 6	57	1	588.2	80.9	600	367.3	800
Cycle 9	57	1	621.9	176.8	600	265.1	1600
Cycle 12	55	1	620.6	218.4	600	200	1600
Cycle 15	52	0	624.4	195	600	259.9	1600
Cycle 18	51	0	639.5	192.9	600	300	1600
Cycle 21	51	0	627.8	139.5	600	300	1200
Cycle 24	56	17	613.8	172.8	600	200	1200

Table DRUG_4 shows the frequency (number of events and number of patients) of dose modifications by cycle and reason:

Table DRUG_4:
Safety set.

	Adverse Event		**Patient Refusal/Non Compliance**		**Scheduling**		**Dosing Error**		**Other**	
Visit	**# Events**	**# Subjs**	**# Events**	**# Subjs**	**# Events**	**# Subjs**	**# Events**	**# Subjs**	**# Events**	**# Subjs**
Cycle 1	41	22	5	2	1	1	3	2	1	1
Cycle 2	16	8	1	1	3	2	1	1	4	4
Cycle 3	16	10	7	5	1	1	1	1		
Cycle 4	6	4	8	3					2	2
Cycle 5	9	4	2	2					1	1
Cycle 6	9	4	16	5					2	2
Cycle 9	17	11	7	4			2	2	6	5
Cycle 12	12	8	7	5					4	3
Cycle 15	16	7	6	4					7	5
Cycle 18	5	4	8	5					10	5
Cycle 21	4	3	15	4	1	1			4	4
Cycle 24	6	4	20	4						

Electrocardiogram

Summaries of results for those patients who had electrocardiogram performed by cycle.

Table ECG_1:
Safety set.

		Electrocardiogram results					
		Normal		Significant Clinical Abnormality		Non-significant Clinical Abnormality	
Visit	Total Subjs	n	%	n	%	n	%
Baseline	59	51	86.4% (51/59)	0		8	13.6% (8/59)
Cycle 1 D1	57	47	82.5% (47/57)	0		10	17.5% (10/57)
Cycle 1 D8	57	48	84.2% (48/57)	0		9	15.8% (9/57)
Cycle 3	56	46	82.1% (46/56)	0		10	17.9% (10/56)
Cycle 6	52	47	90.4% (47/52)	0		5	9.6% (5/52)
Cycle 9	49	43	87.8% (43/49)	0		6	12.2% (6/49)
Cycle 12	44	38	86.4% (38/44)	0		6	13.6% (6/44)
Cycle 15	12	10	83.3% (10/12)	1	8.3% (1/12)	1	8.3% (1/12)
Cycle 18	9	8	88.9% (8/9)	0		1	11.1% (1/9)
Cycle 21	8	6	75% (6/8)	0		2	25% (2/8)
Cycle 24	49	42	85.7% (42/49)	1	2% (1/49)	6	12.2% (6/49)

QT Interval

Summaries of QT intervals for those patients who had electrocardiogram performed by cycle.

Table QT_1:
Safety set.

	QT interval QTcF (msec)					
Visit	Total Subjs	Mean	SD	Median	Min	Max
Baseline	59	409.4	16.8	411	380	450
Cycle 1 D1	57	408.1	17.7	404	378	450
Cycle 1 D8	57	417.2	19	416	384	458
Cycle 3	56	414.9	18.1	412	365	463
Cycle 6	52	414.3	18.2	415	372	464
Cycle 9	49	407.5	43.3	408	141	467
Cycle 12	44	412	17.1	412	374	465
Cycle 15	12	400	18.8	395.5	362	435
Cycle 18	9	406.3	13.1	406	378	420
Cycle 21	8	396.2	16.3	396	379	426
Cycle 24	49	412.3	18.8	412	373	462

Adverse Events

All the 60 patients experienced adverse events. Tables AE_1, AE_2, AE_3, AE_4, AE_5 and AE_6 below summarise adverse events by descending order of number of patients affected.

Frequent non-haematologic adverse events (more than 5%) by preferred term are shown in Table AE_1.

Table AE_1:
Safety set.

Preferred Term (Non-hematological)	Total Subjs	%
Rash	28	46.7% (28/60)
Fatigue	26	43.3% (26/60)
Nausea	21	35% (21/60)
Back pain	19	31.7% (19/60)
Headache	19	31.7% (19/60)
Lipase increased	17	28.3% (17/60)
Constipation	16	26.7% (16/60)
Pruritus	14	23.3% (14/60)
Alanine aminotransferase increased	13	21.7% (13/60)
Alopecia	13	21.7% (13/60)
Arthralgia	12	20% (12/60)
Abdominal pain	11	18.3% (11/60)
Pain	11	18.3% (11/60)
Upper respiratory tract infection	11	18.3% (11/60)
Cough	10	16.7% (10/60)
Abdomen pain	8	13.3% (8/60)
Bone pain	8	13.3% (8/60)
Diarrhoea	8	13.3% (8/60)
Gamma-glutamyltransferase increased	8	13.3% (8/60)
Hyperbilirubinaemia	8	13.3% (8/60)
Musculoskeletal pain	8	13.3% (8/60)
Myalgia	8	13.3% (8/60)
Dry skin	7	11.7% (7/60)
Dyspepsia	7	11.7% (7/60)
Muscle spasms	7	11.7% (7/60)
Night sweats	7	11.7% (7/60)
Pyrexia	7	11.7% (7/60)
Vomiting	7	11.7% (7/60)
Abdominal discomfort	6	10% (6/60)
Anxiety	6	10% (6/60)
Blood glucose increased	6	10% (6/60)
Chest discomfort	6	10% (6/60)
Aspartate aminotransferase increased	5	8.3% (5/60)
Blood chloride increased	5	8.3% (5/60)
Blood phosphorus decreased	5	8.3% (5/60)
Dizziness	5	8.3% (5/60)
Joint stiffness	5	8.3% (5/60)
Pain in extremity	5	8.3% (5/60)
Pollakiuria	5	8.3% (5/60)

Preferred Term (Non-hematological)	Total Subjs	%
Acne	4	6.7% (4/60)
Depressed mood	4	6.7% (4/60)
Dyspnoea	4	6.7% (4/60)
Hypertension	4	6.7% (4/60)
Influenza like illness	4	6.7% (4/60)

Frequent haematologic adverse events (more than 5%) by preferred term are shown in Table AE_2.

Table AE_2:
Safety set.

Preferred Term (Hematological)	Total Subjs	%
Thrombocytopenia	8	13.3% (8/60)
Anaemia	7	11.7% (7/60)

Note that the following applies to all tables below:

- All columns except **Number of events** are subject specific. In the case of more than one event of the same AE per patient, the one with maximum grade is chosen.
- **Highest Grade** is the maximum grade recorded for that AE.
- **Related** includes *Probable* and *Possible* categories.
- **Unrelated** includes *Unlikely* and *None* categories.
- **Dose Modification** includes *Dose Held, Dose Delayed and Reduced, Dose Reduced* and *Dose Delayed* categories.
- **Treatment Interrupted** includes *Treatment Discontinued* and *Interrupted* categories.

A list of all non-haematologic adverse events regardless of relationship to study drug are shown in Table AE_3 (%s have been added for those AEs experienced by more than 5% of the patients).

Table AE_3:
Safety set.

System Organ Class	Preferred Term	Number of Events	Number of Patients	Grades 1 & 2	Grades 3,4,5	Highest Grade	Related	Unrelated	Dose Modification	Treatment Interrupted
		Non-Haematologic								
Gastrointestinal disorders	Nausea	26	21 (35%)	21	0	2	15	6	1	1

System Organ Class	Preferred Term	Number of Events	Number of Patients	Grades 1 & 2	Grades 3,4,5	Highest Grade	Related	Unrelated	Dose Modification	Treatment Interrupted
		Non-Haematologic								
	Constipation	19	16 (26.7%)	16	0	2	7	9	0	0
	Abdominal pain	13	11 (18.3%)	9	2	3	4	7	2	0
	Abdomen pain	12	8 (13.3%)	8	0	2	4	3	3	0
	Diarrhoea	10	8 (13.3%)	7	1	3	4	4	1	0
	Dyspepsia	7	7 (11.7%)	7	0	1	5	2	1	0
	Vomiting	8	7 (11.7%)	6	1	3	3	4	1	0
	Abdominal discomfort	9	6 (10%)	6	0	2	2	4	0	0
	Abdominal pain upper	4	3	3	0	1	2	1	0	0
	Flatulence	3	3	3	0	1	2	1	0	0
	Anal fissure	2	2	1	1	3	0	2	0	0
	Haemorrhoids	3	2	2	0	2	0	2	0	0
	Toothache	3	2	2	0	2	0	2	0	0
	Abdominal distension	1	1	1	0	1	0	1	0	0
	Anal pruritus	1	1	1	0	1	0	1	0	0
	Colitis	1	1	1	0	2	0	1	0	0
	Dry mouth	1	1	1	0	1	1	0	0	0
	Epigastric discomfort	1	1	1	0	1	1	0	0	0
	Gastritis	1	1	1	0	1	1	0	0	0
	Gastrointestinal disorder	1	1	1	0	1	1	0	0	0
	Gastrointestinal pain	1	1	1	0	2	1	0	0	0
	Gingival pain	1	1	1	0	1	0	1	0	0
	Hiatus hernia	1	1	1	0	1	0	1	0	0
	Mouth ulceration	1	1	1	0	1	1	0	1	0
	Pancreatitis	1	1	1	0	1	1	0	1	0
	Proctalgia	1	1	1	0	1	1	0	0	0
	Rectal fissure	1	1	1	0	2	0	1	0	0
	Rectal haemorrhage	1	1	1	0	1	0	1	1	0
Investigations	Lipase increased	45	17 (28.3%)	3	14	4	17	0	11	1
	Alanine aminotransferase increased	36	13 (21.7%)	12	1	3	12	1	7	1
	Gamma-glutamyltransferase increased	11	8 (13.3%)	7	1	3	8	0	1	0
	Blood glucose increased	8	6 (10%)	6	0	2	5	1	0	0
	Aspartate aminotransferase increased	6	5 (8.3%)	5	0	1	5	0	1	0
	Blood chloride increased	7	5 (8.3%)	5	0	1	3	2	0	0
	Blood phosphorus decreased	23	5 (8.3%)	2	3	3	5	0	2	0
	Amylase increased	4	3	2	1	3	2	1	1	0
	Blood bilirubin increased	20	3	2	1	3	3	0	2	0

System Organ Class	Preferred Term	Number of Events	Number of Patients	Grades 1 & 2	Grades 3,4,5	Highest Grade	Related	Unrelated	Dose Modification	Treatment Interrupted
		Non-Haematologic								
	Blood calcium decreased	4	3	3	0	1	3	0	0	0
	Blood lactate dehydrogenase decreased	4	3	3	0	1	3	0	0	0
	Blood potassium increased	4	3	3	0	2	3	0	0	0
	Blood uric acid increased	6	3	3	0	1	0	3	0	0
	Blood alkaline phosphatase increased	2	2	2	0	1	2	0	0	0
	Blood creatinine increased	4	2	2	0	2	0	2	0	0
	Blood uric acid decreased	2	2	2	0	1	1	1	0	0
	Lipase	6	2	1	1	3	2	0	1	0
	Weight decreased	2	2	2	0	1	1	1	0	0
	Amylase	1	1	1	0	1	1	0	0	0
	Blood albumin increased	1	1	1	0	1	1	0	0	0
	Blood lactate dehydrogenase increased	3	1	1	0	1	0	1	0	0
	Blood magnesium decreased	4	1	1	0	1	1	0	0	0
	Blood magnesium increased	2	1	1	0	1	1	0	0	0
	Blood sodium decreased	1	1	1	0	1	1	0	0	0
	Blood urea increased	1	1	1	0	1	1	0	0	0
	Body temperature increased	1	1	1	0	1	1	0	0	0
	Gastric pH decreased	1	1	1	0	1	1	0	0	0
	Heart rate increased	1	1	1	0	1	0	1	0	0
	Liver function test abnormal	3	1	1	0	2	1	0	1	0
	Neutrophil count decreased	1	1	1	0	1	1	0	0	0
	Weight increased	1	1	1	0	1	0	1	0	0
Skin and subcutaneous tissue disorders	Rash	48	28 (46.7%)	28	0	2	20	7	3	0
	Pruritus	16	14 (23.3%)	14	0	2	11	3	1	0
	Alopecia	15	13 (21.7%)	13	0	1	12	1	0	0
	Dry skin	8	7 (11.7%)	7	0	1	5	2	0	0
	Night sweats	7	7 (11.7%)	7	0	2	2	5	0	0
	Acne	6	4 (6.7%)	4	0	1	4	0	0	0
	Hyperhidrosis	3	3	3	0	2	1	2	1	0
	Rash papular	2	2	2	0	1	2	0	0	0
	Dermatitis	1	1	1	0	1	0	1	0	0
	Erysipelas	2	1	1	0	2	0	1	0	0
	Hair growth abnormal	1	1	1	0	1	1	0	0	0
	Hyperkeratosis	1	1	1	0	1	1	0	0	0
	Hypotrichosis	1	1	1	0	1	1	0	0	0

System Organ Class	Preferred Term	Number of Events	Number of Patients	Grades 1 & 2	Grades 3,4,5	Highest Grade	Related	Unrelated	Dose Modification	Treatment Interrupted
		Non-Haematologic								
	Miliaria	1	1	1	0	1	1	0	0	0
	Pain of skin	1	1	1	0	1	1	0	0	0
	Penile blister	1	1	1	0	1	0	1	0	0
	Photosensitivity reaction	1	1	1	0	1	1	0	0	0
	Rash generalised	1	1	1	0	1	1	0	0	0
	Rash maculo-papular	2	1	1	0	1	1	0	0	0
	Rash pruritic	1	1	1	0	1	1	0	0	0
	Skin sensitisation	1	1	1	0	1	1	0	0	0
	Solar keratosis	1	1	1	0	1	0	1	0	0
	Swelling face	1	1	1	0	1	1	0	0	0
Musculoskeletal and connective tissue disorders	Back pain	26	19 (31.7%)	18	1	3	9	10	1	0
	Arthralgia	15	12 (20%)	12	0	2	5	7	0	1
	Bone pain	8	8 (13.3%)	8	0	2	7	1	0	0
	Musculoskeletal pain	10	8 (13.3%)	8	0	2	4	4	1	0
	Myalgia	10	8 (13.3%)	8	0	2	6	2	0	0
	Muscle spasms	8	7 (11.7%)	7	0	2	6	1	0	0
	Joint stiffness	5	5 (8.3%)	5	0	1	5	0	0	0
	Pain in extremity	6	5 (8.3%)	5	0	2	2	2	0	0
	Sciatica	4	3	3	0	2	0	3	0	0
	Joint swelling	2	2	2	0	1	0	2	0	0
	Neck Pain	3	2	2	0	2	0	2	1	0
	Spinal pain	2	2	2	0	1	0	2	0	0
	Arthritis	1	1	1	0	1	0	1	0	0
	Bursitis	2	1	1	0	1	0	1	0	0
	Foot deformity	1	1	1	0	1	0	1	0	0
	Groin pain	1	1	0	1	3	0	1	0	0
	Musculoskeletal chest pain	1	1	1	0	1	0	1	0	0
	Musculoskeletal stiffness	1	1	1	0	1	1	0	0	0
	Periarthritis	2	1	1	0	2	0	1	0	0
	Spinal osteoarthritis	1	1	1	0	1	0	1	0	0
General disorders and administration site conditions	Fatigue	39	26 (43.3%)	25	1	3	19	7	0	1
	Pain	14	11 (18.3%)	9	1	3	6	5	0	0
	Pyrexia	7	7 (11.7%)	6	1	3	0	6	1	0
	Chest discomfort	7	6 (10%)	6	0	2	1	5	0	1
	Influenza like illness	6	4 (6.7%)	4	0	2	1	3	0	0
	Asthenia	3	3	3	0	2	2	1	1	0
	Chest Pain	2	2	2	0	2	1	1	0	0
	Oedema peripheral	2	2	2	0	1	2	0	0	0
	Swelling	2	2	1	1	3	0	2	0	1

System Organ Class	Preferred Term	Number of Events	Number of Patients	Grades 1 & 2	Grades 3,4,5	Highest Grade	Related	Unrelated	Dose Modification	Treatment Interrupted
		Non-Haematologic								
	Chills	2	1	1	0	1	0	1	0	0
	Feeling cold	1	1	1	0	1	1	0	0	0
	Flushing	1	1	1	0	1	0	1	0	0
	Hot flush	1	1	1	0	1	1	0	0	0
	Injection site pain	1	1	1	0	1	0	1	0	0
	Non-cardiac chest pain	1	1	1	0	1	0	1	0	0
	Oedema	1	1	1	0	1	1	0	0	0
	Polyp	1	1	1	0	1	0	1	0	0
Infections and infestations	Upper respiratory tract infection	13	11 (18.3%)	11	0	2	1	10	0	0
	Ear infection	3	3	3	0	2	0	3	0	0
	Influenza	3	3	3	0	2	0	3	0	0
	Lower respiratory tract infection	3	3	2	1	3	0	3	0	0
	Pneumonia	3	3	1	2	3	0	3	0	0
	Nasopharyngitis	2	2	2	0	1	0	2	0	0
	Respiratory tract infection	2	2	2	0	2	0	2	0	0
	Sinusitis	2	2	2	0	1	0	2	0	0
	Urinary tract infection	4	2	1	1	3	0	2	0	0
	Atypical Pneumonia	1	1	1	0	2	0	1	0	0
	Candida infection	1	1	1	0	1	1	0	0	0
	Chronic sinusitis	1	1	1	0	1	0	1	0	0
	Eye infection	1	1	1	0	1	0	1	0	0
	Folliculitis	1	1	1	0	1	0	1	0	0
	Gastroenteritis	1	1	0	1	3	0	1	1	0
	Gastrointestinal viral infection	1	1	1	0	1	0	1	0	1
	Herpes zoster	1	1	1	0	2	1	0	0	0
	Labyrinthitis	1	1	1	0	2	0	1	0	0
	Oral herpes	1	1	1	0	1	0	1	0	0
	Tooth Infection	1	1	1	0	1	1	0	0	0
	Viral Infection	1	1	1	0	1	0	1	0	0
	Viral upper respiratory tract infection	1	1	1	0	1	0	1	0	0
Nervous system disorders	Headache	26	19 (31.7%)	19	0	2	13	5	1	1
	Dizziness	7	5 (8.3%)	5	0	2	2	3	0	0
	Muscular weakness	2	2	2	0	2	1	1	0	0
	Paraesthesia	2	2	2	0	2	0	2	0	0
	Burning sensation	1	1	1	0	1	0	1	0	0
	Dementia	1	1	0	1	4	0	1	0	0
	Dysgeusia	1	1	1	0	1	1	0	0	0
	Hypoaesthesia	1	1	1	0	2	0	1	0	0
	Incontinence	1	1	1	0	1	0	1	0	0
	Lethargy	1	1	1	0	1	0	1	0	0
	Neuropathy peripheral	2	1	1	0	2	0	0	0	0

System Organ Class	Preferred Term	Number of Events	Number of Patients	Grades 1 & 2	Grades 3,4,5	Highest Grade	Related	Unrelated	Dose Modification	Treatment Interrupted
		Non-Haematologic								
	Peripheral motor neuropathy	1	1	1	0	1	1	0	0	0
	Presyncope	1	1	1	0	1	0	0	0	0
	Restless legs syndrome	1	1	1	0	1	0	1	0	0
	Seizure	1	1	1	0	2	0	1	1	0
	Sensory disturbance	1	1	1	0	1	0	1	0	0
	Transient ischaemic attack	1	1	0	1	3	0	1	0	0
	Tremor	1	1	1	0	1	0	1	0	0
Respiratory, thoracic and mediastinal disorders	Cough	16	10 (16.7%)	10	0	2	1	9	0	0
	Dyspnoea	4	4 (6.7%)	4	0	1	1	3	0	0
	Dysphonia	2	2	2	0	1	1	1	0	0
	Nasal congestion	2	2	2	0	1	0	2	0	0
	Oropharyngeal pain	2	2	2	0	2	0	2	0	0
	Chronic Obstructive Pulmonary Disease	1	1	1	0	1	0	1	0	0
	Epistaxis	2	1	1	0	1	0	1	0	0
	Lower respiratory tract infection	1	1	1	0	2	0	1	0	0
	Pulmonary fibrosis	1	1	1	0	1	0	1	0	0
	Throat irritation	1	1	1	0	1	0	1	0	0
	Wheezing	2	1	1	0	1	0	1	0	0
Psychiatric disorders	Anxiety	7	6 (10%)	6	0	2	0	6	1	0
	Depressed mood	4	4 (6.7%)	4	0	1	1	3	0	0
	Depression	4	3	3	0	2	0	3	0	0
	Insomnia	4	2	2	0	2	2	0	0	0
	Nightmare	2	2	2	0	2	2	0	0	0
	Agitation	1	1	0	1	3	0	1	0	0
	Mood altered	1	1	1	0	1	0	1	0	0
	Restlessness	1	1	1	0	1	0	1	0	0
	Stress	1	1	1	0	1	0	1	0	0
	Suicide Attempt	1	1	0	1	4	0	1	0	0
	Tearfulness	1	1	1	0	1	0	1	0	0
Metabolism and nutrition disorders	Hypocalcaemia	3	3	3	0	1	2	1	0	0
	Hypomagnesemia	7	3	3	0	1	1	2	0	0
	Decreased appetite	2	2	2	0	1	2	0	0	0
	Diabetes mellitus	1	1	0	0		0	1	0	0
	Gout	1	1	1	0	1	0	1	0	0
	Hypercalcaemia	1	1	1	0	2	1	0	0	0
	Hypercholesterolaemia	1	1	1	0	1	1	0	0	0
	Hyperglycaemia	1	1	1	0	1	1	0	0	0
	Hypermagnesemia	1	1	1	0	1	1	0	0	0
	Hypernatraemia	2	1	1	0	1	1	0	0	0
	Hypophosphatemia	4	1	1	0	2	1	0	0	0
	Hypothyroidism	1	1	1	0	2	0	0	0	0

System Organ Class	Preferred Term	Number of Events	Number of Patients	Grades 1 & 2	Grades 3,4,5	Highest Grade	Related	Unrelated	Dose Modification	Treatment Interrupted
		Non-Haematologic								
	Increased insulin requirement	1	1	1	0	1	1	0	0	0
	Obesity	1	1	0	1	4	0	1	0	0
Eye disorders	Dry eye	3	3	3	0	2	2	1	0	1
	Conjunctivitis	1	1	1	0	1	1	0	0	1
	Diplopia	1	1	1	0	1	0	1	0	0
	Eye swelling	1	1	1	0	1	1	0	0	0
	Eyelid skin dryness	1	1	1	0	2	1	0	0	0
	Foreign body sensation in eyes	1	1	1	0	1	1	0	0	0
	Ocular hyperaemia	1	1	1	0	1	0	1	0	0
	Periorbital oedema	1	1	1	0	1	1	0	0	0
	Photophobia	1	1	1	0	2	0	1	0	0
	Uveitis	1	1	1	0	2	0	1	0	0
	Vision blurred	1	1	1	0	2	0	1	1	0
	Visual acuity reduced	1	1	1	0	1	0	1	0	0
	Visual impairment	1	1	1	0	1	0	1	0	0
Cardiac disorders	Atrial Fibrillation	3	3	3	0	2	2	1	1	1
	Myocardial infarction	2	2	1	0	1	1	1	0	0
	Palpitations	2	2	2	0	1	2	0	0	0
	Atrioventricular block first degree	1	1	1	0	1	0	1	0	0
	Bradycardia	1	1	1	0	1	0	1	0	0
	Diastolic dysfunction	1	1	1	0	1	1	0	0	0
	Tachyarrhythmia	1	1	1	0	2	0	1	0	0
	Tachycardia	1	1	1	0	1	0	1	1	0
Renal and urinary disorders	Pollakiuria	6	5 (8.3%)	5	0	1	2	3	0	0
	Nocturia	3	3	3	0	2	0	3	0	0
	Dysuria	1	1	1	0	1	0	1	0	0
	Pyuria	1	1	1	0	1	0	1	0	0
	Urinary incontinence	1	1	1	0	2	0	1	0	0
Hepatobiliary disorders	Hyperbilirubinaemia	36	8 (13.3%)	7	1	3	8	0	1	1
	Hepatic pain	1	1	1	0	1	1	0	0	0
	Jaundice	1	1	1	0	1	1	0	0	0
Injury, poisoning and procedural complications	Contusion	6	3	3	0	2	1	2	1	0
	Corneal abrasion	1	1	1	0	2	0	1	0	0
	Fall	1	1	1	0	2	0	1	0	0
	Joint injury	1	1	1	0	1	0	1	0	0
	Lower limb fracture	1	1	1	0	1	0	1	0	0
	Procedural pain	1	1	1	0	2	0	1	0	0
	stress fracture	1	1	1	0	1	0	1	0	0
	Thermal burn	1	1	1	0	2	0	1	0	0
Reproductive system and breast disorders	Breast tenderness	2	2	2	0	1	2	0	0	0
	Pelvic pain	2	2	2	0	2	1	1	0	0
	Areolar glands	1	1	1	0	2	0	1	0	0
	Dysmenorrhoea	1	1	1	0	2	0	1	0	0

System Organ Class	Preferred Term	Number of Events	Number of Patients	Grades 1 & 2	Grades 3,4,5	Highest Grade	Related	Unrelated	Dose Modification	Treatment Interrupted
		Non-Haematologic								
	Libido decreased	1	1	1	0	1	1	0	0	0
	Menometrorrhagia	1	1	1	0	1	1	0	0	0
	Testicular pain	1	1	1	0	2	0	1	0	0
	Vaginal haemorrhage	4	1	0	1	3	0	1	0	0
Vascular disorders	Hypertension	6	4 (6.7%)	4	0	1	2	2	0	0
	Epistaxis	2	2	2	0	1	1	1	0	0
	Circulatory collapse	1	1	1	0	1	1	0	0	0
	Hot flush	2	1	1	0	2	1	0	0	0
Ear and labyrinth disorders	Tinnitus	3	3	3	0	1	2	1	0	0
	Deafness	1	1	0	1	3	0	1	0	0
	Ear pain	2	1	1	0	2	0	1	0	0
Surgical and medical procedures	Anal dilation procedure	1	1	1	0	1	0	1	0	0
	Anal fissure excision	1	1	1	0	1	0	1	0	0
	Cardioversion	1	1	1	0	2	0	1	0	0
	Tenoplasty	1	1	1	0	2	0	1	0	0
Endocrine disorders	Hyperthyroidism	1	1	1	0	2	0	1	0	0
	Hypothyroidism	1	1	1	0	1	0	1	0	0
	Thyroiditis subacute	1	1	1	0	1	0	1	1	0
Immune system disorders	Hypersensitivity	2	2	2	0	1	0	2	0	0
	Conjunctivitis allergic	1	1	1	0	2	0	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Basal cell carcinoma	1	1	0	0		0	1	0	0
	Rectal adenocarcinoma	1	1	0	1	3	0	1	0	1
	Seborrhoeic keratosis	1	1	1	0	1	0	1	0	0
Endocrine disorders, Metabolism and nutrition disorders	Hyperglycaemia	1	1	1	0	2	1	0	0	0
Helicobacter infection	Helicobacter infection	1	1	1	0	1	0	1	0	0

A list of all haematologic adverse events regardless of relationship to study drug are shown in Table AE_4 (%s have been added for those AEs experienced by more than 5% of the patients):

Table AE_4:
Safety set.

System Organ Class	Preferred Term	Number of Events	Number of Patients	Grades 1 & 2	Grades 3,4,5	Highest Grade	Related	Unrelated	Dose Modification	Treatment Interrupted
		Haematologic								
Blood and lymphatic system disorders	Thrombocytopenia	23	8 (13.3%)	5	3	4	8	0	5	1
	Anaemia	15	7 (11.7%)	7	0	2	5	2	1	0

System Organ Class	Preferred Term	Number of Events	Number of Patients	Grades 1 & 2	Grades 3,4,5	Highest Grade	Related	Unrelated	Dose Modification	Treatment Interrupted
					Haematologic					
	Neutropenia	15	3	1	2	4	3	0	3	0
	Iron Deficiency Anaemia	1	1	1	0	1	0	1	0	0
	Leucopenia	6	1	0	1	3	1	0	1	0
	Lymphocytopenia	1	1	1	0	1	1	0	0	0
Investigations	Haemoglobin decreased	3	2	0	2	3	1	1	0	0
	Platelet count decreased	2	2	2	0	1	2	0	0	0
	Lymphocyte count decreased	1	1	1	0	2	0	1	0	0
	White blood cell count decreased	1	1	1	0	1	1	0	0	0

A list of non-haematologic adverse events leading to interruption or discontinuation of treatment are presented in Table AE_5:

Table AE_5:
Safety set.

System Organ Class	Preferred Term	Number of Events	Number of Patients	Grades 1 & 2	Grades 3,4,5	Highest Grade	Related	Unrelated
				Non-Haematologic				
Investigations	Alanine aminotransferase increased	2	2	2	0	2	2	0
	Lipase increased	2	2	1	1	3	2	0
General disorders and administration site conditions	Chest discomfort	1	1	1	0	2	0	1
	Fatigue	1	1	0	1	3	1	0
	Swelling	1	1	0	1	3	0	1
Eye disorders	Conjunctivitis	1	1	1	0	1	1	0
	Dry eye	1	1	1	0	2	1	0
Cardiac disorders	Atrial Fibrillation	1	1	1	0	2	1	0
Gastrointestinal disorders	Nausea	1	1	1	0	1	0	1
Hepatobiliary disorders	Hyperbilirubinaemia	1	1	1	0	2	1	0
Infections and infestations	Gastrointestinal viral infection	1	1	1	0	1	0	1
Musculoskeletal and connective tissue disorders	Arthralgia	1	1	1	0	2	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Rectal adenocarcinoma	1	1	0	1	3	0	1
Nervous system disorders	Headache	1	1	1	0	2	1	0
Skin and subcutaneous tissue disorders	Rash maculo-papular	1	1	1	0	1	1	0

A list of haematologic adverse events leading to interruption or discontinuation of treatment are presented in Table AE_6:

Table AE_6:
Safety set.

System Organ Class	Preferred Term	Number of Events	Number of Patients	Grades 1 & 2	Grades 3,4,5	Highest Grade	Related	Unrelated
		Haematologic						
Blood and lymphatic system disorders	Thrombocytopenia	2	2	0	2	3	2	0
	Neutropenia	4	1	1	0	2	1	0

Serious Adverse Events

A total of 19 subjects experienced at least one serious adverse events. Tables SAE_1, SAE_2, SAE_3 and SAE_4 below summarise all serious adverse events by descending order of number of patients affected.

Non-haematologic serious adverse events by preferred term are shown in Table SAE_1.

Table SAE_1:
Safety set.

Preferred Term (Non-hematological)	Total Subjs	%
Abdominal pain	3	5% (3/60)
Pyrexia	3	5% (3/60)
Lipase increased	2	3.3% (2/60)
Myocardial infarction	2	3.3% (2/60)
Pneumonia	2	3.3% (2/60)
Agitation	1	1.7% (1/60)
Amylase increased	1	1.7% (1/60)
Anal dilation procedure	1	1.7% (1/60)
Anal fissure	1	1.7% (1/60)
Anal fissure excision	1	1.7% (1/60)
Atrial Fibrillation	1	1.7% (1/60)
Atypical Pneumonia	1	1.7% (1/60)
Chest discomfort	1	1.7% (1/60)
Chest Pain	1	1.7% (1/60)
Dementia	1	1.7% (1/60)
Fall	1	1.7% (1/60)
Gastroenteritis	1	1.7% (1/60)
Groin pain	1	1.7% (1/60)
Labyrinthitis	1	1.7% (1/60)
Lower respiratory tract infection	1	1.7% (1/60)
Pancreatitis	1	1.7% (1/60)
Rectal adenocarcinoma	1	1.7% (1/60)
Seizure	1	1.7% (1/60)

Preferred Term (Non-hematological)	Total Subjs	%
Suicide Attempt	1	1.7% (1/60)
Swelling	1	1.7% (1/60)
Tachyarrhythmia	1	1.7% (1/60)
Tenoplasty	1	1.7% (1/60)
Transient ischaemic attack	1	1.7% (1/60)
Urinary tract infection	1	1.7% (1/60)
Vaginal haemorrhage	1	1.7% (1/60)

Haematologic serious adverse events by preferred term are shown in Table SAE_2.

Table SAE_2:
Safety set.

Preferred Term (Hematological)	Total Subjs	%
Haemoglobin decreased	1	1.7% (1/60)
Thrombocytopenia	1	1.7% (1/60)

A list of all non-haematologic serious adverse events regardless of relationship to study drug are shown in Table SAE_3:

Table SAE_3:
Safety set.

System Organ Class	Preferred Term	Number of Events	Number of Patients	Grades 1 & 2	Grades 3,4,5	Highest Grade	Related	Unrelated	Dose Modification	Treatment Interrupted
		Non-Haematologic								
Infections and infestations	Pneumonia	2	2	0	2	3	0	2	0	0
	Atypical Pneumonia	1	1	1	0	2	0	1	0	0
	Gastroenteritis	1	1	0	1	3	0	1	1	0
	Labyrinthitis	1	1	1	0	2	0	1	0	0
	Lower respiratory tract infection	1	1	0	1	3	0	1	0	0
	Urinary tract infection	1	1	0	1	3	0	1	0	0
General disorders and administration site conditions	Pyrexia	3	3	2	1	3	0	3	0	0
	Chest discomfort	1	1	1	0	2	0	1	0	1
	Chest Pain	1	1	1	0	1	1	0	0	0
	Swelling	1	1	0	1	3	0	1	0	1
Gastrointestinal disorders	Abdominal pain	3	3	1	2	3	1	2	1	0
	Anal fissure	1	1	0	1	3	0	1	0	0
	Pancreatitis	1	1	1	0	1	1	0	1	0
Cardiac disorders	Myocardial infarction	2	2	1	0	1	1	1	0	0
	Atrial Fibrillation	1	1	1	0	2	0	1	0	0
	Tachyarrhythmia	1	1	1	0	2	0	1	0	0
Investigations	Lipase increased	2	2	0	2	4	2	0	2	0
	Amylase increased	1	1	0	1	3	1	0	1	0

System Organ Class	Preferred Term	Number of Events	Number of Patients	Grades 1 & 2	Grades 3,4,5	Highest Grade	Related	Unrelated	Dose Modification	Treatment Interrupted
		Non-Haematologic								
Nervous system disorders	Dementia	1	1	0	1	4	0	1	0	0
	Seizure	1	1	1	0	2	0	1	1	0
	Transient ischaemic attack	1	1	0	1	3	0	1	0	0
Surgical and medical procedures	Anal dilation procedure	1	1	1	0	1	0	1	0	0
	Anal fissure excision	1	1	1	0	1	0	1	0	0
	Tenoplasty	1	1	1	0	2	0	1	0	0
Psychiatric disorders	Agitation	1	1	0	1	3	0	1	0	0
	Suicide Attempt	1	1	0	1	4	0	1	0	0
Injury, poisoning and procedural complications	Fall	1	1	1	0	2	0	1	0	0
Musculoskeletal and connective tissue disorders	Groin pain	1	1	0	1	3	0	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Rectal adenocarcinoma	1	1	0	1	3	0	1	0	1
Reproductive system and breast disorders	Vaginal haemorrhage	1	1	0	1	3	0	1	0	0

A list of all haematologic serious adverse events regardless of relationship to study drug are shown in Table SAE_4:

Table SAE_4:
Safety set.

System Organ Class	Preferred Term	Number of Events	Number of Patients	Grades 1 & 2	Grades 3,4,5	Highest Grade	Related	Unrelated	Dose Modification	Treatment Interrupted
		Haematologic								
Blood and lymphatic system disorders	Thrombocytopenia	1	1	0	1	4	1	0	1	0
Investigations	Haemoglobin decreased	1	1	0	1	3	0	1	0	0

Vital Signs

Weight, Height, Heart Rate, Blood Pressure and Temperature by Cycle.

Table VIT_1:
Safety set.

Test	Visit	Vital Signs						
		Total Subjs	MIS	Mean	SD	Median	Min	Max
Weight (kg)	Baseline	60	1	81.14	17.88	79.60	48.0	134.5
	Cycle 1	60	4	80.90	18.03	79.70	48.0	133.5
	Cycle 2	60	5	80.97	17.97	80.30	47.0	132.8
	Cycle 3	60	8	82.12	18.38	79.70	47.0	137.5
	Cycle 6	60	11	82.65	18.99	79.50	49.0	142.0
	Cycle 9	60	9	84.25	19.13	82.20	51.0	142.0
	Cycle 12	60	10	84.06	18.85	82.20	50.0	144.6
	Cycle 15	60	13	83.00	18.56	81.00	47.5	144.0
	Cycle 18	60	11	82.81	18.04	83.00	48.5	143.1
	Cycle 21	60	14	83.70	18.38	83.40	50.5	143.0
	Cycle 24	60	8	82.36	18.04	81.30	50.5	138.0
Height (cm)	Baseline	60	13	167.55	9.40	168.00	151.1	186.0
Heart Rate (beats per minute)	Baseline	60	1	80.6	13.8	80.0	52	111
	Cycle 1	60	2	76.0	13.6	75.0	48	106
	Cycle 2	60	4	74.4	12.3	72.5	46	102
	Cycle 3	60	6	73.4	11.9	73.0	46	102
	Cycle 6	60	6	73.9	11.2	74.0	46	97
	Cycle 9	60	6	75.4	11.0	75.0	51	101
	Cycle 12	60	9	73.6	12.5	74.0	52	106
	Cycle 15	60	13	73.7	13.0	72.0	42	112
	Cycle 18	60	9	73.8	13.6	72.0	48	113
	Cycle 21	60	9	74.3	13.1	72.0	53	110
	Cycle 24	60	4	73.0	11.9	72.5	44	101
Systolic BP (mmHg)	Baseline	60	1	128.8	15.6	125.0	94	164
	Cycle 1	60	1	127.1	17.3	124.0	90	168
	Cycle 2	60	3	126.7	15.1	124.0	97	165
	Cycle 3	60	6	130.6	17.7	131.5	95	199
	Cycle 6	60	6	130.9	16.1	129.0	100	167
	Cycle 9	60	7	132.9	15.7	130.0	100	170
	Cycle 12	60	9	132.4	15.3	133.0	106	160
	Cycle 15	60	12	132.8	16.4	134.0	103	161
	Cycle 18	60	9	131.5	15.4	133.0	93	157
	Cycle 21	60	9	135.3	16.1	133.0	103	173
	Cycle 24	60	4	130.5	15.5	130.0	100	163
Diastolic BP (mmHg)	Baseline	60	1	73.6	9.8	74.0	51	96
	Cycle 1	60	1	70.3	11.3	72.0	40	93
	Cycle 2	60	3	71.8	9.3	72.0	47	91
	Cycle 3	60	6	73.3	10.3	73.0	47	100
	Cycle 6	60	6	74.0	10.8	75.5	46	100
	Cycle 9	60	7	75.0	9.4	74.0	59	96
	Cycle 12	60	9	74.6	10.2	76.0	53	100
	Cycle 15	60	12	76.5	10.7	75.5	57	100
	Cycle 18	60	9	75.7	8.5	76.0	54	92
	Cycle 21	60	9	75.4	9.2	75.0	48	98
	Cycle 24	60	4	74.1	9.7	75.5	53	95
Temperature (°C)	Baseline	60	4	36.56	0.37	36.60	35.5	37.6
	Cycle 1	60	2	36.41	0.36	36.50	35.3	37.2
	Cycle 2	60	5	36.44	0.35	36.50	35.6	37.2
	Cycle 3	60	6	36.48	0.44	36.50	35.2	37.8
	Cycle 6	60	7	36.36	0.38	36.40	35.3	37.0

Test	Visit	Vital Signs						
		Total Subjs	MIS	Mean	SD	Median	Min	Max
	Cycle 9	60	9	36.40	0.45	36.40	35.3	37.4
	Cycle 12	60	10	36.44	0.44	36.50	35.3	37.6
	Cycle 15	60	12	36.45	0.38	36.50	35.3	37.6
	Cycle 18	60	11	36.44	0.29	36.40	35.5	37.1
	Cycle 21	60	15	36.52	0.27	36.50	35.8	37.1
	Cycle 24	60	8	36.38	0.50	36.50	33.5	36.9

Haematology and Biochemistry

Lab Results - Summaries by Cycle - **Haematology**

Table HEM_1:
Safety set.

Test	Visit	Total Subjs	MIS	Haematology								
									Outside normal range		Clinically Significant	
				Mean	SD	Median	Min	Max	MIS	%	MIS	%
Haemoglobin (g/dl)	Baseline	60	0	12.01	1.89	11.95	7.2	16.3	0	66.7% (40/60)	0	3.3% (2/60)
	Cycle 1 D1	60	0	12.08	1.86	12.00	7.7	17.4	0	65% (39/60)	0	3.3% (2/60)
	Cycle 1 D8	60	1	11.68	1.56	11.70	7.8	15.2	1	74.6% (44/59)	1	1.7% (1/59)
	Cycle 1 D15	60	0	11.61	1.54	11.45	9.0	16.1	0	80% (48/60)	0	0% (0/60)
	Cycle 1 D28	60	1	11.90	1.40	12.10	8.7	16.0	2	75.9% (44/58)	2	0% (0/58)
	Cycle 2	60	2	12.90	1.43	12.80	9.2	16.3	3	43.9% (25/57)	4	0% (0/56)
	Cycle 3	60	3	13.56	1.49	13.70	9.4	17.7	3	21.1% (12/57)	3	0% (0/57)
	Cycle 4	60	3	13.56	1.49	13.60	9.9	16.7	3	19.3% (11/57)	4	0% (0/56)
	Cycle 5	60	6	13.60	1.50	13.95	10.3	16.6	6	18.5% (10/54)	7	0% (0/53)
	Cycle 6	60	4	13.41	1.41	13.60	10.3	17.1	4	26.8% (15/56)	5	0% (0/55)
	Cycle 9	60	4	13.81	1.57	13.97	9.1	17.3	7	15.1% (8/53)	7	1.9% (1/53)
	Cycle 12	60	6	13.56	1.68	13.57	8.3	16.7	8	17.3% (9/52)	8	0% (0/52)
	Cycle 15	60	10	13.85	1.55	13.65	10.8	18.0	15	20% (9/45)	17	0% (0/43)
	Cycle 18	60	9	13.94	1.42	13.80	11.2	18.3	18	14.3% (6/42)	20	0% (0/40)
	Cycle 21	60	9	13.96	1.42	14.00	10.7	17.1	18	14.3% (6/42)	19	0% (0/41)
	Cycle 24	60	3	13.85	1.63	13.80	9.8	17.6	11	16.3% (8/49)	15	0% (0/45)
Haematocrit (L/L)	Baseline	60	0	0.536	1.297	0.378	0.20	10.40	0	68.3% (41/60)	0	0% (0/60)

				Haematology								
									Outside normal range		Clinically Significant	
Test	Visit	Total Subjs	MIS	Mean	SD	Median	Min	Max	MIS	%	MIS	%
	Cycle 1 D1	60	0	0.372	0.052	0.379	0.24	0.52	0	68.3% (41/60)	0	0% (0/60)
	Cycle 1 D8	60	2	0.362	0.046	0.361	0.23	0.46	2	77.6% (45/58)	2	0% (0/58)
	Cycle 1 D15	60	0	0.360	0.045	0.359	0.28	0.49	0	80% (48/60)	0	0% (0/60)
	Cycle 1 D28	60	1	0.366	0.041	0.370	0.27	0.50	2	79.3% (46/58)	2	0% (0/58)
	Cycle 2	60	2	0.395	0.041	0.400	0.28	0.50	4	39.3% (22/56)	4	0% (0/56)
	Cycle 3	60	3	0.412	0.041	0.410	0.30	0.54	3	24.6% (14/57)	3	0% (0/57)
	Cycle 4	60	3	0.409	0.041	0.410	0.29	0.49	3	22.8% (13/57)	4	0% (0/56)
	Cycle 5	60	6	0.409	0.042	0.415	0.29	0.50	6	27.8% (15/54)	7	0% (0/53)
	Cycle 6	60	4	0.404	0.036	0.402	0.34	0.50	4	28.6% (16/56)	6	0% (0/54)
	Cycle 9	60	4	0.412	0.044	0.411	0.26	0.52	6	18.5% (10/54)	7	0% (0/53)
	Cycle 12	60	6	0.405	0.046	0.401	0.26	0.52	8	28.8% (15/52)	8	0% (0/52)
	Cycle 15	60	10	0.414	0.045	0.406	0.33	0.53	15	28.9% (13/45)	17	0% (0/43)
	Cycle 18	60	9	1.157	5.228	0.413	0.36	37.76	17	20.9% (9/43)	20	0% (0/40)
	Cycle 21	60	9	0.416	0.037	0.413	0.33	0.51	16	18.2% (8/44)	19	0% (0/41)
	Cycle 24	60	3	0.413	0.046	0.410	0.29	0.50	11	20.4% (10/49)	15	0% (0/45)
White Blood Cell Count ($x10^9/L$)	Baseline	60	0	66.12	69.16	46.38	6.7	425.0	0	93.3% (56/60)	0	5% (3/60)
	Cycle 1 D1	60	0	56.75	59.10	44.15	4.4	297.8	0	88.3% (53/60)	0	3.3% (2/60)
	Cycle 1 D8	60	1	38.30	44.14	25.00	3.1	214.8	1	79.7% (47/59)	1	1.7% (1/59)
	Cycle 1 D15	60	0	17.24	20.35	10.18	2.3	101.0	0	50% (30/60)	0	1.7% (1/60)
	Cycle 1 D28	60	1	7.06	5.27	5.50	2.8	34.5	2	25.9% (15/58)	2	1.7% (1/58)
	Cycle 2	60	2	6.02	2.05	5.72	2.9	11.5	4	21.4% (12/56)	4	0% (0/56)
	Cycle 3	60	3	6.86	2.10	6.40	3.9	12.3	3	10.5% (6/57)	3	0% (0/57)
	Cycle 4	60	3	7.29	2.17	7.10	3.1	13.0	4	10.7% (6/56)	4	0% (0/56)
	Cycle 5	60	6	7.44	2.01	7.10	4.3	14.6	7	7.5% (4/53)	7	0% (0/53)
	Cycle 6	60	4	7.56	2.14	7.10	3.7	14.1	5	16.4% (9/55)	5	0% (0/55)
	Cycle 9	60	4	7.57	2.38	7.20	2.2	13.6	6	22.2% (12/54)	7	1.9% (1/53)

				Haematology								
									Outside normal range		Clinically Significant	
Test	Visit	Total Subjs	MIS	Mean	SD	Median	Min	Max	MIS	%	MIS	%
	Cycle 12	60	6	7.61	2.22	7.30	3.9	13.7	8	13.5% (7/52)	8	0% (0/52)
	Cycle 15	60	10	7.44	2.12	6.85	3.9	13.4	15	15.6% (7/45)	17	0% (0/43)
	Cycle 18	60	9	7.58	2.25	6.91	3.9	13.1	17	16.3% (7/43)	20	0% (0/40)
	Cycle 21	60	9	7.64	2.25	7.40	3.1	12.9	17	20.9% (9/43)	19	0% (0/41)
	Cycle 24	60	3	7.75	3.01	7.30	3.3	19.4	11	16.3% (8/49)	15	0% (0/45)
Platelets ($x10^9$/L)	Baseline	60	0	475.4	360.8	369.5	105	1715	0	46.7% (28/60)	0	3.3% (2/60)
	Cycle 1 D1	60	0	467.4	321.5	376.0	121	1719	0	45% (27/60)	0	0% (0/60)
	Cycle 1 D8	60	1	436.4	316.6	350.0	125	1891	1	39% (23/59)	1	0% (0/59)
	Cycle 1 D15	60	0	320.8	205.9	273.0	95	1352	0	26.7% (16/60)	0	0% (0/60)
	Cycle 1 D28	60	1	214.1	89.2	207.0	41	510	2	24.1% (14/58)	2	3.4% (2/58)
	Cycle 2	60	2	224.9	83.6	220.5	64	424	4	17.9% (10/56)	4	1.8% (1/56)
	Cycle 3	60	3	222.4	70.4	215.0	90	415	3	8.8% (5/57)	3	0% (0/57)
	Cycle 4	60	3	219.0	69.1	218.0	39	388	4	8.9% (5/56)	4	1.8% (1/56)
	Cycle 5	60	6	220.5	70.1	221.0	33	431	7	9.4% (5/53)	7	1.9% (1/53)
	Cycle 6	60	4	229.7	70.9	224.5	107	451	5	9.1% (5/55)	5	0% (0/55)
	Cycle 9	60	4	227.5	82.3	221.0	4	472	6	14.8% (8/54)	7	1.9% (1/53)
	Cycle 12	60	6	230.2	77.8	209.0	112	503	7	7.5% (4/53)	8	0% (0/52)
	Cycle 15	60	10	225.7	75.8	211.5	91	509	16	6.8% (3/44)	17	0% (0/43)
	Cycle 18	60	9	228.8	83.1	213.0	110	516	18	11.9% (5/42)	20	0% (0/40)
	Cycle 21	60	9	226.3	82.7	204.0	109	519	17	14% (6/43)	18	2.4% (1/42)
	Cycle 24	60	3	224.8	77.7	210.0	33	446	12	10.4% (5/48)	15	2.2% (1/45)
Absolute Neutrophil Count ($x10^9$/L)	Baseline	60	4	38.51	30.81	31.75	4.1	140.1	3	84.2% (48/57)	3	1.8% (1/57)
	Cycle 1 D1	60	4	32.98	29.40	28.50	3.3	144.3	4	85.7% (48/56)	4	3.6% (2/56)
	Cycle 1 D8	60	6	24.86	25.24	17.47	2.8	109.5	6	75.9% (41/54)	6	1.9% (1/54)
	Cycle 1 D15	60	3	13.46	15.86	7.39	1.3	75.2	3	49.1% (28/57)	3	1.8% (1/57)
	Cycle 1 D28	60	2	4.77	3.64	3.73	1.3	21.9	3	14% (8/57)	3	1.8% (1/57)

				Haematology								
									Outside normal range		Clinically Significant	
Test	Visit	Total Subjs	MIS	Mean	SD	Median	Min	Max	MIS	%	MIS	%
	Cycle 2	60	3	3.81	1.58	3.60	1.0	8.0	6	11.1% (6/54)	6	0% (0/54)
	Cycle 3	60	3	4.37	1.74	4.00	1.2	9.2	3	7% (4/57)	3	0% (0/57)
	Cycle 4	60	4	4.70	1.80	4.58	1.6	8.6	5	9.1% (5/55)	5	0% (0/55)
	Cycle 5	60	6	4.78	1.72	4.50	1.7	10.2	7	5.7% (3/53)	7	0% (0/53)
	Cycle 6	60	4	4.89	1.81	4.40	1.7	9.7	5	10.9% (6/55)	5	0% (0/55)
	Cycle 9	60	4	4.89	1.93	4.62	0.3	9.4	7	13.2% (7/53)	7	1.9% (1/53)
	Cycle 12	60	6	4.91	1.79	4.50	1.7	9.7	8	11.5% (6/52)	8	0% (0/52)
	Cycle 15	60	11	4.81	1.72	4.60	2.1	9.3	17	9.3% (4/43)	18	0% (0/42)
	Cycle 18	60	9	4.73	1.87	4.50	0.0	8.6	18	11.9% (5/42)	20	0% (0/40)
	Cycle 21	60	10	5.03	1.74	5.00	2.1	9.0	19	9.8% (4/41)	20	0% (0/40)
	Cycle 24	60	4	4.98	2.59	4.28	1.3	16.6	13	12.8% (6/47)	15	0% (0/45)
Bands ($x10^9$/L)	Baseline	60	34	4.08	5.16	2.61	0.0	20.0	34	23.1% (6/26)	34	0% (0/26)
	Cycle 1 D1	60	36	6.80	14.48	2.44	0.0	67.2	36	33.3% (8/24)	36	0% (0/24)
	Cycle 1 D8	60	39	4.75	8.53	1.06	0.0	32.8	38	18.2% (4/22)	38	0% (0/22)
	Cycle 1 D15	60	46	3.27	6.49	0.36	0.0	22.2	46	21.4% (3/14)	46	0% (0/14)
	Cycle 1 D28	60	49	0.17	0.30	0.00	0.0	1.0	49	9.1% (1/11)	49	0% (0/11)
	Cycle 2	60	50	0.04	0.05	0.02	0.0	0.1	48	0% (0/12)	48	0% (0/12)
	Cycle 3	60	51	0.33	0.67	0.11	0.0	2.1	50	0% (0/10)	50	0% (0/10)
	Cycle 4	60	50	0.12	0.14	0.09	0.0	0.5	49	0% (0/11)	49	0% (0/11)
	Cycle 5	60	51	0.16	0.28	0.09	0.0	0.9	51	0% (0/9)	51	0% (0/9)
	Cycle 6	60	52	0.20	0.22	0.11	0.0	0.7	50	10% (1/10)	50	0% (0/10)
	Cycle 9	60	54	0.05	0.08	0.00	0.0	0.2	54	0% (0/6)	54	0% (0/6)
	Cycle 12	60	49	0.13	0.16	0.08	0.0	0.4	49	0% (0/11)	49	0% (0/11)
	Cycle 15	60	52	0.26	0.33	0.16	0.0	1.1	54	16.7% (1/6)	54	0% (0/6)
	Cycle 18	60	53	0.38	0.44	0.12	0.0	1.0	56	25% (1/4)	56	0% (0/4)
	Cycle 21	60	52	0.04	0.05	0.02	0.0	0.1	55	0% (0/5)	55	0% (0/5)

				Haematology								
									Outside normal range		Clinically Significant	
Test	Visit	Total Subjs	MIS	Mean	SD	Median	Min	Max	MIS	%	MIS	%
	Cycle 24	60	51	0.09	0.14	0.04	0.0	0.4	53	0% (0/7)	53	0% (0/7)
Lymphocytes ($x10^9$/L)	Baseline	60	4	4.30	3.05	3.50	0.0	15.9	4	57.1% (32/56)	4	1.8% (1/56)
	Cycle 1 D1	60	4	3.95	3.08	3.45	0.7	17.3	4	55.4% (31/56)	4	0% (0/56)
	Cycle 1 D8	60	5	2.94	2.29	2.40	0.6	12.1	5	52.7% (29/55)	5	0% (0/55)
	Cycle 1 D15	60	4	1.93	1.30	1.60	0.5	9.1	4	42.9% (24/56)	4	0% (0/56)
	Cycle 1 D28	60	2	1.31	0.55	1.25	0.4	3.5	2	41.4% (24/58)	3	0% (0/57)
	Cycle 2	60	2	1.53	0.54	1.50	0.5	3.0	4	26.8% (15/56)	4	0% (0/56)
	Cycle 3	60	3	1.74	0.55	1.74	0.8	2.9	3	28.1% (16/57)	3	0% (0/57)
	Cycle 4	60	3	1.85	0.53	1.74	0.9	3.3	4	17.9% (10/56)	4	0% (0/56)
	Cycle 5	60	6	1.91	0.59	1.89	0.7	3.5	7	17% (9/53)	7	0% (0/53)
	Cycle 6	60	4	1.89	0.53	1.83	0.9	3.1	4	16.1% (9/56)	6	0% (0/54)
	Cycle 9	60	4	1.85	0.60	1.80	0.4	3.3	5	20% (11/55)	7	0% (0/53)
	Cycle 12	60	6	1.91	0.60	1.96	0.8	3.6	8	17.3% (9/52)	9	0% (0/51)
	Cycle 15	60	12	1.81	0.52	1.80	0.8	3.1	17	18.6% (8/43)	18	0% (0/42)
	Cycle 18	60	10	1.92	0.56	1.90	0.7	3.4	17	16.3% (7/43)	20	0% (0/40)
	Cycle 21	60	10	1.93	0.55	1.85	0.9	3.4	20	12.5% (5/40)	21	0% (0/39)
	Cycle 24	60	4	1.92	0.65	1.90	0.6	3.5	14	19.6% (9/46)	15	0% (0/45)
Monocytes ($x10^9$/L)	Baseline	60	7	1.94	2.27	1.30	0.0	10.7	7	62.3% (33/53)	7	0% (0/53)
	Cycle 1 D1	60	5	2.29	2.46	1.84	0.0	14.1	5	63.6% (35/55)	5	0% (0/55)
	Cycle 1 D8	60	7	1.57	1.41	1.11	0.2	5.9	7	47.2% (25/53)	7	0% (0/53)
	Cycle 1 D15	60	4	0.73	0.63	0.54	0.1	3.0	4	21.4% (12/56)	4	0% (0/56)
	Cycle 1 D28	60	2	0.43	0.33	0.36	0.1	1.9	3	15.8% (9/57)	3	0% (0/57)
	Cycle 2	60	2	0.46	0.21	0.40	0.1	1.2	4	8.9% (5/56)	4	0% (0/56)
	Cycle 3	60	3	0.51	0.19	0.50	0.1	1.1	3	7% (4/57)	3	0% (0/57)
	Cycle 4	60	3	0.53	0.23	0.50	0.0	1.5	4	7.1% (4/56)	4	0% (0/56)
	Cycle 5	60	6	0.53	0.25	0.50	0.0	1.5	7	11.3% (6/53)	7	0% (0/53)

				Haematology								
									Outside normal range		Clinically Significant	
Test	Visit	Total Subjs	MIS	Mean	SD	Median	Min	Max	MIS	%	MIS	%
	Cycle 6	60	4	0.54	0.24	0.50	0.2	1.3	5	9.1% (5/55)	5	0% (0/55)
	Cycle 9	60	4	0.55	0.24	0.50	0.1	1.5	6	9.3% (5/54)	7	0% (0/53)
	Cycle 12	60	6	0.55	0.21	0.51	0.2	1.3	8	7.7% (4/52)	8	0% (0/52)
	Cycle 15	60	12	0.54	0.20	0.50	0.2	1.3	16	6.8% (3/44)	18	0% (0/42)
	Cycle 18	60	10	0.56	0.24	0.50	0.2	1.4	18	7.1% (3/42)	20	0% (0/40)
	Cycle 21	60	10	0.57	0.23	0.56	0.2	1.4	18	11.9% (5/42)	20	0% (0/40)
	Cycle 24	60	4	0.53	0.26	0.50	0.0	1.6	13	10.6% (5/47)	15	0% (0/45)
Eosinophils ($x10^9$/L)	Baseline	60	13	1.638	3.200	0.800	0.00	18.69	13	66% (31/47)	13	0% (0/47)
	Cycle 1 D1	60	10	1.191	1.649	0.650	0.00	9.72	10	56% (28/50)	10	0% (0/50)
	Cycle 1 D8	60	7	1.082	2.584	0.491	0.00	17.62	7	50.9% (27/53)	7	0% (0/53)
	Cycle 1 D15	60	5	0.408	0.400	0.300	0.00	2.27	5	27.3% (15/55)	5	0% (0/55)
	Cycle 1 D28	60	2	0.189	0.163	0.130	0.00	0.81	3	7% (4/57)	3	1.8% (1/57)
	Cycle 2	60	2	0.140	0.108	0.100	0.00	0.41	4	3.6% (2/56)	4	0% (0/56)
	Cycle 3	60	3	0.186	0.144	0.134	0.00	0.62	3	3.5% (2/57)	3	0% (0/57)
	Cycle 4	60	3	0.177	0.117	0.170	0.00	0.50	4	3.6% (2/56)	4	0% (0/56)
	Cycle 5	60	6	0.164	0.106	0.145	0.00	0.50	7	7.5% (4/53)	7	0% (0/53)
	Cycle 6	60	4	0.185	0.103	0.200	0.02	0.50	5	1.8% (1/55)	5	0% (0/55)
	Cycle 9	60	4	0.173	0.120	0.135	0.00	0.60	7	3.8% (2/53)	7	0% (0/53)
	Cycle 12	60	6	0.176	0.125	0.132	0.00	0.50	8	3.8% (2/52)	8	0% (0/52)
	Cycle 15	60	12	0.188	0.117	0.170	0.04	0.50	18	4.8% (2/42)	18	0% (0/42)
	Cycle 18	60	10	0.206	0.128	0.200	0.02	0.60	18	4.8% (2/42)	20	0% (0/40)
	Cycle 21	60	10	0.222	0.132	0.200	0.00	0.53	19	4.9% (2/41)	20	0% (0/40)
	Cycle 24	60	4	0.218	0.170	0.200	0.00	0.85	12	8.3% (4/48)	15	0% (0/45)
Basophils ($x10^9$/L)	Baseline	60	11	1.84	2.49	1.08	0.0	15.2	11	85.7% (42/49)	11	0% (0/49)
	Cycle 1 D1	60	5	1.94	3.83	0.96	0.0	25.7	5	78.2% (43/55)	5	0% (0/55)
	Cycle 1 D8	60	9	0.81	1.30	0.50	0.0	8.8	9	68.6% (35/51)	9	0% (0/51)

				Haematology								
									Outside normal range		Clinically Significant	
Test	Visit	Total Subjs	MIS	Mean	SD	Median	Min	Max	MIS	%	MIS	%
	Cycle 1 D15	60	6	0.39	0.81	0.15	0.0	4.5	6	51.9% (28/54)	6	0% (0/54)
	Cycle 1 D28	60	3	0.08	0.13	0.03	0.0	0.8	3	17.5% (10/57)	4	0% (0/56)
	Cycle 2	60	2	0.03	0.03	0.02	0.0	0.1	4	5.4% (3/56)	4	0% (0/56)
	Cycle 3	60	4	0.02	0.03	0.01	0.0	0.1	4	0% (0/56)	4	0% (0/56)
	Cycle 4	60	3	0.03	0.03	0.01	0.0	0.1	4	3.6% (2/56)	4	0% (0/56)
	Cycle 5	60	6	0.03	0.03	0.02	0.0	0.1	7	0% (0/53)	7	0% (0/53)
	Cycle 6	60	4	0.04	0.04	0.02	0.0	0.1	5	1.8% (1/55)	5	0% (0/55)
	Cycle 9	60	4	0.03	0.03	0.03	0.0	0.1	7	1.9% (1/53)	8	0% (0/52)
	Cycle 12	60	6	0.04	0.04	0.02	0.0	0.2	8	3.8% (2/52)	8	0% (0/52)
	Cycle 15	60	12	0.03	0.04	0.02	0.0	0.1	18	4.8% (2/42)	18	0% (0/42)
	Cycle 18	60	10	0.03	0.04	0.02	0.0	0.1	19	2.4% (1/41)	20	0% (0/40)
	Cycle 21	60	10	0.04	0.05	0.03	0.0	0.2	20	7.5% (3/40)	20	0% (0/40)
	Cycle 24	60	5	0.03	0.04	0.02	0.0	0.1	15	6.7% (3/45)	16	0% (0/44)
Promyelocytes ($x10^9$/L)	Baseline	60	28	2.08	3.35	0.73	0.0	13.9	28	21.9% (7/32)	28	0% (0/32)
	Cycle 1 D1	60	30	2.08	4.01	0.42	0.0	19.1	30	20% (6/30)	30	0% (0/30)
	Cycle 1 D8	60	43	1.68	3.51	0.00	0.0	10.7	42	16.7% (3/18)	42	0% (0/18)
	Cycle 1 D15	60	49	0.07	0.23	0.00	0.0	0.8	49	9.1% (1/11)	49	0% (0/11)
	Cycle 1 D28	60	51	0.11	0.33	0.00	0.0	1.0	51	11.1% (1/9)	51	0% (0/9)
	Cycle 2	60	50	0.00	0.00	0.00	0.0	0.0	50	0% (0/10)	50	0% (0/10)
	Cycle 3	60	50	0.00	0.00	0.00	0.0	0.0	49	0% (0/11)	49	0% (0/11)
	Cycle 4	60	49	0.00	0.00	0.00	0.0	0.0	48	0% (0/12)	48	0% (0/12)
	Cycle 5	60	52	0.00	0.00	0.00	0.0	0.0	51	0% (0/9)	51	0% (0/9)
	Cycle 6	60	52	0.00	0.00	0.00	0.0	0.0	52	0% (0/8)	52	0% (0/8)
	Cycle 9	60	54	0.00	0.00	0.00	0.0	0.0	54	0% (0/6)	54	0% (0/6)
	Cycle 12	60	50	0.00	0.00	0.00	0.0	0.0	51	0% (0/9)	51	0% (0/9)
	Cycle 15	60	53	0.00	0.00	0.00	0.0	0.0	55	0% (0/5)	55	0% (0/5)

				Haematology								
									Outside normal range		Clinically Significant	
Test	Visit	Total Subjs	MIS	Mean	SD	Median	Min	Max	MIS	%	MIS	%
	Cycle 18	60	54	0.00	0.00	0.00	0.0	0.0	57	0% (0/3)	57	0% (0/3)
	Cycle 21	60	53	0.00	0.00	0.00	0.0	0.0	56	0% (0/4)	56	0% (0/4)
	Cycle 24	60	51	0.00	0.00	0.00	0.0	0.0	53	0% (0/7)	53	0% (0/7)
Myleocytes ($x10^9$/L)	Baseline	60	19	10.27	15.72	3.90	0.0	56.8	19	53.7% (22/41)	19	0% (0/41)
	Cycle 1 D1	60	19	6.27	7.02	5.00	0.0	40.3	19	58.5% (24/41)	19	0% (0/41)
	Cycle 1 D8	60	33	4.15	7.18	1.45	0.0	34.4	32	57.1% (16/28)	32	0% (0/28)
	Cycle 1 D15	60	44	0.89	1.72	0.15	0.0	6.8	44	56.2% (9/16)	44	0% (0/16)
	Cycle 1 D28	60	51	0.74	2.20	0.00	0.0	6.6	51	22.2% (2/9)	51	0% (0/9)
	Cycle 2	60	50	0.00	0.01	0.00	0.0	0.0	50	10% (1/10)	50	0% (0/10)
	Cycle 3	60	50	0.00	0.00	0.00	0.0	0.0	49	0% (0/11)	49	0% (0/11)
	Cycle 4	60	49	0.01	0.03	0.00	0.0	0.1	48	8.3% (1/12)	48	0% (0/12)
	Cycle 5	60	52	0.01	0.02	0.00	0.0	0.1	51	11.1% (1/9)	51	0% (0/9)
	Cycle 6	60	52	0.03	0.05	0.00	0.0	0.1	52	37.5% (3/8)	52	0% (0/8)
	Cycle 9	60	54	0.07	0.09	0.04	0.0	0.2	54	50% (3/6)	54	0% (0/6)
	Cycle 12	60	50	0.02	0.05	0.00	0.0	0.1	51	22.2% (2/9)	51	0% (0/9)
	Cycle 15	60	53	0.04	0.08	0.00	0.0	0.2	55	40% (2/5)	55	0% (0/5)
	Cycle 18	60	54	0.02	0.04	0.00	0.0	0.1	57	33.3% (1/3)	57	0% (0/3)
	Cycle 21	60	53	0.00	0.00	0.00	0.0	0.0	56	0% (0/4)	56	0% (0/4)
	Cycle 24	60	51	0.00	0.00	0.00	0.0	0.0	53	0% (0/7)	53	0% (0/7)
Metamyelocytes ($x10^9$/L)	Baseline	60	22	4.58	5.67	2.60	0.0	28.3	22	71.1% (27/38)	22	0% (0/38)
	Cycle 1 D1	60	20	4.34	5.16	2.38	0.0	22.4	20	57.5% (23/40)	20	0% (0/40)
	Cycle 1 D8	60	33	4.60	8.56	0.90	0.0	40.8	32	64.3% (18/28)	32	0% (0/28)
	Cycle 1 D15	60	45	1.36	2.15	0.20	0.0	6.1	45	53.3% (8/15)	45	0% (0/15)
	Cycle 1 D28	60	50	0.17	0.54	0.00	0.0	1.7	50	10% (1/10)	50	0% (0/10)
	Cycle 2	60	50	0.00	0.00	0.00	0.0	0.0	50	0% (0/10)	50	0% (0/10)
	Cycle 3	60	50	0.02	0.03	0.00	0.0	0.1	49	18.2% (2/11)	49	0% (0/11)

				Haematology								
									Outside normal range		Clinically Significant	
Test	Visit	Total Subjs	MIS	Mean	SD	Median	Min	Max	MIS	%	MIS	%
	Cycle 4	60	49	0.00	0.00	0.00	0.0	0.0	48	0% (0/12)	48	0% (0/12)
	Cycle 5	60	52	0.01	0.03	0.00	0.0	0.1	51	11.1% (1/9)	51	0% (0/9)
	Cycle 6	60	52	0.00	0.00	0.00	0.0	0.0	52	0% (0/8)	52	0% (0/8)
	Cycle 9	60	54	0.00	0.00	0.00	0.0	0.0	54	0% (0/6)	54	0% (0/6)
	Cycle 12	60	50	0.01	0.03	0.00	0.0	0.1	51	11.1% (1/9)	51	0% (0/9)
	Cycle 15	60	53	0.00	0.00	0.00	0.0	0.0	55	0% (0/5)	55	0% (0/5)
	Cycle 18	60	54	0.00	0.00	0.00	0.0	0.0	57	0% (0/3)	57	0% (0/3)
	Cycle 21	60	53	0.00	0.00	0.00	0.0	0.0	56	0% (0/4)	56	0% (0/4)
	Cycle 24	60	51	0.03	0.07	0.00	0.0	0.2	53	14.3% (1/7)	53	0% (0/7)
Blasts (x10^9/L)	Baseline	60	32	1.41	4.19	0.28	0.0	22.0	32	32.1% (9/28)	32	0% (0/28)
	Cycle 1 D1	60	36	2.58	7.60	0.08	0.0	36.7	36	20.8% (5/24)	36	0% (0/24)
	Cycle 1 D8	60	43	1.06	2.08	0.00	0.0	7.7	42	22.2% (4/18)	42	0% (0/18)
	Cycle 1 D15	60	48	0.10	0.29	0.00	0.0	1.0	48	8.3% (1/12)	48	0% (0/12)
	Cycle 1 D28	60	51	0.00	0.00	0.00	0.0	0.0	51	0% (0/9)	51	0% (0/9)
	Cycle 2	60	50	0.00	0.00	0.00	0.0	0.0	50	0% (0/10)	50	0% (0/10)
	Cycle 3	60	50	0.00	0.00	0.00	0.0	0.0	49	0% (0/11)	49	0% (0/11)
	Cycle 4	60	49	0.00	0.00	0.00	0.0	0.0	48	0% (0/12)	48	0% (0/12)
	Cycle 5	60	52	0.00	0.00	0.00	0.0	0.0	51	0% (0/9)	51	0% (0/9)
	Cycle 6	60	52	0.01	0.02	0.00	0.0	0.1	52	12.5% (1/8)	52	0% (0/8)
	Cycle 9	60	54	0.00	0.00	0.00	0.0	0.0	54	0% (0/6)	54	0% (0/6)
	Cycle 12	60	50	0.00	0.00	0.00	0.0	0.0	51	0% (0/9)	51	0% (0/9)
	Cycle 15	60	53	0.00	0.00	0.00	0.0	0.0	55	0% (0/5)	55	0% (0/5)
	Cycle 18	60	54	0.05	0.13	0.00	0.0	0.3	57	0% (0/3)	57	0% (0/3)
	Cycle 21	60	53	0.00	0.00	0.00	0.0	0.0	56	0% (0/4)	56	0% (0/4)
	Cycle 24	60	51	0.00	0.00	0.00	0.0	0.0	53	0% (0/7)	53	0% (0/7)

Table CHE_1:
Safety set.

				Biochemistry								
									Outside normal range		Clinically Significant	
Test	Visit	Total Subjs	MIS	Mean	SD	Median	Min	Max	MIS	%	MIS	%
AST (U/L)	Baseline	60	1	27.3	7.5	25.0	15	48	1	6.8% (4/59)	1	0% (0/59)
	Cycle 1 D1	60	1	27.2	9.3	25.0	12	70	2	10.3% (6/58)	2	0% (0/58)
	Cycle 1 D8	60	3	23.2	9.6	21.0	7	57	3	10.5% (6/57)	3	0% (0/57)
	Cycle 1 D15	60	3	21.8	10.6	20.0	7	65	3	10.5% (6/57)	3	0% (0/57)
	Cycle 1 D28	60	1	21.2	7.7	20.0	8	44	3	7% (4/57)	4	0% (0/56)
	Cycle 2	60	2	24.6	9.7	23.0	13	62	4	7.1% (4/56)	4	0% (0/56)
	Cycle 3	60	6	25.2	7.7	25.0	14	45	6	7.4% (4/54)	6	1.9% (1/54)
	Cycle 4	60	4	26.6	11.4	22.0	16	71	8	11.5% (6/52)	8	0% (0/52)
	Cycle 5	60	9	26.9	10.3	25.0	13	73	10	8% (4/50)	11	0% (0/49)
	Cycle 6	60	6	29.0	14.1	25.0	13	101	7	18.9% (10/53)	8	1.9% (1/52)
	Cycle 9	60	4	27.0	11.4	24.0	14	72	9	7.8% (4/51)	13	0% (0/47)
	Cycle 12	60	6	27.0	10.0	25.0	16	70	13	10.6% (5/47)	14	0% (0/46)
	Cycle 15	60	10	27.2	9.4	24.5	15	49	20	17.5% (7/40)	21	0% (0/39)
	Cycle 18	60	10	27.8	13.7	25.0	12	84	21	20.5% (8/39)	24	2.8% (1/36)
	Cycle 21	60	10	25.8	11.4	22.5	13	83	22	18.4% (7/38)	26	0% (0/34)
	Cycle 24	60	4	29.3	15.1	25.0	14	86	15	24.4% (11/45)	20	0% (0/40)
ALT (U/L)	Baseline	60	2	29.2	13.7	29.0	7	72	2	15.5% (9/58)	2	0% (0/58)
	Cycle 1 D1	60	2	30.0	16.6	28.0	7	92	3	21.1% (12/57)	3	0% (0/57)
	Cycle 1 D8	60	3	32.4	21.3	28.0	11	97	3	24.6% (14/57)	3	0% (0/57)
	Cycle 1 D15	60	3	34.6	27.8	29.0	7	150	3	26.3% (15/57)	3	1.8% (1/57)
	Cycle 1 D28	60	2	30.4	16.7	26.0	8	88	3	19.3% (11/57)	4	0% (0/56)
	Cycle 2	60	3	35.6	21.8	29.0	12	135	3	24.6% (14/57)	4	1.8% (1/56)
	Cycle 3	60	6	37.2	18.2	32.0	13	97	6	31.5% (17/54)	6	0% (0/54)
	Cycle 4	60	5	39.9	26.1	32.0	12	142	6	35.2% (19/54)	8	1.9% (1/52)

				Biochemistry								
									Outside normal range		Clinically Significant	
Test	Visit	Total Subjs	MIS	Mean	SD	Median	Min	Max	MIS	%	MIS	%
	Cycle 5	60	9	39.9	20.9	38.0	12	107	9	39.2% (20/51)	10	0% (0/50)
	Cycle 6	60	6	43.9	34.4	34.0	13	227	5	32.7% (18/55)	7	1.9% (1/53)
	Cycle 9	60	6	41.6	25.6	33.0	12	131	7	28.3% (15/53)	14	4.3% (2/46)
	Cycle 12	60	7	38.6	23.6	32.0	12	150	12	25% (12/48)	15	4.4% (2/45)
	Cycle 15	60	12	37.2	18.0	32.0	17	75	18	33.3% (14/42)	22	0% (0/38)
	Cycle 18	60	10	42.4	29.3	34.0	11	171	16	40.9% (18/44)	23	2.7% (1/37)
	Cycle 21	60	12	37.0	20.4	33.5	13	112	20	32.5% (13/40)	27	0% (0/33)
	Cycle 24	60	7	40.7	27.9	36.0	11	158	13	40.4% (19/47)	21	2.6% (1/39)
Lactate Dehydrogenase (U/L)	Baseline	60	9	699.8	381.2	592.0	203	1951	9	94.1% (48/51)	9	0% (0/51)
	Cycle 1 D1	60	7	650.9	381.2	547.0	167	2143	7	84.9% (45/53)	8	0% (0/52)
	Cycle 1 D8	60	11	416.6	245.0	350.0	146	1305	11	55.1% (27/49)	11	0% (0/49)
	Cycle 1 D15	60	9	267.9	119.2	245.0	134	676	9	17.6% (9/51)	9	0% (0/51)
	Cycle 1 D28	60	7	222.5	98.1	210.0	101	705	9	17.6% (9/51)	10	0% (0/50)
	Cycle 2	60	9	221.6	81.2	218.0	103	417	10	14% (7/50)	10	0% (0/50)
	Cycle 3	60	11	241.5	77.9	245.0	117	409	11	4.1% (2/49)	11	0% (0/49)
	Cycle 4	60	12	237.1	79.3	219.0	114	411	14	8.7% (4/46)	15	0% (0/45)
	Cycle 5	60	14	240.6	91.6	204.5	123	450	14	6.5% (3/46)	15	0% (0/45)
	Cycle 6	60	12	243.0	81.0	230.5	123	382	13	8.5% (4/47)	13	0% (0/47)
	Cycle 9	60	10	249.8	82.2	245.5	122	422	13	6.4% (3/47)	17	0% (0/43)
	Cycle 12	60	9	237.6	79.2	213.0	128	393	15	6.7% (3/45)	16	0% (0/44)
	Cycle 15	60	12	239.3	79.2	212.5	130	391	22	13.2% (5/38)	23	0% (0/37)
	Cycle 18	60	11	238.2	84.0	197.0	133	417	22	7.9% (3/38)	25	0% (0/35)
	Cycle 21	60	12	233.1	77.4	208.0	131	376	23	10.8% (4/37)	28	0% (0/32)
	Cycle 24	60	6	243.8	101.6	216.0	133	682	15	15.6% (7/45)	22	0% (0/38)
Serum Albumin (g/L)	Baseline	60	0	44.0	3.1	44.0	35	50	0	1.7% (1/60)	0	0% (0/60)
	Cycle 1 D1	60	1	44.3	2.9	44.0	36	51	2	1.7% (1/58)	2	0% (0/58)

				Biochemistry								
									Outside normal range		Clinically Significant	
Test	Visit	Total Subjs	MIS	Mean	SD	Median	Min	Max	MIS	%	MIS	%
	Cycle 1 D8	60	2	43.5	3.2	43.0	35	49	2	0% (0/58)	2	0% (0/58)
	Cycle 1 D15	60	1	43.1	3.3	43.0	35	52	1	1.7% (1/59)	1	0% (0/59)
	Cycle 1 D28	60	1	43.3	3.2	43.0	37	52	3	1.8% (1/57)	4	0% (0/56)
	Cycle 2	60	2	44.3	3.2	44.0	37	54	4	5.4% (3/56)	4	0% (0/56)
	Cycle 3	60	6	44.6	3.1	45.0	38	52	6	5.6% (3/54)	6	0% (0/54)
	Cycle 4	60	4	44.1	3.3	44.0	38	51	8	3.8% (2/52)	8	0% (0/52)
	Cycle 5	60	6	44.3	3.6	45.0	38	52	8	5.8% (3/52)	8	0% (0/52)
	Cycle 6	60	4	44.1	3.3	44.0	38	50	5	3.6% (2/55)	6	0% (0/54)
	Cycle 9	60	4	44.0	3.5	44.0	36	50	9	2% (1/51)	13	0% (0/47)
	Cycle 12	60	6	43.0	6.5	43.0	4	53	13	2.1% (1/47)	14	0% (0/46)
	Cycle 15	60	10	43.8	3.5	44.0	38	53	20	7.5% (3/40)	21	0% (0/39)
	Cycle 18	60	9	43.8	3.3	43.0	36	51	20	7.5% (3/40)	23	0% (0/37)
	Cycle 21	60	9	43.6	3.4	43.0	35	52	21	2.6% (1/39)	25	0% (0/35)
	Cycle 24	60	3	43.9	3.5	44.0	37	53	14	6.5% (3/46)	20	0% (0/40)
Alkaline Phosphatase (U/L)	Baseline	60	0	78.2	29.4	74.0	1	194	0	10% (6/60)	0	0% (0/60)
	Cycle 1 D1	60	1	81.6	28.4	76.0	45	212	2	12.1% (7/58)	2	0% (0/58)
	Cycle 1 D8	60	2	84.5	29.2	77.5	34	186	2	12.1% (7/58)	2	0% (0/58)
	Cycle 1 D15	60	1	89.3	41.9	78.0	36	281	1	18.6% (11/59)	1	0% (0/59)
	Cycle 1 D28	60	1	89.8	31.6	82.0	44	207	2	12.1% (7/58)	4	1.8% (1/56)
	Cycle 2	60	2	88.7	27.8	88.0	41	161	4	10.7% (6/56)	4	0% (0/56)
	Cycle 3	60	6	84.1	24.2	80.5	40	136	6	13% (7/54)	6	0% (0/54)
	Cycle 4	60	4	82.1	27.5	76.5	37	174	8	9.6% (5/52)	8	0% (0/52)
	Cycle 5	60	6	75.9	24.4	72.0	0	147	8	9.6% (5/52)	8	0% (0/52)
	Cycle 6	60	4	73.8	20.5	72.0	33	129	6	1.9% (1/54)	6	0% (0/54)
	Cycle 9	60	4	72.7	20.4	72.0	35	136	8	5.8% (3/52)	13	0% (0/47)
	Cycle 12	60	6	71.0	20.0	70.0	37	132	13	4.3% (2/47)	14	0% (0/46)

				Biochemistry								
									Outside normal range		Clinically Significant	
Test	Visit	Total Subjs	MIS	Mean	SD	Median	Min	Max	MIS	%	MIS	%
	Cycle 15	60	10	68.8	21.1	68.5	1	123	19	4.9% (2/41)	21	0% (0/39)
	Cycle 18	60	9	74.8	27.7	68.0	39	179	18	11.9% (5/42)	23	0% (0/37)
	Cycle 21	60	9	76.0	29.2	71.0	39	193	20	12.5% (5/40)	25	0% (0/35)
	Cycle 24	60	3	77.5	31.9	74.0	37	232	13	10.6% (5/47)	19	0% (0/41)
Total Bilirubin (umol/L)	Baseline	60	0	8.1	3.8	7.4	1	22	0	1.7% (1/60)	0	0% (0/60)
	Cycle 1 D1	60	1	8.9	5.8	7.0	3	42	2	3.4% (2/58)	2	0% (0/58)
	Cycle 1 D8	60	3	16.8	11.3	13.0	3	55	3	29.8% (17/57)	3	0% (0/57)
	Cycle 1 D15	60	3	14.1	9.4	10.8	4	45	3	21.1% (12/57)	3	0% (0/57)
	Cycle 1 D28	60	1	15.2	10.0	13.7	5	58	3	19.3% (11/57)	4	1.8% (1/56)
	Cycle 2	60	2	15.2	11.0	12.0	4	50	3	22.8% (13/57)	4	3.6% (2/56)
	Cycle 3	60	6	15.1	11.6	11.0	2	53	6	25.9% (14/54)	6	0% (0/54)
	Cycle 4	60	4	15.3	9.3	12.0	2	55	7	32.1% (17/53)	8	0% (0/52)
	Cycle 5	60	7	18.1	10.9	14.7	4	58	9	31.4% (16/51)	9	0% (0/51)
	Cycle 6	60	5	17.5	13.4	13.0	4	67	7	30.2% (16/53)	7	0% (0/53)
	Cycle 9	60	4	16.8	12.7	13.0	1	81	9	37.3% (19/51)	13	2.1% (1/47)
	Cycle 12	60	6	15.5	9.7	12.6	3	48	12	27.1% (13/48)	14	2.2% (1/46)
	Cycle 15	60	10	16.4	10.5	14.5	2	54	17	39.5% (17/43)	21	2.6% (1/39)
	Cycle 18	60	9	17.2	11.5	13.7	4	56	16	38.6% (17/44)	23	2.7% (1/37)
	Cycle 21	60	10	16.6	12.5	12.5	1	65	19	34.1% (14/41)	26	0% (0/34)
	Cycle 24	60	3	16.6	13.1	12.0	4	76	10	30% (15/50)	19	0% (0/41)
Blood Urea Nitrogen (BUN) or Urea (mmol/L)	Baseline	60	0	7.26	3.47	6.25	3.6	18.2	0	16.7% (10/60)	0	1.7% (1/60)
	Cycle 1 D1	60	1	7.00	3.22	6.07	2.9	20.3	1	18.6% (11/59)	2	1.7% (1/58)
	Cycle 1 D8	60	2	6.70	2.70	6.03	2.5	16.4	2	20.7% (12/58)	2	1.7% (1/58)
	Cycle 1 D15	60	1	6.73	2.69	6.30	2.9	15.7	1	20.3% (12/59)	2	0% (0/58)
	Cycle 1 D28	60	1	6.24	2.61	5.70	3.2	18.2	3	14% (8/57)	4	1.8% (1/56)
	Cycle 2	60	2	6.27	2.73	5.50	2.8	16.4	4	16.1% (9/56)	4	0% (0/56)

				Biochemistry								
									Outside normal range		Clinically Significant	
Test	Visit	Total Subjs	MIS	Mean	SD	Median	Min	Max	MIS	%	MIS	%
	Cycle 3	60	6	6.30	2.90	5.68	2.2	17.1	6	18.5% (10/54)	6	1.9% (1/54)
	Cycle 4	60	4	6.08	2.66	5.76	2.2	17.1	8	17.3% (9/52)	8	0% (0/52)
	Cycle 5	60	6	6.15	2.68	5.65	2.2	16.1	8	15.4% (8/52)	8	0% (0/52)
	Cycle 6	60	4	6.23	3.17	5.33	2.5	17.5	6	18.5% (10/54)	6	0% (0/54)
	Cycle 9	60	4	6.22	2.87	5.60	2.9	18.2	8	13.5% (7/52)	13	0% (0/47)
	Cycle 12	60	6	5.78	2.73	5.19	1.7	16.1	13	12.8% (6/47)	14	0% (0/46)
	Cycle 15	60	10	6.43	2.73	5.76	1.4	16.8	20	17.5% (7/40)	21	0% (0/39)
	Cycle 18	60	9	6.01	2.83	5.40	2.5	15.7	18	14.3% (6/42)	23	0% (0/37)
	Cycle 21	60	9	6.32	3.59	5.10	2.7	22.0	21	7.7% (3/39)	25	0% (0/35)
	Cycle 24	60	3	6.20	2.74	5.32	2.7	15.8	14	10.9% (5/46)	19	0% (0/41)
Calcium (mmol/L)	Baseline	60	0	2.284	0.114	2.295	2.04	2.58	0	10% (6/60)	0	1.7% (1/60)
	Cycle 1 D1	60	1	2.297	0.119	2.280	2.06	2.58	2	8.6% (5/58)	2	0% (0/58)
	Cycle 1 D8	60	4	2.241	0.102	2.230	2.03	2.45	4	17.9% (10/56)	4	0% (0/56)
	Cycle 1 D15	60	1	2.225	0.106	2.220	2.02	2.52	1	18.6% (11/59)	1	0% (0/59)
	Cycle 1 D28	60	1	2.209	0.107	2.200	1.97	2.45	3	24.6% (14/57)	4	0% (0/56)
	Cycle 2	60	2	2.232	0.123	2.225	1.97	2.48	4	26.8% (15/56)	4	0% (0/56)
	Cycle 3	60	6	2.252	0.115	2.250	1.96	2.48	6	22.2% (12/54)	6	0% (0/54)
	Cycle 4	60	4	2.267	0.129	2.265	1.97	2.67	7	18.9% (10/53)	8	0% (0/52)
	Cycle 5	60	6	2.263	0.109	2.250	2.00	2.50	7	17% (9/53)	8	0% (0/52)
	Cycle 6	60	4	2.263	0.117	2.260	2.02	2.58	6	14.8% (8/54)	6	0% (0/54)
	Cycle 9	60	4	2.280	0.117	2.275	2.04	2.55	9	13.7% (7/51)	13	0% (0/47)
	Cycle 12	60	6	2.267	0.113	2.268	2.05	2.55	13	14.9% (7/47)	14	0% (0/46)
	Cycle 15	60	10	2.283	0.106	2.280	2.08	2.54	20	15% (6/40)	21	0% (0/39)
	Cycle 18	60	9	2.292	0.111	2.300	1.98	2.55	20	12.5% (5/40)	23	0% (0/37)
	Cycle 21	60	9	2.324	0.106	2.310	2.08	2.60	21	5.1% (2/39)	25	0% (0/35)
	Cycle 24	60	3	2.448	0.913	2.325	2.15	9.18	14	2.2% (1/46)	19	0% (0/41)

				Biochemistry								
									Outside normal range		Clinically Significant	
Test	Visit	Total Subjs	MIS	Mean	SD	Median	Min	Max	MIS	%	MIS	%
Creatinine (umol/L)	Baseline	60	0	80.4	18.0	79.0	49	135	0	13.3% (8/60)	0	1.7% (1/60)
	Cycle 1 D1	60	1	79.9	16.9	79.6	51	133	2	13.8% (8/58)	2	1.7% (1/58)
	Cycle 1 D8	60	2	81.1	19.8	79.6	44	150	2	17.2% (10/58)	2	1.7% (1/58)
	Cycle 1 D15	60	1	77.1	17.0	75.0	43	133	1	10.2% (6/59)	1	1.7% (1/59)
	Cycle 1 D28	60	1	76.1	15.1	75.0	42	121	2	6.9% (4/58)	4	1.8% (1/56)
	Cycle 2	60	2	75.6	16.7	73.6	40	122	4	8.9% (5/56)	4	1.8% (1/56)
	Cycle 3	60	6	77.6	17.7	78.3	45	141	6	11.1% (6/54)	6	1.9% (1/54)
	Cycle 4	60	4	76.6	14.6	76.5	49	112	8	9.6% (5/52)	8	0% (0/52)
	Cycle 5	60	6	76.4	15.1	78.0	46	111	8	9.6% (5/52)	8	0% (0/52)
	Cycle 6	60	4	79.3	25.6	77.0	46	227	6	7.4% (4/54)	6	0% (0/54)
	Cycle 9	60	4	78.1	18.4	76.0	44	135	7	13.2% (7/53)	13	0% (0/47)
	Cycle 12	60	6	76.1	15.6	76.0	44	126	13	10.6% (5/47)	14	0% (0/46)
	Cycle 15	60	10	78.5	18.9	78.5	32	137	19	14.6% (6/41)	21	0% (0/39)
	Cycle 18	60	9	77.5	16.8	79.0	41	132	20	10% (4/40)	23	0% (0/37)
	Cycle 21	60	9	78.0	17.1	78.7	47	147	20	10% (4/40)	25	0% (0/35)
	Cycle 24	60	3	78.2	18.4	75.0	47	167	15	8.9% (4/45)	18	0% (0/42)
Magnesium (mmol/L)	Baseline	60	2	0.859	0.092	0.855	0.62	1.05	2	5.2% (3/58)	2	1.7% (1/58)
	Cycle 1 D1	60	3	0.852	0.079	0.863	0.70	1.04	4	5.4% (3/56)	4	0% (0/56)
	Cycle 1 D8	60	3	0.895	0.104	0.880	0.70	1.32	3	7% (4/57)	3	0% (0/57)
	Cycle 1 D15	60	1	0.861	0.075	0.860	0.70	1.05	1	1.7% (1/59)	1	0% (0/59)
	Cycle 1 D28	60	2	0.834	0.074	0.822	0.69	1.03	3	3.5% (2/57)	4	0% (0/56)
	Cycle 2	60	3	0.838	0.076	0.840	0.65	1.03	4	5.4% (3/56)	4	0% (0/56)
	Cycle 3	60	7	0.835	0.084	0.822	0.67	1.07	7	7.5% (4/53)	7	1.9% (1/53)
	Cycle 4	60	7	0.831	0.068	0.822	0.67	1.00	10	6% (3/50)	10	0% (0/50)
	Cycle 5	60	9	0.825	0.072	0.822	0.62	0.97	10	8% (4/50)	10	0% (0/50)
	Cycle 6	60	5	0.832	0.060	0.830	0.67	0.97	6	1.9% (1/54)	6	0% (0/54)

				Biochemistry								
									Outside normal range		Clinically Significant	
Test	Visit	Total Subjs	MIS	Mean	SD	Median	Min	Max	MIS	%	MIS	%
	Cycle 9	60	8	0.826	0.067	0.822	0.69	1.03	12	8.3% (4/48)	15	0% (0/45)
	Cycle 12	60	8	0.817	0.076	0.815	0.66	0.99	14	17.4% (8/46)	17	0% (0/43)
	Cycle 15	60	11	0.846	0.215	0.810	0.66	2.20	20	12.5% (5/40)	22	0% (0/38)
	Cycle 18	60	12	0.809	0.072	0.795	0.69	0.95	20	20% (8/40)	25	0% (0/35)
	Cycle 21	60	9	0.811	0.070	0.820	0.66	1.02	20	15% (6/40)	26	0% (0/34)
	Cycle 24	60	6	0.827	0.061	0.822	0.72	0.96	18	0% (0/42)	21	0% (0/39)
Potassium (mmol/L)	Baseline	60	0	4.14	0.46	4.10	2.9	5.2	0	6.7% (4/60)	0	1.7% (1/60)
	Cycle 1 D1	60	1	4.20	0.37	4.10	3.6	5.4	2	1.7% (1/58)	2	0% (0/58)
	Cycle 1 D8	60	2	4.20	0.38	4.15	3.5	5.0	2	0% (0/58)	2	0% (0/58)
	Cycle 1 D15	60	2	4.34	0.39	4.30	3.7	5.3	2	0% (0/58)	2	0% (0/58)
	Cycle 1 D28	60	1	4.22	0.38	4.20	3.3	5.3	3	3.5% (2/57)	4	0% (0/56)
	Cycle 2	60	2	4.12	0.37	4.15	3.4	5.0	4	1.8% (1/56)	4	0% (0/56)
	Cycle 3	60	6	4.07	0.37	4.10	3.2	5.1	6	3.7% (2/54)	6	0% (0/54)
	Cycle 4	60	4	4.16	0.44	4.10	3.4	5.8	8	3.8% (2/52)	8	1.9% (1/52)
	Cycle 5	60	7	4.17	0.35	4.20	3.3	5.2	9	3.9% (2/51)	9	0% (0/51)
	Cycle 6	60	5	4.08	0.35	4.10	3.3	5.1	7	3.8% (2/53)	7	0% (0/53)
	Cycle 9	60	5	4.11	0.42	4.10	3.1	5.3	10	6% (3/50)	14	0% (0/46)
	Cycle 12	60	6	4.09	0.37	4.05	3.4	5.3	13	2.1% (1/47)	14	0% (0/46)
	Cycle 15	60	10	4.03	0.39	4.00	3.2	5.2	20	2.5% (1/40)	21	0% (0/39)
	Cycle 18	60	9	4.03	0.36	4.00	3.0	4.8	20	5% (2/40)	23	0% (0/37)
	Cycle 21	60	10	4.07	0.35	4.10	3.3	4.8	22	5.3% (2/38)	26	0% (0/34)
	Cycle 24	60	3	4.18	0.39	4.20	3.4	5.6	14	4.3% (2/46)	20	0% (0/40)
Sodium (mmol/L)	Baseline	60	0	139.6	2.1	140.0	135	144	0	3.3% (2/60)	0	0% (0/60)
	Cycle 1 D1	60	1	139.9	2.4	140.0	135	145	2	3.4% (2/58)	2	0% (0/58)
	Cycle 1 D8	60	2	139.0	2.3	139.0	134	146	2	10.3% (6/58)	2	0% (0/58)
	Cycle 1 D15	60	1	139.3	2.3	139.0	135	145	1	0% (0/59)	1	0% (0/59)

				Biochemistry								
									Outside normal range		Clinically Significant	
Test	Visit	Total Subjs	MIS	Mean	SD	Median	Min	Max	MIS	%	MIS	%
	Cycle 1 D28	60	1	139.7	2.6	139.0	134	148	3	7% (4/57)	4	0% (0/56)
	Cycle 2	60	2	139.5	2.0	139.5	135	144	4	1.8% (1/56)	4	0% (0/56)
	Cycle 3	60	6	139.6	2.4	139.0	135	147	6	3.7% (2/54)	6	0% (0/54)
	Cycle 4	60	4	139.9	2.3	140.0	136	146	8	1.9% (1/52)	8	0% (0/52)
	Cycle 5	60	6	139.7	1.9	139.5	136	144	8	0% (0/52)	8	0% (0/52)
	Cycle 6	60	4	139.7	2.5	140.0	133	146	6	3.7% (2/54)	6	0% (0/54)
	Cycle 9	60	4	139.8	2.0	140.0	135	145	10	0% (0/50)	13	0% (0/47)
	Cycle 12	60	6	139.8	2.2	140.0	134	144	13	4.3% (2/47)	14	0% (0/46)
	Cycle 15	60	10	136.7	19.7	139.0	1	147	20	5% (2/40)	21	0% (0/39)
	Cycle 18	60	9	139.2	2.4	139.0	131	146	20	2.5% (1/40)	23	0% (0/37)
	Cycle 21	60	9	139.4	2.2	140.0	134	143	21	5.1% (2/39)	25	0% (0/35)
	Cycle 24	60	3	139.8	2.4	140.0	134	145	13	4.3% (2/47)	20	0% (0/40)
Total Protein (g/L)	Baseline	60	6	73.4	4.3	73.0	63	82	5	3.6% (2/55)	5	0% (0/55)
	Cycle 1 D1	60	9	73.3	4.6	72.0	65	84	10	8% (4/50)	10	0% (0/50)
	Cycle 1 D8	60	8	73.4	4.1	73.0	62	82	8	1.9% (1/52)	8	0% (0/52)
	Cycle 1 D15	60	9	72.7	4.1	73.0	64	81	9	3.9% (2/51)	9	0% (0/51)
	Cycle 1 D28	60	9	72.3	4.0	73.0	61	81	11	2% (1/49)	12	0% (0/48)
	Cycle 2	60	8	73.3	4.3	73.0	64	82	10	4% (2/50)	10	0% (0/50)
	Cycle 3	60	12	73.9	4.1	74.0	64	84	12	4.2% (2/48)	12	0% (0/48)
	Cycle 4	60	10	72.2	10.1	74.0	8	82	14	0% (0/46)	14	0% (0/46)
	Cycle 5	60	11	73.5	4.2	74.0	65	84	13	2.1% (1/47)	13	0% (0/47)
	Cycle 6	60	11	73.0	4.1	74.0	64	79	13	2.1% (1/47)	13	0% (0/47)
	Cycle 9	60	12	73.9	4.2	74.0	62	82	16	0% (0/44)	20	0% (0/40)
	Cycle 12	60	12	72.8	3.6	73.0	64	80	19	2.4% (1/41)	20	0% (0/40)
	Cycle 15	60	14	73.0	4.6	73.0	61	86	24	0% (0/36)	25	0% (0/35)
	Cycle 18	60	14	73.5	4.5	74.0	63	84	25	5.7% (2/35)	28	0% (0/32)

				Biochemistry								
									Outside normal range		Clinically Significant	
Test	Visit	Total Subjs	MIS	Mean	SD	Median	Min	Max	MIS	%	MIS	%
	Cycle 21	60	12	72.9	5.0	72.0	62	89	24	8.3% (3/36)	28	0% (0/32)
	Cycle 24	60	4	73.1	5.2	73.0	62	89	15	6.7% (3/45)	20	0% (0/40)
Phosphorus (mmol/L)	Baseline	60	0	1.130	0.218	1.110	0.72	1.81	0	11.7% (7/60)	0	0% (0/60)
	Cycle 1 D1	60	2	1.157	0.231	1.190	0.74	1.74	3	14% (8/57)	3	0% (0/57)
	Cycle 1 D8	60	4	2.391	10.154	1.000	0.61	77.00	4	21.4% (12/56)	4	0% (0/56)
	Cycle 1 D15	60	1	2.127	8.594	1.001	0.62	67.00	1	20.3% (12/59)	1	0% (0/59)
	Cycle 1 D28	60	1	0.948	0.204	0.970	0.40	1.49	3	21.1% (12/57)	4	0% (0/56)
	Cycle 2	60	3	0.964	0.242	0.950	0.43	1.58	3	28.1% (16/57)	4	0% (0/56)
	Cycle 3	60	6	0.943	0.206	0.935	0.56	1.58	6	27.8% (15/54)	6	1.9% (1/54)
	Cycle 4	60	6	0.943	0.195	0.940	0.50	1.32	8	26.9% (14/52)	9	0% (0/51)
	Cycle 5	60	9	0.929	0.214	0.900	0.37	1.62	10	20% (10/50)	10	0% (0/50)
	Cycle 6	60	5	0.899	0.174	0.904	0.60	1.42	5	36.4% (20/55)	7	0% (0/53)
	Cycle 9	60	7	0.899	0.204	0.930	0.48	1.55	10	32% (16/50)	16	0% (0/44)
	Cycle 12	60	6	0.891	0.216	0.850	0.48	1.48	10	36% (18/50)	14	2.2% (1/46)
	Cycle 15	60	10	0.863	0.169	0.855	0.58	1.41	17	41.9% (18/43)	21	2.6% (1/39)
	Cycle 18	60	9	0.892	0.194	0.890	0.51	1.49	17	32.6% (14/43)	23	0% (0/37)
	Cycle 21	60	9	0.900	0.204	0.900	0.53	1.30	16	36.4% (16/44)	25	2.9% (1/35)
	Cycle 24	60	3	0.912	0.196	0.900	0.38	1.42	10	26% (13/50)	19	0% (0/41)
Uric Acid (mmol/L)	Baseline	60	31	10.40	54.07	0.35	0.1	291.6	31	31% (9/29)	31	3.4% (1/29)
	Cycle 1 D1	60	33	0.35	0.11	0.37	0.1	0.6	32	46.4% (13/28)	32	3.6% (1/28)
	Cycle 1 D8	60	33	9.80	49.17	0.37	0.1	255.8	32	35.7% (10/28)	32	3.6% (1/28)
	Cycle 1 D15	60	34	9.90	48.95	0.30	0.2	249.9	34	23.1% (6/26)	34	3.8% (1/26)
	Cycle 1 D28	60	34	25.63	94.31	0.31	0.1	437.0	34	19.2% (5/26)	34	3.8% (1/26)
	Cycle 2	60	29	11.21	60.86	0.27	0.0	339.1	31	20.7% (6/29)	31	3.4% (1/29)
	Cycle 3	60	35	12.17	59.44	0.29	0.1	297.5	34	7.7% (2/26)	34	0% (0/26)
	Cycle 4	60	34	10.80	53.64	0.30	0.1	273.8	35	8% (2/25)	35	0% (0/25)

				Biochemistry								
									Outside normal range		Clinically Significant	
Test	Visit	Total Subjs	MIS	Mean	SD	Median	Min	Max	MIS	%	MIS	%
	Cycle 5	60	32	11.14	57.31	0.32	0.1	303.6	33	3.7% (1/27)	33	0% (0/27)
	Cycle 6	60	33	17.39	65.09	0.33	0.2	309.5	33	7.4% (2/27)	33	0% (0/27)
	Cycle 9	60	36	20.09	70.37	0.31	0.0	309.5	38	0% (0/22)	40	0% (0/20)
	Cycle 12	60	33	20.77	76.62	0.33	0.0	351.2	36	4.2% (1/24)	37	0% (0/23)
	Cycle 15	60	33	22.55	80.16	0.35	0.1	309.5	40	10% (2/20)	41	0% (0/19)
	Cycle 18	60	31	35.77	92.12	0.33	0.1	315.5	38	13.6% (3/22)	40	0% (0/20)
	Cycle 21	60	29	38.26	104.74	0.30	0.1	386.8	36	20.8% (5/24)	38	0% (0/22)
	Cycle 24	60	27	42.83	104.73	0.32	0.1	380.8	31	20.7% (6/29)	34	0% (0/26)
Glucose (mmol/L)	Baseline	60	2	5.655	1.759	5.250	4.05	14.15	3	15.8% (9/57)	3	0% (0/57)
	Cycle 1 D1	60	2	5.781	1.978	5.350	3.05	16.20	3	26.3% (15/57)	3	0% (0/57)
	Cycle 1 D8	60	3	6.326	2.938	5.273	3.83	15.82	3	26.3% (15/57)	3	0% (0/57)
	Cycle 1 D15	60	2	6.257	2.877	5.447	3.16	19.70	2	25.9% (15/58)	2	0% (0/58)
	Cycle 1 D28	60	3	6.275	2.248	5.500	3.60	13.82	5	41.8% (23/55)	6	0% (0/54)
	Cycle 2	60	3	6.137	2.117	5.500	3.83	13.76	4	32.1% (18/56)	5	0% (0/55)
	Cycle 3	60	9	6.323	2.509	5.300	3.80	14.20	9	35.3% (18/51)	9	0% (0/51)
	Cycle 4	60	7	6.565	2.886	5.800	3.94	20.48	11	36.7% (18/49)	11	0% (0/49)
	Cycle 5	60	8	6.109	1.562	5.603	4.44	12.50	10	36% (18/50)	10	2% (1/50)
	Cycle 6	60	7	6.419	1.829	5.828	4.38	15.20	8	44.2% (23/52)	9	0% (0/51)
	Cycle 9	60	5	6.171	2.342	5.400	4.20	17.48	10	34% (17/50)	14	0% (0/46)
	Cycle 12	60	7	5.992	1.734	5.661	3.70	11.60	13	44.7% (21/47)	15	0% (0/45)
	Cycle 15	60	13	6.530	2.682	5.900	3.21	18.40	18	54.8% (23/42)	23	0% (0/37)
	Cycle 18	60	13	6.600	2.593	5.606	3.80	16.50	19	46.3% (19/41)	26	0% (0/34)
	Cycle 21	60	9	6.262	1.845	5.770	3.94	12.40	17	51.2% (22/43)	25	0% (0/35)
	Cycle 24	60	5	5.956	2.576	5.400	0.57	15.71	13	29.8% (14/47)	21	0% (0/39)
Chloride (mmol/L)	Baseline	60	6	103.0	2.6	103.0	96	108	6	1.9% (1/54)	6	0% (0/54)
	Cycle 1 D1	60	7	103.3	2.6	103.0	96	109	9	7.8% (4/51)	9	0% (0/51)

				Biochemistry								
									Outside normal range		Clinically Significant	
Test	Visit	Total Subjs	MIS	Mean	SD	Median	Min	Max	MIS	%	MIS	%
	Cycle 1 D8	60	8	103.9	3.2	104.0	97	110	8	17.3% (9/52)	8	0% (0/52)
	Cycle 1 D15	60	4	104.4	2.4	105.0	98	109	4	8.9% (5/56)	4	0% (0/56)
	Cycle 1 D28	60	4	104.6	2.6	104.5	99	111	6	14.8% (8/54)	7	0% (0/53)
	Cycle 2	60	6	104.2	2.4	104.0	100	111	7	13.2% (7/53)	8	0% (0/52)
	Cycle 3	60	7	104.0	2.6	104.0	98	109	8	7.7% (4/52)	8	0% (0/52)
	Cycle 4	60	7	103.8	2.7	104.0	99	111	11	14.3% (7/49)	11	0% (0/49)
	Cycle 5	60	8	104.1	2.2	104.0	100	109	10	10% (5/50)	10	0% (0/50)
	Cycle 6	60	4	102.2	12.9	104.0	9	111	6	9.3% (5/54)	6	0% (0/54)
	Cycle 9	60	6	104.0	2.6	104.0	99	110	10	8% (4/50)	14	0% (0/46)
	Cycle 12	60	9	104.2	2.0	104.0	100	109	14	4.3% (2/46)	16	0% (0/44)
	Cycle 15	60	11	103.8	2.5	104.0	99	110	19	9.8% (4/41)	22	0% (0/38)
	Cycle 18	60	11	103.7	2.3	104.0	98	108	19	9.8% (4/41)	24	0% (0/36)
	Cycle 21	60	11	103.3	2.3	103.0	98	108	21	2.6% (1/39)	27	0% (0/33)
	Cycle 24	60	8	103.8	2.3	103.0	99	109	19	7.3% (3/41)	22	0% (0/38)
Lipase (U/L)	Baseline	60	2	49.3	49.2	35.0	9	287	2	10.3% (6/58)	2	0% (0/58)
	Cycle 1 D1	60	11	59.3	64.9	34.0	11	315	11	12.2% (6/49)	11	2% (1/49)
	Cycle 1 D8	60	12	148.5	218.3	65.5	11	1073	11	42.9% (21/49)	11	12.2% (6/49)
	Cycle 1 D15	60	10	71.7	94.4	38.5	8	489	10	20% (10/50)	10	6% (3/50)
	Cycle 1 D28	60	9	59.3	70.4	34.0	7	379	10	16% (8/50)	10	0% (0/50)
	Cycle 2	60	6	51.5	52.2	32.5	10	249	7	15.1% (8/53)	7	3.8% (2/53)
	Cycle 3	60	11	85.0	161.3	37.0	12	1020	11	12.2% (6/49)	11	0% (0/49)
	Cycle 4	60	16	59.6	60.0	40.0	11	259	17	11.6% (5/43)	18	0% (0/42)
	Cycle 5	60	13	57.4	55.8	43.0	11	249	14	10.9% (5/46)	15	0% (0/45)
	Cycle 6	60	9	63.0	77.2	34.0	9	384	10	16% (8/50)	11	2% (1/49)
	Cycle 9	60	13	71.9	173.3	35.0	12	1201	16	13.6% (6/44)	20	2.5% (1/40)
	Cycle 12	60	8	52.5	65.6	33.5	9	330	13	6.4% (3/47)	14	2.2% (1/46)

				Biochemistry								
									Outside normal range		Clinically Significant	
Test	Visit	Total Subjs	MIS	Mean	SD	Median	Min	Max	MIS	%	MIS	%
	Cycle 15	60	14	43.9	38.3	31.5	9	184	20	10% (4/40)	23	0% (0/37)
	Cycle 18	60	17	47.8	43.8	38.0	8	203	26	11.8% (4/34)	29	0% (0/31)
	Cycle 21	60	20	51.1	54.8	37.5	6	329	28	12.5% (4/32)	33	0% (0/27)
	Cycle 24	60	15	65.1	89.3	32.0	9	484	20	12.5% (5/40)	23	5.4% (2/37)
GGT (U/L)	Baseline	60	3	50.0	40.7	39.0	16	242	3	31.6% (18/57)	3	0% (0/57)
	Cycle 1 D1	60	3	49.1	39.4	38.0	12	242	4	26.8% (15/56)	4	0% (0/56)
	Cycle 1 D8	60	4	51.8	43.2	40.0	11	214	4	30.4% (17/56)	4	1.8% (1/56)
	Cycle 1 D15	60	3	58.0	63.2	37.0	13	347	3	29.8% (17/57)	4	0% (0/56)
	Cycle 1 D28	60	3	45.1	43.5	35.0	10	264	4	21.4% (12/56)	6	0% (0/54)
	Cycle 2	60	4	46.1	51.3	35.5	10	300	5	16.4% (9/55)	5	0% (0/55)
	Cycle 3	60	7	52.1	59.0	38.0	9	347	7	26.4% (14/53)	7	0% (0/53)
	Cycle 4	60	6	63.9	109.0	42.5	10	717	9	31.4% (16/51)	9	0% (0/51)
	Cycle 5	60	10	57.2	69.6	42.0	11	380	11	24.5% (12/49)	11	0% (0/49)
	Cycle 6	60	6	52.9	60.7	42.5	12	441	7	32.1% (17/53)	7	0% (0/53)
	Cycle 9	60	7	51.6	43.0	41.0	12	265	11	30.6% (15/49)	15	0% (0/45)
	Cycle 12	60	6	56.9	57.8	44.0	11	399	11	40.8% (20/49)	15	0% (0/45)
	Cycle 15	60	11	53.3	56.8	38.0	11	375	20	30% (12/40)	22	0% (0/38)
	Cycle 18	60	10	69.5	107.1	43.0	12	708	18	38.1% (16/42)	25	2.9% (1/35)
	Cycle 21	60	9	67.3	95.7	43.0	11	582	17	34.9% (15/43)	25	0% (0/35)
	Cycle 24	60	3	64.2	87.4	43.0	12	487	12	39.6% (19/48)	18	4.8% (2/42)
Amylase (U/dL)	Baseline	60	4	55.3	21.1	55.0	20	119	4	7.1% (4/56)	4	0% (0/56)
	Cycle 1 D1	60	6	57.6	23.0	57.0	18	126	5	10.9% (6/55)	5	0% (0/55)
	Cycle 1 D8	60	8	72.9	34.0	66.0	26	167	8	19.2% (10/52)	8	3.8% (2/52)
	Cycle 1 D15	60	8	59.4	21.4	55.5	20	118	8	5.8% (3/52)	8	0% (0/52)
	Cycle 1 D28	60	6	55.5	21.4	51.5	19	115	6	5.6% (3/54)	8	0% (0/52)
	Cycle 2	60	6	56.1	20.6	54.0	20	122	7	3.8% (2/53)	7	0% (0/53)

				Biochemistry								
									Outside normal range		Clinically Significant	
Test	Visit	Total Subjs	MIS	Mean	SD	Median	Min	Max	MIS	%	MIS	%
	Cycle 3	60	9	59.8	22.0	59.0	20	127	9	5.9% (3/51)	9	0% (0/51)
	Cycle 4	60	9	60.4	23.0	61.0	6	116	11	8.2% (4/49)	12	0% (0/48)
	Cycle 5	60	16	58.8	21.7	56.0	19	101	17	7% (3/43)	17	0% (0/43)
	Cycle 6	60	8	58.6	21.2	58.0	21	116	9	7.8% (4/51)	9	0% (0/51)
	Cycle 9	60	11	58.0	21.4	57.0	17	104	14	4.3% (2/46)	19	0% (0/41)
	Cycle 12	60	11	56.3	19.2	58.0	22	101	17	11.6% (5/43)	18	0% (0/42)
	Cycle 15	60	14	60.6	20.8	61.0	22	124	22	7.9% (3/38)	24	0% (0/36)
	Cycle 18	60	13	61.8	20.8	60.0	25	118	22	15.8% (6/38)	27	0% (0/33)
	Cycle 21	60	13	61.3	25.8	59.0	22	163	23	10.8% (4/37)	28	0% (0/32)
	Cycle 24	60	11	64.7	28.7	62.0	21	184	22	15.8% (6/38)	25	0% (0/35)

Summary and Conclusions

This was a phase II study of Nilotinib at a 300 mg dose twice daily in adult patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia in chronic phase (CML-CP). Sixty two patients were enrolled in this study but 2 of them withdrew before receiving any treatment (one withdrew consent and the other one did not meet MG level requirements for treatment at day 1 on cycle 1, even though s/he met all inclusion/exclusion criteria).

Thirty-four participants had the primary outcome measured at cycle 6 and 32 achieved CCyR which was the primary outcome of this study. Therefore, the success rate was 94.1% (95% CI 80.9% to 98.4%) which is significantly higher than the 54% reported for Imatinib in the protocol and the rate originally declared as clinically useful for Nilotinib, 72%. After imputing missing values using “last value carried forward” criteria, the estimated response rate was still significantly higher than 72% (estimated % after imputing 84%, 95% CI 72.6% to 91.5%). Note that this high success response rate is consistent with results previously reported in the literature (see Section 2.1.2 of the protocol).

All the patients who took at least one dose of the study drug experienced one or more adverse events and 19 of them had at least one serious adverse event. Adverse events and patient refusal/non-compliance were the most frequent reasons for dose modifications.

The most frequent non-haematologic adverse events were Rash (46.7%), Fatigue (43.3%), Nausea (35%), Headache (31.7%), Back pain (31.7%), Lipase increased (28.3%), Constipation (26.7%), Pruritus (23.3%), Alanine aminotransferase increased (21.7%), Alopecia (21.7%) and Arthralgia (20%). Most of these events were mild or moderate (grades 1 and 2, respectively) except "Lipase increased" where 14 out of 17 patients experienced grades 3 or 4. Furthermore, the most frequent haematologic AEs were Thrombocytopenia (13.3%) and Anaemia (11.7%). All the Anaemia cases were mild or moderate whereas 3 out of 8 patients had grades 3 or higher of Thrombocytopenia.

The most frequent non-haematologic serious adverse events were Abdominal pain (5% of patients), Pyrexia (5%), Lipase increased (3.3%), Myocardial infarction (3.3%) and Pneumonia (3.3%). In addition to this, 2 participants had a heamatologic serious adverse event, Hemoglobin decreased (grade 3) and Thrombocytopenia (grade 4).

There was only one reported death of a 76-year-old male Caucasian patient after 1 year after registration. This patient completed 9 cycles of the study drug. The cause of death was a pre-existing neurological condition.

Note that based on the data collected for this study, the analysis presented in this report supports the hypothesis that nilotinib has significant efficacy in newly diagnosed chronic phase CML patients (in terms of Cytogenetic responses) which is consistent with other preclinical studies. Moreover, the most frequently reported AEs (non-haematologic and haematologic) were also reported in previous studies (see Section 2.2.5.3 of the protocol). However, one should take into consideration that this is not a randomised trial, and in the absence of an active comparator, the observed effect cannot be attributed solely to the treatment, as this could be the work of observed or unobserved confounders.