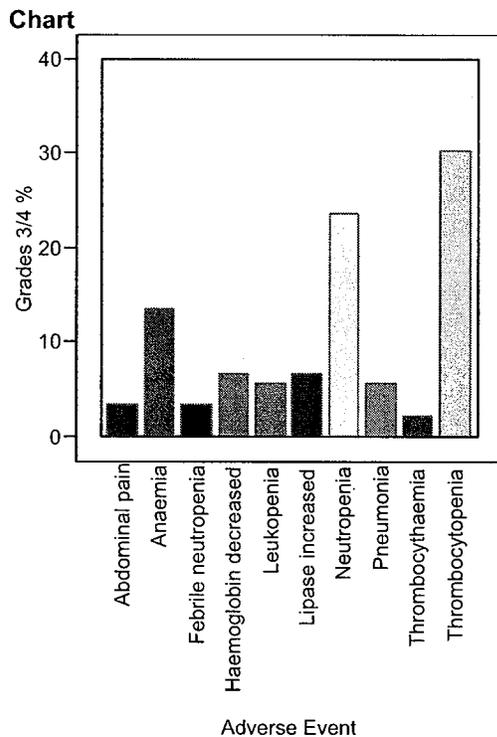


<b>Hepatobiliary disorders</b>						
Hyperbilirubinaemia	3	2.5	0	0.0	3	2.5
<b>Investigations</b>						
Lipase increased	8	6.7	3	2.5	11	9.2
Platelet count decreased	2	1.7	1	0.8	3	2.5
Blood amylase increased	3	2.5	0	0.0	3	2.5
Blood bilirubin increased	3	2.5	0	0.0	3	2.5
Neutrophil count decreased	1	0.8	2	1.7	3	2.5
<b>Musculoskeletal and connective tissue disorders</b>						
Pain in extremity	2	1.7	0	0.0	2	1.7
<b>Nervous system disorders</b>						
Headache	2	1.7	0	0.0	2	1.7
<b>Respiratory, thoracic and mediastinal disorders</b>						
Dyspnoea	3	2.5	0	0.0	3	2.5

Source: A\_AEV.xpt

Figure 6 Grade 3/4 Adverse Events CML-AP (Reviewer's Chart)



In the CML-AP patients, AEs leading to hospitalizations in at least two patients included pneumonia, neutropenia, thrombocytopenia, pyrexia, febrile neutropenia, myocardial infarction, abdominal pain, diarrhea, anorexia, bone pain, intracranial hemorrhage and respiratory failure.

**Table 43 Adverse Events leading to Hospitalizations in at least 2 Patients CML-AP N=89 (Reviewer's Table)**

<b>Adverse Event</b>	<b>All grades</b>	<b>All grades %</b>	<b>Grades 3/4</b>	<b>Grades 3/4 %</b>
Pneumonia	5	5.6	5	5.6
Neutropenia	4	4.5	4	4.5
Thrombocytopenia	4	4.5	3	3.4
Pyrexia	3	3.4	1	1.1
Febrile neutropenia	2	2.2	1	1.1
Myocardial infarction	2	2.2	1	1.1
Abdominal pain	2	2.2	2	2.2
Diarrhoea	2	2.2	1	1.1
Anorexia	2	2.2	0	0.0
Bone pain	2	2.2	1	1.1
Haemorrhage intracranial	2	2.2	2	2.2
Respiratory failure	2	2.2	2	2.2

Source: A\_AEV.xpt

**Serious Adverse Events: Compassionate Use Protocol**

The applicant provided the following serious AE table to describe the safety data in the 94 patients enrolled in the compassionate use protocol. The drug related serious AEs were death due to arrhythmia, acute pain syndrome, diarrhea, maculopapular rash, QTc prolongation and edema/rash/fatigue.

**Table 44 Serious Adverse Events Listing (Applicant's Table)**

**Appears This Way  
On Original**

Patient	Case Number	Suspected	Reason	Comments
	PHH02005US20164	Yes	Death - arrythmia	Type of arrhythmia (pulmonary or cardiac) could not be determined since no autopsy was performed
	PHH02006AU07518	No	Death- sepsis with multi-organ failure	Pancytopenia (suspected) led to sepsis which caused an ileus.
	PHH02006BR05934	No	Death- disease progression	
	PHH02006CH02217	No	Death- disease progression	
	PHH02006CH02236	No	Death- disease progression	
	PHH02006US02506	No	Death- disease progression	
	PHH02005US15104	Yes	SAE-Acute pain syndrome with elevated heart rate, blood pressure an myocardial strain to a normal heart	
	PHH02006AT05894	Yes	SAE-Diarrhea	
	PHH02006US03767	Yes	SAE-Scattered maculopapular rash on face, trunk and extremities	
	PHH02006US06167	No	SAE-fevers	D/C
	N/A	Yes	QTc > 500 ms after 1 week on drug	D/C due to AE
	N/A	Yes	Edema, rash and fatigue	D/C due to AE

Source: compassionate.pdf

*Reviewer's Comments:*

*There was a discrepancy in the incidence of serious AEs between the applicant's and the reviewer's. The applicant coded AEs as serious based on the investigator's assessment. The*

reviewer calculated the incidence of Grade 3 and 4 AEs. Grade 3 and 4 AEs provides a meaningful assessment of serious AEs in the cancer population.

In CML-CP patients, the body systems most affected by Grade 3 and 4 AEs were blood and lymphatic system disorders(52.2%), investigations(24.8%) and cardiac disorders(7.2%).

In the CML-AP patients, the body systems most affected by grade 3 and 4 AEs were blood and lymphatic system disorders(81.7), investigations(30.8%), infections and infestations (17.5%) and gastrointestinal disorders(10.8%).

### 7.1.3 Dropouts and Other Significant Adverse Events

#### 7.1.3.1 Overall profile of dropouts

##### CML-CP

In the CML-CP patients, the incidence of treatment discontinuation was 37.9% over the course of the trial. The most common reason for treatment discontinuation was due to an adverse event (19.7%), followed by disease progression (11.4%), withdrawn consent (3.8%), death (1.5%), protocol violation (0.8%) and lost to follow-up (0.8%).

**Table 45 Reasons for Treatment Discontinuation CML-CP (Reviewer's Table)**

<b>Discontinuation</b>	<b>N=132 (%)</b>
Discontinued treatment	50 (37.9)
Reasons for Treatment Discontinuation	
Adverse events	26 (19.7)
thrombocytopenia (5)	
thrombocytopenia & neutropenia (1)	
neutropenia (1)	
patient did not wish to continue due to AE (1)	
increased bilirubin/liver toxicity (2)	
skin rash (1)	
myocardial infarction hospitalization (1)	
Disease Progression	15 (11.4)
pancreatitis (1)	
neutropenia grade 4 (1)	
Withdrew consent	5 (3.8)
patient went to BMT (2)	
lack of response (1)	

patient will have treatment done locally (1)	
Death myocardial infarction (1) multi-organ failure (1)	2 (1.5)
Protocol violation Abnormal ECG at baseline (1)	1 (0.8)
Lost to follow-up	1 (0.8)

Source: A\_CMP.xpt

### CML-AP

In the CML-AP patients, the incidence of treatment discontinuation was 48.4% over the course of the trial. The most common reason for treatment discontinuation was due to disease progression (21.9%), followed by an adverse event (14.1%), withdrawn consent (6.3%), death (3.1%), lost to follow-up (1.6%) and administrative problems (1.6%).

**Table 46 Reasons for Treatment Discontinuation CML-AP (Reviewer's Table)**

<b>Discontinuation</b>	<b>N=64 (%)</b>
Discontinued treatment	31 (48.4)
Reasons for Treatment Discontinuation	
Disease Progression	14 (21.9)
Adverse events	9 (14.1)
ongoing drug intolerance (1)	
unable to discontinue his amiodarone (1)	
developed rash after taking 2 doses of drug (1)	
Pancreatitis (1)	
myocardial infarction and progressive disease (1)	
repeated grade 3 thrombocytopenia and neutropenia (1)	
abnormal laboratory values (1)	
Withdrew consent	4 (6.3)
Death	2 (3.1)
Intracerebral hemorrhage (1)	
Cardiac failure (1)	
Lost to follow-up	1 (1.6)
Administrative problems	1 (1.6)

Source: A\_CMP.xpt

#### 7.1.3.2 Adverse events associated with dropouts

### CML-CP

The most common AEs leading to study discontinuation in the CML-CP patients were neutropenia (2.8%) and thrombocytopenia (2.5%) and thrombocythemia (1.4%).

**Table 47 Adverse Events Leading to Discontinuation CML-CP (N=282) (Reviewer's Table)**

Adverse Event	All grades	All grades %	Grade 3/4	Grade 3/4 %
<b>Blood and lymphatic system disorders</b>				
Neutropenia	8	2.8	8	2.8
Thrombocytopenia	7	2.5	7	2.5
Thrombocythaemia	4	1.4	3	1.1
Leukopenia	1	0.4	1	0.4
<b>Cardiac disorders</b>				
Angina pectoris	1	0.4	1	0.4
Arteriosclerosis coronary artery	1	0.4	1	0.4
Myocardial infarction	1	0.4	1	0.4
<b>Gastrointestinal disorders</b>				
Pancreatitis	2	0.7	0	0.0
Abdominal pain	1	0.4	1	0.4
Diarrhoea	1	0.4	0	0.0
Gastrointestinal ulcer perforation	1	0.4	1	0.4
<b>General disorders and administration site conditions</b>				
Fatigue	1	0.4	0	0.0
Mucosal inflammation	1	0.4	0	0.0
<b>Hepatobiliary disorders</b>				
Hepatic failure	1	0.4	1	0.4
Hepatitis toxic	1	0.4	0	0.0
Hepatotoxicity	1	0.4	1	0.4
<b>Injury, poisoning and procedural complications</b>				
Subdural haemorrhage	1	0.4	1	0.4
<b>Investigations</b>				
Alanine aminotransferase increased	1	0.4	0	0.0
Aspartate aminotransferase increased	1	0.4	1	0.4
Blood bilirubin increased	1	0.4	0	0.0
Platelet count decreased	1	0.4	0	0.0
Platelet count increased	1	0.4	1	0.4
<b>Metabolism and nutrition disorders</b>				
Anorexia	1	0.4	0	0.0
<b>Musculoskeletal and connective tissue disorders</b>				

Myalgia	2	0.7	1	0.4
Arthralgia	1	0.4	1	0.4
<b>Nervous system disorders</b>				
Headache	1	0.4	1	0.4
<b>Renal and urinary disorders</b>				
Dysuria	1	0.4	0	0.0
Renal failure	1	0.4	1	0.4
<b>Skin and subcutaneous tissue disorders</b>				
Dermatitis allergic	1	0.4	1	0.4
Pruritus	1	0.4	0	0.0
Rash	1	0.4	0	0.0
Rash generalised	1	0.4	0	0.0
<b>Vascular disorders</b>				
Flushing	1	0.4	0	0.0

Source: A\_AEV.xpt

### CML-AP

The most common AEs leading to study discontinuation in the CML-AP patients was thrombocytopenia (3.4%) and rash (2.2%).

**Table 48 Adverse Events Leading to Discontinuation CML-AP N=89 (Reviewer's Table)**

Adverse Event	All grades	All grades %	Grade 3	Grade 3%	Grade 4	Grade 4%
<b>Blood and lymphatic system disorders</b>						
Thrombocytopenia	3	3.4	0	0.0	2	2.2
Thrombocythaemia	1	1.1	0	0.0	0	0.0
<b>Cardiac disorders</b>						
Atrial fibrillation	1	1.1	1	1.1	0	0.0
Myocardial infarction	1	1.1	0	0.0	1	1.1
<b>Congenital, familial and genetic disorders</b>						
Factor XIII deficiency	1	1.1	1	1.1	0	0.0
<b>Gastrointestinal disorders</b>						
Pancreatitis	1	1.1	0	0.0	0	0.0
Retroperitoneal haemorrhage	1	1.1	1	1.1	0	0.0
<b>General disorders and administration site conditions</b>						
General physical health deterioration	1	1.1	0	0.0	1	1.1
<b>Infections and infestations</b>						
Pneumonia	1	1.1	0	0.0	1	1.1

Sepsis	1	1.1	0	0.0	1	1.1
<b>Nervous system disorders</b>						
Brain oedema	1	1.1	1	1.1	0	0.0
Haemorrhage intracranial	1	1.1	1	1.1	0	0.0
<b>Skin and subcutaneous tissue disorders</b>						
Rash	2	2.2	0	0.0	0	0.0
Skin burning sensation	1	1.1	0	0.0	0	0.0
Urticaria	1	1.1	0	0.0	0	0.0

Source: A\_AEV.xpt

### CML-CP

The most common AEs leading to discontinuations suspected as treatment related in the CML-CP patients were neutropenia (2.8%) and thrombocytopenia/platelet count decreased (2.5%). Other AEs (<1%) included pancreatitis, myalgia, coronary arteriosclerosis, myocardial infarction, abdominal pain, diarrhea, fatigue, hepatitis, GI ulcer perforation, hemorrhage, increased AST/ALT, hyperbilirubinemia, anorexia, myalgia, arthralgia, headache, dysuria, renal failure, allergic dermatitis, pruritus, rash and flushing.

**Table 49 Adverse Events Leading to Discontinuations Suspected as Treatment-related CML-CP N=282 (Reviewer's Table)**

Adverse Event	All grades	All grades %	Grades 3/4	grades 3/4%
<b>Blood and lymphatic system disorders</b>				
Neutropenia	8	2.8	8	2.8
Thrombocytopenia	6	2.1	6	2.1
Leukopenia	1	0.4	1	0.4
<b>Cardiac disorders</b>				
Arteriosclerosis coronary artery	1	0.4	1	0.4
Myocardial infarction	1	0.4	1	0.4
<b>Gastrointestinal disorders</b>				
Pancreatitis	2	0.7	0	0.0
Abdominal pain	1	0.4	1	0.4
Diarrhoea	1	0.4	0	0.0
Gastrointestinal ulcer perforation	1	0.4	1	0.4
<b>General disorders and administration site conditions</b>				
Fatigue	1	0.4	0	0.0
Mucosal inflammation	1	0.4	0	0.0
<b>Hepatobiliary disorders</b>				
Hepatitis toxic	1	0.4	0	0.0
Hepatotoxicity	1	0.4	1	0.4

<b>Injury, poisoning and procedural complications</b>				
Subdural haemorrhage	1	0.4	1	0.4
<b>Investigations</b>				
Alanine aminotransferase increased	1	0.4	0	0.0
Aspartate aminotransferase increased	1	0.4	1	0.4
Blood bilirubin increased	1	0.4	0	0.0
Platelet count decreased	1	0.4	0	0.0
<b>Metabolism and nutrition disorders</b>				
Anorexia	1	0.4	0	0.0
<b>Musculoskeletal and connective tissue disorders</b>				
Myalgia	2	0.7	1	0.4
Arthralgia	1	0.4	1	0.4
<b>Nervous system disorders</b>				
Headache	1	0.4	1	0.4
<b>Renal and urinary disorders</b>				
Dysuria	1	0.4	0	0.0
Renal failure	1	0.4	1	0.4
<b>Skin and subcutaneous tissue disorders</b>				
Dermatitis allergic	1	0.4	1	0.4
Pruritus	1	0.4	0	0.0
Rash	1	0.4	0	0.0
Rash generalised	1	0.4	0	0.0
<b>Vascular disorders</b>				
Flushing	1	0.4	0	0.0

Source: A\_AEV.xpt

## CML-AP

The most common AEs leading to discontinuations suspected as treatment related in the CML-AP patients was thrombocytopenia (3.4%) and rash (2.2%). Other AEs (n=1) included myocardial infarction, pancreatitis, factor XIII deficiency, retro-peritoneal hemorrhage, brain edema, intracranial hemorrhage and urticaria.

**Table 50** Adverse Events Leading to Discontinuations Suspected as Treatment-related CML-AP (N=89)  
(Reviewer's Table)

Adverse Event	All grades	All grades %	Grades 3/4	Grades 3/4 %
<b>Blood and lymphatic system disorders</b>				
Thrombocytopenia	3	3.4	2	2.2
<b>Cardiac disorders</b>				
Myocardial infarction	1	1.1	1	1.1

<b>Congenital, familial and genetic disorders</b>				
Factor XIII deficiency	1	1.1	1	1.1
<b>Gastrointestinal disorders</b>				
Pancreatitis	1	1.1	0	0.0
Retroperitoneal haemorrhage	1	1.1	1	1.1
<b>General disorders and administration site conditions</b>				
General physical health deterioration	1	1.1	1	1.1
<b>Nervous system disorders</b>				
Brain oedema	1	1.1	1	1.1
Haemorrhage intracranial	1	1.1	1	1.1
<b>Skin and subcutaneous tissue disorders</b>				
Rash	2	2.2	0	0.0
Urticaria	1	1.1	0	0.0

Source: A\_AEV.xpt

### 7.1.3.3 Other significant adverse events

The reviewer analyzed adverse reactions leading to concomitant medication use.

### CML-CP

In the CML-CP population in this study, 49 (15.4%) patients were given red blood cells, 28 (8.8%) patients received platelets or human blood, and three (0.9%) patients received blood or related products (WBC).

In the CML-CP population, the common AEs leading to concomitant medication use were rash (11.3%), pruritus (10.6%), constipation (9.9%), nausea (9.2%), headache (9.2%), abdominal pain/upper (8.5%), arthralgia (7.8%), diarrhea (7.4%), nasopharyngitis (7.1%), myalgia (6.4%), pyrexia (6%), neutropenia (5.3%), anemia (5%) and vomiting (5%), extremity pain (4.6%), insomnia (4.6%), dyspepsia (4.3%), upper respiratory tract infection (4.3%), bone pain (3.9%), back Pain (3.2%), peripheral edema (3.5%), bronchitis (3.2%), erythema (3.2%), hypomagnesemia (3.2%), hypertension (3.2%), herpes simplex (2.5%), urinary tract infection (2.8%), muscle spasma (2.8%), thrombocytopenia (2.1%), hypocalcemia (2.1%), hypokalemia (2.1%), musculoskeletal pain (2.1%) and dyspnea (2.1%).

**Table 51 Adverse Events Leading to Concomitant Medications >2% CML-CP N=282 (Reviewer's Table)**

<b>Adverse Event</b>	<b>All grades</b>	<b>All grades %</b>	<b>Grades 3/4</b>	<b>Grades 3/4 %</b>
<b>Blood and lymphatic system disorders</b>				
Anaemia	14	5.0	3	1.1
Neutropenia	15	5.3	15	5.3

Thrombocytopenia	6	2.1	6	2.1
<b>Gastrointestinal disorders</b>				
Abdominal pain	10	3.5	2	0.7
Abdominal pain upper	14	5.0	1	0.4
Constipation	28	9.9	1	0.4
Diarrhoea	21	7.4	2	0.7
Dyspepsia	12	4.3	1	0.4
Nausea	26	9.2	0	0.0
Vomiting	14	5.0	1	0.4
<b>General disorders and administration site conditions</b>				
Oedema peripheral	10	3.5	0	0.0
Pyrexia	17	6.0	2	0.7
<b>Infections and infestations</b>				
Bronchitis	9	3.2	0	0.0
Herpes simplex	7	2.5	0	0.0
Nasopharyngitis	20	7.1	1	0.4
Upper respiratory tract infection	12	4.3	0	0.0
Urinary tract infection	8	2.8	0	0.0
<b>Injury, poisoning and procedural complications</b>				
Procedural pain	6	2.1	0	0.0
<b>Metabolism and nutrition disorders</b>				
Hypocalcaemia	6	2.1	0	0.0
Hypokalaemia	6	2.1	1	0.4
Hypomagnesaemia	9	3.2	0	0.0
<b>Musculoskeletal and connective tissue disorders</b>				
Arthralgia	22	7.8	6	2.1
Back pain	9	3.2	1	0.4
Bone pain	11	3.9	1	0.4
Muscle spasms	8	2.8	1	0.4
Musculoskeletal pain	6	2.1	1	0.4
Myalgia	18	6.4	4	1.4
Pain in extremity	13	4.6	1	0.4
<b>Nervous system disorders</b>				
Headache	26	9.2	3	1.1
Psychiatric disorders				
Insomnia	13	4.6	0	0.0
<b>Respiratory, thoracic and mediastinal disorders</b>				
Cough	20	7.1	2	0.7
Dyspnoea	6	2.1	0	0.0
<b>Skin and subcutaneous tissue disorders</b>				
Erythema	9	3.2	1	0.4
Pruritus	30	10.6	1	0.4

Rash	32	11.3	3	1.1
<b>Vascular disorders</b>				
Hypertension	9	3.2	3	1.1

Source: A\_AEV.xpt

### CML-AP

In the CML-AP population in this study, 55 (45.8%) patients were given red blood cells, 37 (30.8%) patients received platelets or human blood, and one (0.8%) patient received blood or related products (WBC).

In the CML-AP patients, AEs leading to concomitant medication use were neutropenia/febrile neutropenia/white blood count decreased (20.2%), pyrexia 916.9%), abdominal pain/upper (14.6%), anemia/decreased hemoglobin (13.4%), cough/productive cough (13.4%), rash/pruritic rash (11.2%), constipation (10.1%), muscle spasms (10.1%), arthralgia (9%), headache (7.9%), myalgia (7.9%), extremity pain (7.9%), pruritus (6.7%), nausea (6.7%), back pain (6.7%), bone pain (5.6%), diarrhea (5.6%), thrombocytopenia (4.5%), thrombocythemia (4.5%), nasopharyngitis (4.5%), pneumonia (4.5%), insomnia (4.5%), edema /peripheral (4.4%), leukocytosis (3.4%), hemorrhoids (3.4%), cellulitis (3.4%), influenza (3.4%), pharyngolaryngeal pain (3.4%), hypocalcemia (3.4%) and hypertension (3.4%). Other AEs (> 2%) included myocardial infarction, conjunctivitis, stomatitis, vomiting, chills, bacterial infection, sinusitis, tooth infection, upper respiratory tract infection, urinary tract infection, decreased creatinine, anorexia, gout, hyperkalemia, buttock pain, musculoskeletal pain, anxiety, depression, pleural effusion, erythema

**Table 52 Adverse events Leading to Concomitant medications >2% CML-AP N=89 (Reviewer's Table)**

Adverse Event	All grades	All grades %	Grades 3/4	Grades 3/4 %
<b>Blood and lymphatic system disorders</b>				
Anaemia	10	11.2	2	2.2
Febrile neutropenia	4	4.5	2	2.2
Leukocytosis	3	3.4	1	1.1
Neutropenia	12	13.5	11	12.4
Thrombocythemia	4	4.5	2	2.2
Thrombocytopenia	4	4.5	4	4.5
<b>Cardiac disorders</b>				
Myocardial infarction	2	2.2	1	1.1
<b>Eye disorders</b>				
Conjunctivitis	2	2.2	0	0.0
<b>Gastrointestinal disorders</b>				
Abdominal pain	8	9.0	2	2.2

Abdominal pain upper	5	5.6	1	1.1
Constipation	9	10.1	0	0.0
Diarrhoea	5	5.6	1	1.1
Haemorrhoids	3	3.4	0	0.0
Nausea	6	6.7	0	0.0
Stomatitis	2	2.2	1	1.1
Vomiting	2	2.2	0	0.0
<b>General disorders and administration site conditions</b>				
Chills	2	2.2	0	0.0
Oedema	2	2.2	0	0.0
Oedema peripheral	2	2.2	0	0.0
Pyrexia	15	16.9	1	1.1
<b>Infections and infestations</b>				
Bacterial infection	2	2.2	1	1.1
Cellulitis	3	3.4	2	2.2
Influenza	3	3.4	0	0.0
Nasopharyngitis	4	4.5	0	0.0
Pneumonia	4	4.5	4	4.5
Sinusitis	2	2.2	0	0.0
Tooth infection	2	2.2	0	0.0
Upper respiratory tract infection	2	2.2	0	0.0
Urinary tract infection	5	5.6	2	2.2
<b>Investigations</b>				
Blood creatinine increased	2	2.2	0	0.0
Haemoglobin decreased	2	2.2	0	0.0
White blood cell count increased	2	2.2	1	1.1
<b>Metabolism and nutrition disorders</b>				
Anorexia	2	2.2	0	0.0
Gout	2	2.2	0	0.0
Hyperkalaemia	2	2.2	2	2.2
Hypocalcaemia	3	3.4	1	1.1
Hypokalaemia	2	2.2	0	0.0
<b>Musculoskeletal and connective tissue disorders</b>				
Arthralgia	8	9.0	0	0.0
Back pain	6	6.7	1	1.1
Bone pain	5	5.6	0	0.0
Buttock pain	2	2.2	1	1.1
Muscle spasms	9	10.1	0	0.0
Musculoskeletal pain	2	2.2	0	0.0
Myalgia	7	7.9	0	0.0
Pain in extremity	7	7.9	0	0.0
<b>Nervous system disorders</b>				

Headache	7	7.9	0	0.0
<b>Psychiatric disorders</b>				
Anxiety	2	2.2	0	0.0
Depression	2	2.2	0	0.0
Insomnia	4	4.5	0	0.0
<b>Respiratory, thoracic and mediastinal disorders</b>				
Cough	10	11.2	0	0.0
Pharyngolaryngeal pain	3	3.4	0	0.0
Pleural effusion	2	2.2	0	0.0
Productive cough	2	2.2	0	0.0
<b>Skin and subcutaneous tissue disorders</b>				
Erythema	2	2.2	0	0.0
Pruritus	6	6.7	0	0.0
Rash	8	9.0	0	0.0
Rash pruritic	2	2.2	0	0.0
Urticaria	2	2.2	0	0.0
<b>Vascular disorders</b>				
Hypertension	3	3.4	0	0.0

Source: A\_AEV.xpt

#### 7.1.4 Other Search Strategies

##### Concerns with Pharmacologically Related Drugs

Nilotinib is pharmacologically related to imatinib mesylate (Gleevec®) and dasatinib (Sprycel®), both of which are inhibitors of Bcr-Abl tyrosine kinase. Resistance to imatinib develops over time.

Imatinib mesylate (Gleevec®) was approved on May 10, 2001 for the treatment of CML in three clinical settings: CML-BC, CML-AP and CML-CP. The most frequently reported drug related adverse events were edema, nausea and vomiting, muscle cramps, musculoskeletal pain, diarrhea and rash (cutaneous toxicity). A variety of adverse events represented local or general fluid retention including pleural effusion, ascites, pulmonary edema and rapid weight gain with or without superficial edema. Cytopenias included neutropenia and thrombocytopenia. Severe hepatotoxicity including elevations of transaminases or bilirubin lead to liver failure or death. Post marketing safety reports included cardiotoxicity including severe congestive heart failure in ten patients [2]; and hypophosphatemia, with associated changes in bone and mineral metabolism [3] [4].

Dasatinib was approved on June 28, 2006 for the treatment of adult patients with imatinib resistant/intolerant CML-CP, CML-AP and Ph + ALL. In this NDA submission, the most common severe toxicities associated with dasatinib were hematologic, including neutropenia

thrombocytopenia and anemia. Others included neutropenic fever, bleeding events, pyrexia, dyspnea, pleural effusion, and diarrhea. Other significant adverse events included cardiac failure, QTc prolongation and CNS hemorrhages, most of which were fatal.

The reviewer analyzed the AEs related to pharmacologically related drugs and those related to nilotinib in greater detail. These included myelosuppression; cardiac disorders including QT interval prolongation and left ventricular dysfunction; syncope, hepatobiliary events including hyperbilirubinemia, elevated hepatic transaminases, elevations in serum lipase and pancreatitis; bleeding events; skin and subcutaneous disorders; fluid retention; hyperglycemia; electrolyte abnormalities; infection and sepsis.

### **Myelosuppression**

Thrombocytopenia, neutropenia, and anemia were the most frequently reported grade 3 and 4 laboratory abnormalities in CML-CP and CML-AP patients without prior TKI treatment other than imatinib.

The incidences of treatment-emergent CTC grade 3-4 thrombocytopenia in CML-CP and CML-AP patients were 27% and 40%, respectively. The incidences of treatment-emergent CTC grade 3-4 neutropenia in CML-CP and CML-AP patients were 28% and 38%, respectively. The incidences of treatment-emergent CTC grade 3-4 anemia in CML-CP and CML-AP patients were 9% and 28% respectively.

Thrombocytopenia was seen in 173 (54.4%) and 78 (65%) patients with CML-CP and CML-AP, respectively. Neutropenia was seen in 156 (49%) and 67 (55.8%) patients with CML-CP and CML-AP respectively. Anemia was seen in 164 (51.6%) and 77 (64.2%) patients with CML-CP and CML-AP respectively.

Per the applicant:

“In CML-CP patients, the majority of first episodes of CTC grade 3 and 4 neutropenia and thrombocytopenia occurred within the first 2 months of therapy, with median times to first episode of 49.5 days and 39 days, respectively. In CML-AP patients, the majority of first episodes of CTC grade 3 and 4 neutropenia and thrombocytopenia occurred within the first 2 months of therapy, with median times to first episode of 19 days and 14 days, respectively. In CML-CP patients, the combined rates of dose adjustment and/or study drug interruption due to thrombocytopenia and neutropenia were 19.2% and 9.4%, respectively. In CML-AP patients, the combined rates of dose adjustment and/or study drug interruption due to thrombocytopenia and neutropenia were 20.8% and 15.0%, respectively. In CML-CP patients, nilotinib was discontinued in 2.5% and 2.8% of patients due to thrombocytopenia and neutropenia, respectively. In CML-AP patients, nilotinib was discontinued in 4.2% and 0% of patients due to thrombocytopenia and neutropenia, respectively”.

Febrile neutropenia occurred in 4 (1.3%) and 6 (5.0%) CML-CP and CML-AP patients, respectively.

Infections including the following MedDRA preferred terms: ‘multi-organ failure’, ‘sepsis’, ‘sepsis syndrome’, ‘bacteremia’, ‘lung infection’, ‘lung infiltration’, ‘herpes zoster’, ‘herpes zoster ophthalmic’, ‘herpes virus infection’ and ‘herpes ophthalmic’ occurred in 16 (5.0%) CML-CP and 5 (4.2%) CML-AP patients respectively.

The rates of CML-CP and CML-AP patients who received blood and related products in the course of the study were 19.2% and 51.7%, respectively.

Three patients (See Section 7.1) died of myelosuppression-related events; one of intracerebral bleeding which was preceded by thrombocytopenia.

*Reviewer’s Comments:*

*Myelosuppression was a common laboratory abnormality. Febrile neutropenia was less common. More patients with CML-AP received blood and related products than CML-CP.*

**Cardiac Disorders**

The common grade 3/4 cardiac disorders seen in both CML-CP and CML-AP patients were myocardial infarction, coronary artery disease, chest pain, atrial fibrillation, coronary artery stenosis and cardiac failure. Overall, arrhythmic events were more common than left ventricular dysfunction events. Four patients (See Section 7.1) had cardiac related deaths while on study drug. Other cardiac disorders are shown in the table below.

**Table 53 Cardiac Disorders (Reviewer’s Table)**

Adverse Event	CML-CP N=318				CML-AP N=120			
	All grades	All grades %	Grades 3/4	Grades 3/4 %	All grades	All grades %	Grades 3/4	Grade 3/4 %
Myocardial infarction	4	1.3	4	1.3	2	1.7	1	0.8
Coronary artery disease	3	0.9	3	0.9	0	0.0	0	0.0
Chest pain	7	2.2	1	0.3	2	1.7	0	0.0
Atrial fibrillation	5	1.6	1	0.3	3	2.5	1	0.8
Coronary artery stenosis	2	0.6	1	0.3	0	0.0	0	0.0
Tachyarrhythmia	1	0.3	1	0.3	0	0.0	0	0.0
Cardiac failure	0	0.0	0	0.0	1	0.8	1	0.8

Ventricular dysfunction	2	0.6	0	0.0	1	0.8	1	0.8
Atrial flutter	1	0.3	0	0.0	0	0.0	0	0.0
Cardiac failure congestive	1	0.3	0	0.0	0	0.0	0	0.0
Cardiac flutter	2	0.6	0	0.0	0	0.0	0	0.0
Extrasystoles	3	0.9	0	0.0	0	0.0	0	0.0
Myocardial ischaemia	1	0.3	0	0.0	0	0.0	0	0.0
Palpitations	8	2.5	0	0.0	5	4.2	0	0.0
Supraventricular tachycardia	0	0.0	0	0.0	1	0.8	0	0.0
Tachycardia	2	0.6	0	0.0	0	0.0	0	0.0
Ventricular extrasystoles	2	0.6	0	0.0	0	0.0	0	0.0
Heart rate irregular	1	0.3	0	0.0	0	0.0	0	0.0

Source: 120-day safety update, A\_AEV dataset

### Arrhythmias

AEs related to arrhythmias including any of the following MedDRA preferred terms: ‘atrial fibrillation’, ‘atrial flutter’, ‘tachyarrhythmia’, ‘supraventricular tachycardia’, ‘ventricular extrasystoles’, ‘heart rate irregular’, ‘palpitations’, occurred in 26 (6.0%) CML patients.

### Left Ventricular Function

AEs related to cardiac failure or dysfunction including any of the following MedDRA preferred terms: ‘ventricular dysfunction’, ‘cardiac failure’, ‘cardiac failure congestive’, ‘cardiomyopathy’, ‘congestive cardiomyopathy’, ‘ejection fraction decreased’ and ‘left ventricular failure’ occurred in 3 (1.0%) CML patients.

### QT prolongation

Nilotinib had an IC50 value of 0.13  $\mu$ M in the hERG channel assay indicating the potential for QT prolongation of nilotinib. Studies conducted in patients with hematologic malignancies and in healthy volunteers indicate that nilotinib has the potential to significantly prolong the QT interval at therapeutic concentrations.

Per the applicant:

“In CML-CP patients without prior TKI other than imatinib, 6 patients (1.9%) had a > 60 msec change from baseline in QTcF interval and 3 patients (0.9%) had a post-baseline QTcF interval >

500 msec. In CML-AP patients without prior TKI other than imatinib, 3 patients (2.5%) had > 60 msec change from baseline and no patient had a post-baseline QTcF interval > 500 msec. Over the entire phase 2 CML population in Study 2101 (n = 633) treated with 400 mg b.i.d. of nilotinib, 4 patients (0.6%) had a QTcF interval exceeding 500 msec”.

There were 55 patients in both CML-CP and CML-AP patients who had a corrected QT interval (Freiderich) > 450. The cardiac events in these patients are shown in the table below. Most of these events were seen in patients with CML-CP. Arrhythmias appeared to be common in these patients with a baseline corrected QTc interval of > 450.

**Table 54 Cardiac Events in Patients with QTc > 450**

<b>Adverse Event</b>	<b>CML-CP N=318</b>	<b>CML-AP N=120</b>
Angina pectoris	4 ( 9.76%)	0 ( 0.00%)
Myocardial infarction	2 ( 4.88%)	1 ( 7.14%)
Atrial fibrillation	2 ( 4.88%)	0 ( 0.00%)
Palpitations	2 ( 4.88%)	0 ( 0.00%)
Bradycardia	2 ( 4.88%)	0 ( 0.00%)
Dilatation atrial	1 ( 2.44%)	0 ( 0.00%)
Dilatation ventricular	1 ( 2.44%)	0 ( 0.00%)
Extrasystoles	1 ( 2.44%)	0 ( 0.00%)
Mitral valve incompetence	1 ( 2.44%)	0 ( 0.00%)
Cardiomegaly	1 ( 2.44%)	0 ( 0.00%)
Atrial flutter	1 ( 2.44%)	0 ( 0.00%)
Sinus bradycardia	1 ( 2.44%)	0 ( 0.00%)
Tachyarrhythmia	1 ( 2.44%)	0 ( 0.00%)
Tricuspid valve incompetence	1 ( 2.44%)	0 ( 0.00%)
Ventricular dysfunction	1 ( 2.44%)	0 ( 0.00%)
Ventricular extrasystoles	1 ( 2.44%)	0 ( 0.00%)

Source: 120-day safety update, A\_AEV dataset

Although no episode of torsades de pointe was noted in this study population, it is unknown whether torsade de pointe may have occurred. There were ten sudden deaths, most with uncertain causes.

The serum concentration of nilotinib is increased when it is taken with or immediately after food, and particularly when it is taken with or after a high fat meal. Concomitant administration of strong CYP3A4 inhibitors significantly increases the serum concentration as well.

*Reviewer’s Comments:*

1. Patients who presented with cardiac events within 12 months prior to nilotinib administration, such as myocardial infarction, unstable angina, clinically significant atrial and ventricular arrhythmia, congestive heart failure and QT interval of > 450 were excluded from nilotinib trials. It is therefore unknown whether patients with these concomitant conditions may be safely treated with nilotinib.
2. Use of concomitant medications and the timing of administration relative to food are important to reduce the potential for QT interval prolongation. The Agency has requested a Medication Guide incorporating these measures along with the potential to significantly prolong QT interval.
3. Arrhythmia events were more common than left ventricular dysfunction events.
4. Kerkela et al suggests a possible link between pharmacologic inhibition of BCR-ABL and effects on left ventricular function.

### Syncope

Syncopal episodes occurred in both CML-CP and CML-AP patients and included the terms syncope, syncope vasovagal and dizziness. Other syncopal-related terms are shown in the table below.

AEs including the MedDRA terms ‘syncope’, ‘syncope vasovagal’ and ‘loss of consciousness’ occurred in 9 (2.0%) CML patients, 6 (1.9%) CML-CP and 3 (2.5%) CML-AP patients respectively.

**Table 55 Syncope (Reviewer’s Table)**

Adverse Event	CML-CP N=318				CML-AP N=120			
	All grades	All grades %	Grade 3/4	Grade 3/4 %	All grades	All grades %	Grade 3/4	Grade 3/4%
Syncope	2	0.6	2	0.6	3	2.5	1	0.8
Syncope vasovagal	3	0.9	2	0.6	0	0.0	0	0.0
Loss of consciousness	1	0.3	0	0.0	0	0.0	0	0.0

Source: 120-day safety update, A\_AEV dataset

### Hepatobiliary Events including Hyperbilirubinemia, Elevated Hepatic Transaminases, Elevations in Serum Lipase and Pancreatitis

Hepatobiliary events occurred in both CML-CP and CML-AP patients and included cytolytic hepatitis, hepatic failure, hepatotoxicity, elevations in bilirubin, transaminases, serum lipase and pancreatitis. Other hepatic events are shown in the table below.

**Table 56 Hepatic Events (Reviewer’s Table)**

Adverse Event	CML-CP N=318				CML-AP N=120			
	All grades	All grades %	Grade 3/4	Grade 3/4 %	All grades	All grades %	Grade 3/4	Grade 3/4 %
Cytolytic hepatitis	2	0.6	1	0.3	0	0.0	0	0.0
Hepatic failure	1	0.3	1	0.3	0	0.0	0	0.0
Hepatotoxicity	2	0.6	1	0.3	1	0.8	1	0.8
Hepatitis toxic	1	0.3	0	0.0	0	0.0	0	0.0
Liver disorder	1	0.3	0	0.0	0	0.0	0	0.0
Pancreatitis	4	1.3	0	0.0	1	0.8	0	0.0

Source: 120-day safety update, A\_AEV dataset

AEs including the MedDRA terms ‘hepatic failure’, ‘cytolytic hepatitis’, ‘hepatotoxicity’ and ‘hepatic pain’ occurred in 13 (4.1%) CML-CP and 2 (1.7%) CML-AP patients respectively.

In CML-CP patients, all grades and grade 3-4 treatment-emergent total serum bilirubin elevations occurred in 69.8% and 8.8% of patients, respectively. In CML-AP patients, all grades and grade 3-4 treatment-emergent total serum bilirubin elevations occurred in 65.8% and 10% of patients, respectively.

Per the applicant:

“The worst post-baseline total serum bilirubin elevations from baseline by grade in CML-CP patients were as follows: 102 patients (33.9%) worsened to grade 1, 88 (28.7%) to grade 2, 25 (8.0%) to grade 3, and 2 (0.6%) to grade 4. The worst post-baseline total serum bilirubin elevations from baseline by grade in CML-AP patients were as follows: 35 patients (31.8%) worsened to grade 1, 30 (26.5%) to grade 2, 11 (9.5%) to grade 3, and 1 (0.9%) to grade 4”.

All grades and grade 3-4 treatment-emergent serum ALT elevations occurred in 61.9/3.8 % of CML-CP patients, respectively. All grades and grade 3-4 treatment-emergent serum AST elevations occurred in 46.2/1.3% of CML-CP patients, respectively. All grades and grade 3-4 treatment-emergent serum ALT elevations occurred in 51.7/2.5% of CML-AP patients, respectively. All grades and grade 3-4 treatment-emergent serum AST elevations occurred in 35.8/0.8% of CML-AP patients, respectively. One patient (patient 0305\_04006) was a 62 year old male who on day 28 was diagnosed with Grade 4 renal failure and sepsis. The patient further deteriorated, developing Grade 4 hepatic failure and died on study day 30.

Per the applicant:

“The worst post-baseline serum AST elevations by grade in CML-CP patients were as follows: 125 patients (45.8%) worsened to grade 1, 16 (5.1%) to grade 2, 3 (1.3%) to grade 3, and 0 to grade 4. The worst post-baseline serum AST elevations by grade in CML-AP patients were as follows: 29 patients (31.2%) worsened to grade 1, 3 (2.6%) to grade 2, 1 (0.9%) to grade 3, and 0 to grade 4. In CML-CP patients, serum bilirubin elevation led to discontinuation in only 1 (0.3%) patient. Elevated serum AST or ALT led to treatment discontinuation in 2 patients each (0.6%). In CML-AP patients, serum bilirubin, AST or ALT elevations did not lead to discontinuation in any patient.

In CML-CP patients, the majority of first episodes of CTC grade 3 and 4 hyperbilirubinemia occurred within the first 2 months of therapy with a median time to first episode of 29 days. In CML-AP patients, the majority of first episodes of CTC grade 3 and 4 hyperbilirubinemia occurred within the first 3 months of therapy with a median time to first episode of 40.5 days”.

Elevations in serum lipase, not observed in preclinical toxicology studies, were an unexpected finding in this patient population. The incidence of asymptomatic serum lipase laboratory abnormalities far exceeds the incidence of these abnormalities seen in the presence of clinical symptoms such as abdominal pain or a diagnosis of pancreatitis. Overall, this finding was clinically manageable and reversible with continued therapy in the majority of CML-CP and CML-AP patients.

In CML-CP patients, all grades and grade 3-4 treatment-emergent serum lipase elevations occurred in 40.3% and 14.5% of patients, respectively. In CML-AP patients, all grades and grade 3-4 treatment-emergent serum lipase elevations occurred in 35.8% and 15.8% of patients, respectively. Pancreatitis occurred in 3 (0.9%) and 1 (0.8%) of CML-CP and CML-AP patients without prior TKI treatment other than imatinib, respectively. One patient (patient 0504\_03006) discontinued study drug on day 128 due to pancreatitis which was suspected related to study drug. Patient died on day 316.

Per the applicant:

“ Pancreatitis resulted in treatment discontinuation in the 2 cases in the CML-CP patients and in the one case in CML-AP patients. Elevations in serum lipase lead to treatment discontinuation in one CML-AP patient. In CML-CP patients, the majority of first episodes of CTC grade 3 and 4 lipase elevations occurred within the first 2 months of therapy with a median time to first episode of 7 days. In CML-AP patients, the majority of first episodes of CTC grade 3 and 4 lipase elevations occurred within the first 2 months of therapy with a median time to first episode of 7 days”.

### **Bleeding Events**

Gastrointestinal, CNS and ophthalmic bleeding events occurred in both CML-CP and CML-AP patients. The common grade 3/4 gastrointestinal bleeding events in both the CML-CP and CML-AP patients were gastrointestinal hemorrhage, gastric ulcer and duodenal ulcer hemorrhage and

melena. The common grade 3/4 CNS bleeding events in both CML-CP and CML-AP patients were intracranial hemorrhage and subdural hemorrhage. Other grade 3/4 hemorrhage events were retroperitoneal hemorrhage, hemorrhagic shock and hematoma. Although low grade, ophthalmic bleeding events occurred in both patient populations. These included conjunctival hemorrhage, eye hemorrhage, retinal hemorrhage and scleral hemorrhage. One patient (See Section 7.1) died of intracerebral bleeding related to thrombocytopenia. Other bleeding events are shown in the table below.

Bleeding-related events are not uncommon in a CML patients with compromised marrow function at baseline. Gastrointestinal tract and CNS bleeding are well recognized comorbid conditions in an acutely ill population of leukemic patients, typically resulting from platelet dysfunction or thrombocytopenia.

CML-CP patients reported 5 (1.5%) grade 3/4 gastrointestinal hemorrhage cases (MedDRA preferred terms: 'gastrointestinal hæmorrhage', 'retroperitoneal hæmorrhage', 'hæmorrhoidal hæmorrhage', 'rectal hæmorrhage', 'duodenal ulcer hæmorrhage', 'gastric ulcer hæmorrhage', 'melæna').

CML-AP patients reported 3 (2.4%) grade 3/4 gastrointestinal hemorrhages (MedDRA preferred terms: 'gastrointestinal hæmorrhage', 'retroperitoneal hæmorrhage', 'hæmorrhoidal hæmorrhage', 'rectal hæmorrhage', 'duodenal ulcer hæmorrhage', 'gastric ulcer hæmorrhage', 'melæna').

Intracranial bleeding (MedDRA preferred terms: 'subdural hæmorrhage', 'hæmorrhage intracranial') occurred in a 1 (0.3%) and 3 (2.3%) CML-CP and CML-AP patients, respectively.

One patient (patient 0302\_03002) was a 60 year old Caucasian male with imatinib resistant CML. At baseline this patient had Grade 4 thrombocytopenia. On Day 4 the patient was hospitalized for Grade 3 aphasia, Grade 3 disorientation and Grade 3 disturbance in attention. The patient died on Day 6 and death was preceded by an adverse event of intracerebral bleeding.

**Table 57 Bleeding Events (Reviewer's Table)**

Adverse Event	CML-CP N=318				CML-AP N=120			
	All grades	All grades %	Grade 3/4	Grade 3/4 %	All grades	All grades %	Grade 3/4	Grade 3/4 %
Conjunctival hæmorrhage	2	0.6	0	0.0	0	0.0	0	0.0
Eye hæmorrhage	4	1.3	0	0.0	1	0.8	0	0.0
Papilloedema	1	0.3	0	0.0	0	0.0	0	0.0

Photophobia	4	1.3	0	0.0	1	0.8	0	0.0
Retinal haemorrhage	1	0.3	0	0.0	0	0.0	0	0.0
Scleral haemorrhage	1	0.3	0	0.0	0	0.0	0	0.0
Duodenal ulcer haemorrhage	1	0.3	1	0.3	0	0.0	0	0.0
Gastric ulcer haemorrhage	1	0.3	1	0.3	0	0.0	0	0.0
Gastrointestinal haemorrhage	2	0.6	1	0.3	0	0.0	0	0.0
Diarrhoea haemorrhagic	1	0.3	0	0.0	0	0.0	0	0.0
Gingival bleeding	3	0.9	0	0.0	1	0.8	0	0.0
Haematemesis	1	0.3	0	0.0	0	0.0	0	0.0
Haematochezia	1	0.3	0	0.0	1	0.8	0	0.0
Haemorrhoidal haemorrhage	2	0.6	0	0.0	2	1.7	0	0.0
Melaena	1	0.3	0	0.0	1	0.8	1	0.8
Pancreatitis	3	0.9	0	0.0	1	0.8	0	0.0
Pancreatitis chronic	1	0.3	0	0.0	0	0.0	0	0.0
Rectal haemorrhage	0	0.0	0	0.0	1	0.8	0	0.0
Retroperitoneal haemorrhage	0	0.0	0	0.0	1	0.8	1	0.8
Subdural haemorrhage	1	0.3	1	0.3	0	0.0	0	0.0
Haemorrhage intracranial	0	0.0	0	0.0	2	1.7	2	1.7
Haematuria	1	0.3	0	0.0	2	1.7	0	0.0
Menorrhagia	1	0.3	0	0.0	1	0.8	1	0.8
Metrorrhagia	4	1.3	0	0.0	1	0.8	0	0.0
Haematoma	7	2.2	1	0.3	3	2.5	0	0.0
Shock haemorrhagic	1	0.3	1	0.3	0	0.0	0	0.0

Source: 120-day safety update, A\_AEV dataset

### Skin and Subcutaneous Disorders

While rash and pruritus were common AEs, grade 3/4 events were less common. The common grade 3/4 AEs in both CML-CP and CML-AP patients were rash, pruritus, generalized rash, pruritic rash, exfoliative rash, allergic dermatitis and erythema. Other skin and subcutaneous disorders are shown in the table below.

Skin and subcutaneous tissue disorders frequently reported included rash (CML-CP: 33.3%, CML-AP: 28.3%), pruritus (CML-CP: 28.6%, CML-AP: 20.0%), erythema (CML-CP: 7.9%, CML-AP: 3.3%), night sweats (CML-CP: 8.5%, CML-AP: 6.7%), alopecia (CML-CP: 8.8%, CML-AP: 9.2%), dry skin (CML-CP: 8.2%, CML-AP: 2.5%). Seventeen and 0 CML-CP and CML-AP patients, respectively, reported CTC grade 3 or 4 AEs related to skin and subcutaneous disorders.

Per the applicant:

“In CML-CP patients without prior TKI treatment other than imatinib, skin and subcutaneous tissue disorders were the most frequently reported AEs (54.1%) determined by the investigator to be study drug-related, in particular rash, pruritus, alopecia, erythema, dry skin, night sweats and hyperhidrosis occurring in 28.3%, 23.6%, 7.2%, 6.3%, 5.7%, 2.8% and 2.5% of patients, respectively, with most classified as CTC grade 1 (28.9%) or CTC grade 2 (20.4%). Four CML-CP patients (1.3%) discontinued due AEs related to skin and skin and subcutaneous tissue disorders: 2 cases of rash or rash generalized, 1 case of dermatitis allergic, 1 case of pruritus, all suspected of study drug relationship.

In CML-AP patients without prior TKI treatment other than imatinib, skin and subcutaneous tissue disorders were the second most frequently reported AEs (40.0%) determined by the investigator to be study drug-related (the first being drug related blood and lymphatic system disorders, reported by 43.3% of CML-AP patients), in particular rash, pruritus, alopecia, night sweats, dry skin, rash papular, urticaria, erythema, rash pruritic and skin odor abnormal occurred in 20.8%, 17.5%, 5.8%, 3.3%, 2.5%, 2.5%, 2.5%, 1.7%, 1.7%, and 1.7% of patients, respectively, all classified as CTC grade 1 (25.0%) or CTC grade 2 (15.0%). Two CML-AP patients (1.7%) discontinued due to 4 AEs related to skin and skin and subcutaneous tissue disorders: 2 cases of rash, 1 case of urticaria and 1 case of skin burning sensation, all but the latter suspected of study drug relationship”.

**Table 58 Skin and Subcutaneous Disorders (Reviewer’s Table)**

Adverse Event	CML-CP N=318				CML-AP N=120			
	All grades	All grades %	Grade 3/4	Grade 3/4 %	All grades	All grades %	Grade 3/4	Grade 3/4 %
Excoriation	1	0.3	0	0.0	1	0.8	0	0.0
Rash	107	33.6	5	1.6	34	28.3	0	0.0
Pruritus	91	28.6	3	0.9	24	20.0	0	0.0

Rash generalised	6	1.9	2	0.6	1	0.8	0	0.0
Dermatitis allergic	1	0.3	1	0.3	0	0.0	0	0.0
Erythema	25	7.9	1	0.3	4	3.3	0	0.0
Exfoliative rash	2	0.6	1	0.3	1	0.8	0	0.0
Rash pruritic	7	2.2	1	0.3	2	1.7	0	0.0
Rash pustular	3	0.9	0	0.0	2	1.7	0	0.0
Dermatitis	1	0.3	0	0.0	1	0.8	0	0.0
Dermatitis acneiform	1	0.3	0	0.0	0	0.0	0	0.0
Dermatitis atopic	1	0.3	0	0.0	0	0.0	0	0.0
Drug eruption	0	0.0	0	0.0	1	0.8	0	0.0
Ecchymosis	3	0.9	0	0.0	1	0.8	0	0.0
Eczema	8	2.5	0	0.0	0	0.0	0	0.0
Erythema nodosum	1	0.3	0	0.0	0	0.0	0	0.0
Generalised erythema	2	0.6	0	0.0	0	0.0	0	0.0
Heat rash	2	0.6	0	0.0	1	0.8	0	0.0
Hyperkeratosis	1	0.3	0	0.0	0	0.0	0	0.0
Photosensitivity reaction	2	0.6	0	0.0	0	0.0	0	0.0
Pruritus generalised	1	0.3	0	0.0	1	0.8	0	0.0
Rash erythematous	4	1.3	0	0.0	1	0.8	0	0.0
Rash follicular	1	0.3	0	0.0	0	0.0	0	0.0
Rash macular	3	0.9	0	0.0	1	0.8	0	0.0
Rash maculo-papular	3	0.9	0	0.0	0	0.0	0	0.0
Rash papular	7	2.2	0	0.0	3	2.5	0	0.0
Skin exfoliation	5	1.6	0	0.0	1	0.8	0	0.0
Skin toxicity	0	0.0	0	0.0	1	0.8	0	0.0
Toxic skin eruption	1	0.3	0	0.0	0	0.0	0	0.0
Urticaria	5	1.6	0	0.0	3	2.5	0	0.0

Source: 120-day safety update, A\_AEV dataset

### Fluid retention

The common grade 3/4 AEs in both CML-CP and CML-AP patients were pulmonary edema, fluid retention, pleural effusion and pericardial effusion. Other fluid retention terms are shown in the table below.

Per the applicant, no Phase 2 patient discontinued study-drug treatment due to an AE related to fluid retention.

**Table 59 Fluid Retention Events (Reviewer's Table)**

Adverse Events	CML-CP N=318				CML-AP N=120			
	All grades	All grades %	Grade 3/4	Grade 3/4 %	All grades	All grades %	Grade 3/4 %	Grade 3/4 %
Oedema peripheral	34	10.7	0	0.0	13	10.8	0	0.0
Periorbital oedema	6	1.9	0	0.0	1	0.8	0	0.0
Oedema	3	0.9	0	0.0	0	0.0	0	0.0
Pleural effusion	3	0.9	1	0.3	2	1.7	0	0.0
Fluid retention	2	0.6	1	0.3	1	0.8	0	0.0
Pericardial effusion	2	0.6	1	0.3	0	0.0	0	0.0
Pulmonary oedema	2	0.6	2	0.6	1	0.8	1	0.8
Cardiac failure congestive	1	0.3	0	0.0	0	0.0	0	0.0
Pitting oedema	1	0.3	0	0.0	0	0.0	0	0.0
Gravitational oedema	1	0.3	0	0.0	1	0.8	0	0.0
Ascites	0	0.0	0	0.0	1	0.8	0	0.0
Cardiac failure	0	0.0	0	0.0	1	0.8	1	0.8

Source: 120-day safety update, A\_AEV dataset

### Hyperglycemia

The overall incidence of all grades of hyperglycemia was 66.7% in CML-CP patients and 54.2% in CML-AP patients. The incidence of grade 3 or 4 hyperglycemia was 11% and 5% in CML-CP and CML-AP patients respectively.

Per the applicant:

“No CML-CP or CML-AP patients required dose adjustment and/or study drug interruption due to hyperglycemia. No CML-CP or CML-AP patients discontinued nilotinib due to hyperglycemia. There were no reports of diabetic ketoacidosis or hyperosmolar non-ketotic acidosis (MedDRA preferred terms: ‘ketoacidosis’, ‘diabetic ketoacidosis’, ‘hyperosmolar non-ketotic acidosis’). Furthermore, no clear signal was observed in healthy volunteers who received single and multiple doses of nilotinib”.

### **Electrolyte Abnormalities**

Electrolyte abnormalities occurred in both CML-CP and CML-AP patients.

All grades and grade 3/4 hypophosphatemia occurred in 42.8%/10.1% CML-CP patients and in 40%/12.5% CML-AP patients.

All grades and grade 3/4 hypocalcemia occurred in 40.9%/0.6% CML-CP patients and in 52.5%/4.2% CML-AP patients. All grades and grade 3/4 hyponatremia occurred in 22%/3.1% CML-CP patients and in 25.8%/2.5% CML-AP patients. All grades and grade 3/4 hypokalemia occurred in 18.6%/1.3% CML-CP patients and in 22.5%/5% CML-AP patients. All grades and grade 3/4 hypomagnesemia occurred in 12.9%/0% CML-CP patients and in 14.2%/0% CML-AP patients. Hyperkalemia, hypernatremia, hypermagnesemia and hypercalcemia were also seen in both patient populations.

### **Infection /Sepsis**

Infections, sepsis and multi-organ failure occurred in both CML-CP and CML-AP patients. Infections were bacterial, fungal or viral. Other infections are shown in the table below.

Infections including the following MedDRA preferred terms: ‘multi-organ failure’, ‘sepsis’, ‘sepsis syndrome’, ‘bacteremia’, ‘lung infection’, ‘lung infiltration’, ‘herpes zoster’, ‘herpes zoster ophthalmic’, ‘herpes virus infection’ and ‘herpes ophthalmic’ occurred in 16 (5.0%) CML-CP and 5 (4.2%) CML-AP patients respectively.

The most commonly involved organ system was respiratory.

One patient (patient 0501-03008) died on day 98 preceded by the AE sepsis. Another patient (Patient 0305\_04006) was a 62 year old male who on day 28 was diagnosed with Grade 4 renal failure and sepsis. The patient further deteriorated, developing Grade 4 hepatic failure and died on study day 30. A third patient (patient 0501\_3008) was a 76 year old Caucasian female who died on study day 98 and death was preceded by an adverse event of sepsis. On study day 78, Grade 4 sepsis and Grade 3 nocardia infection was diagnosed. Nilotinib was discontinued on day 79, 20 days prior to death.

**Table 60 Infection /Sepsis Events (Reviewer's Table)**

Adverse Event	CML-CP N=318				CML-AP N=120			
	All grades	All grades %	Grade 3/4	Grade 3/4 %	All grades	All grades %	Grade 3/4 %	Grade 3/4 %
Multi-organ failure	1	0.3	1	0.3	1	0.8	1	0.8
Chest discomfort	6	1.9	0	0.0	1	0.8	0	0.0
Chills	10	3.1	0	0.0	6	5.0	0	0.0
Inflammation	0	0.0	0	0.0	2	1.7	0	0.0
Influenza like illness	6	1.9	0	0.0	1	0.8	0	0.0
No adverse effect	0	0.0	0	0.0	0	0.0	0	0.0
Lower respiratory tract infection	6	1.9	2	0.6	3	2.5	1	0.8
Sepsis	2	0.6	2	0.6	1	0.8	1	0.8
Sepsis syndrome	1	0.3	1	0.3	0	0.0	0	0.0
Bacterial infection	1	0.3	1	0.3	2	1.7	1	0.8
Bronchitis	16	5.0	1	0.3	2	1.7	0	0.0
Bronchopulmonary aspergillosis	1	0.3	1	0.3	0	0.0	0	0.0
Escherichia urinary tract infection	1	0.3	1	0.3	0	0.0	0	0.0
Infection	1	0.3	1	0.3	0	0.0	0	0.0
Staphylococcal infection	2	0.6	1	0.3	0	0.0	0	0.0
Viral infection	4	1.3	1	0.3	0	0.0	0	0.0
Bacteraemia	0	0.0	0	0.0	1	0.8	1	0.8
Bronchitis acute	1	0.3	0	0.0	0	0.0	0	0.0
Enterococcal infection	0	0.0	0	0.0	1	0.8	1	0.8
Fungal infection	2	0.6	0	0.0	1	0.8	0	0.0
Fungal rash	1	0.3	0	0.0	0	0.0	0	0.0
Fungal skin infection	4	1.3	0	0.0	1	0.8	0	0.0
Furuncle	2	0.6	0	0.0	3	2.5	0	0.0
Gastroenteritis	4	1.3	0	0.0	0	0.0	0	0.0
Gastroenteritis viral	3	0.9	0	0.0	1	0.8	0	0.0
Gastrointestinal infection	1	0.3	0	0.0	0	0.0	0	0.0

Herpes ophthalmic	1	0.3	0	0.0	0	0.0	0	0.0
Herpes simplex	9	2.8	0	0.0	4	3.3	0	0.0
Herpes virus infection	4	1.3	0	0.0	0	0.0	0	0.0
Herpes zoster	4	1.3	0	0.0	1	0.8	0	0.0
Herpes zoster ophthalmic	1	0.3	0	0.0	0	0.0	0	0.0
Influenza	5	1.6	0	0.0	7	5.8	0	0.0
Lung infection	1	0.3	0	0.0	1	0.8	1	0.8
Mucocutaneous candidiasis	0	0.0	0	0.0	1	0.8	0	0.0
Subcutaneous abscess	1	0.3	0	0.0	0	0.0	0	0.0
Tinea infection	1	0.3	0	0.0	0	0.0	0	0.0
Tinea pedis	2	0.6	0	0.0	1	0.8	0	0.0
Tooth abscess	3	0.9	0	0.0	2	1.7	0	0.0
Tooth infection	2	0.6	0	0.0	2	1.7	0	0.0
Upper respiratory tract infection	27	8.5	0	0.0	7	5.8	0	0.0
Urinary tract infection	11	3.5	0	0.0	6	5.0	2	1.7
Vaginitis bacterial	1	0.3	0	0.0	0	0.0	0	0.0
Vulvovaginal mycotic infection	2	0.6	0	0.0	0	0.0	0	0.0
Wound infection	0	0.0	0	0.0	1	0.8	0	0.0
Lung infiltration	2	0.6	1	0.3	0	0.0	0	0.0

Source: 120-day safety update, A\_AEV dataset

## 7.1.5 Common Adverse Events

### 7.1.5.1 Eliciting adverse events data in the development program

There were 5,076 AEs reported in 317 CML-CP patients and 1798 AEs were reported in 118 CML-AP patients.

### 7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Verbatim terms for AEs were not included in the datasets. A random audit revealed that lower level terms appear to have been appropriately converted by the applicant into preferred terms using MedDRA.

Four patients were not assigned a preferred term by the applicant in the clinical databases.

The applicant was queried regarding patient #0202\_04002 from the 280 patient dataset. There was a grade 2 adverse event (AE) noted without the SOC term and PT term description. The AE name was "prolonged QTC". It was not clear why this AE was not coded and therefore not included in the AE dataset. The applicant responded with the following explanation:

"Following previous FDA discussions, it was agreed that patient narratives would be provided for specific criteria, including for all cases where a QTcF prolongation > 60 ms compared with baseline was identified. The determination for such a prolongation was made on the ECG data available for each case.

Patient #202-4002 had a QTcF >60 ms over baseline on two occasions (with the baseline calculated as the average of the Day 1 pre-dose intervals), and a narrative was provided for this case. There were no corresponding adverse events noted by the investigator for QT prolongation, however, the determination of the presence of QTcF prolongation was based on the actual ECG data, as stated above, not on the reported AE terms. Using the actual ECG data is considered to be more appropriate than using the AE dataset for this type of ECG findings".

#### 7.1.5.3 Incidence of common adverse events

There were 5,076 treatment emergent AEs reported in 317 CML-CP patients and 1798 treatment emergent AEs reported in 118 CML-AP patients. In the CML-CP patients, 317/318 patients experienced toxicities in the study, and most experienced multiple toxicities. In the CML-AP patients, 118/120 patients experienced toxicities in the study, and most experienced multiple toxicities.

Please see Section 7.1.5.4 for common adverse event tables.

#### *Reviewer Comment:*

*Due to variable reporting by investigators of laboratory abnormalities as adverse events, the incidence of laboratory-related AEs under-represents the true incidence of these toxicities. Use of the incidence of abnormal laboratory parameters provides a more accurate and objective picture of the laboratory toxicity profile which is reviewed in Section 7.*

#### 7.1.5.4 Common adverse event tables

### **120-Day Safety Update**

#### **CML-CP**

The common all grade AEs in the CML-CP patients were rash (33.6%), nausea (31.1%), headache (30.8%), thrombocytopenia (29.6%), pruritus (28.6%), fatigue (28.3%), diarrhea (22.6%), abdominal pain/upper (21.4%), vomiting (21.1%), hyperbilirubinemia/blood bilirubin increased (20.6%) constipation (20.8%) anemia/decreased hemoglobin (19.8%), arthralgia (18.1%), cough (17%), neutropenia (16.7%), nasopharyngitis (15.4%), myalgia (14.5%), pyrexia (14.2%), asthenia (13.8%), extremity pain (13.2%), elevated lipase (13.2%), bone pain (11.3%), peripheral edema (10.7%), muscle spasms (10.7%) and back pain (10.4%). Others common AEs (>5- 10%) included leukopenia, thrombocytopenia, leukocytosis, febrile neutropenia, dyspepsia, pain, chills, , upper respiratory tract infection, bronchitis, urinary tract infection, influenza, pneumonia, increased ALT/AST, decreased weight, anorexia, hypokalemia, dizziness, insomnia, anxiety, musculoskeletal pain, dyspnea, exertional dyspnea, pharyngolaryngeal pain, hyperhidrosis, erythema, dry skin, night sweats and alopecia. These are shown in the table below.

#### CML-AP

The common all grade AEs in the CML-AP patients were thrombocytopenia (39.2%), anemia/decreased hemoglobin (36.7%), rash (28.3%), pyrexia (24.2%), neutropenia (22.5%), abdominal pain/ upper (22.5%), headache (21.7%), pruritus (20%), diarrhea (19.2%), constipation (18.3%), nausea (18.3%), arthralgia (15.8%), extremity pain (15.8%), fatigue (15.8%), myalgia (15%), muscle spasms (14.2%), bone pain (13.3%), hyperbilirubinemia/blood bilirubin increased (13%), elevated lipase (12.5%), cough (12.5%), back pain (11.7%), asthenia (10.7%), peripheral edema (10.8%), nasopharyngitis (10.8%), vomiting (10%) and anorexia (10%), Other common AEs (>5-10%) were thrombocytopenia, leukopenia, leukocytosis, febrile neutropenia, dyspepsia, pain, chills, urinary tract infection, upper respiratory tract infection, bronchitis, pneumonia, influenza, elevated ALT/ALT, decreased weight, hypokalemia, musculoskeletal pain, night sweats, insomnia, alopecia, dizziness, anxiety, dyspnea, pharyngolaryngeal pain, erythema, dry skin and hyperhidrosis. These are shown in the table below.

**Table 61 Adverse Events in ≥ 5% CML-CP and CML-AP (Reviewer's Table)**

Adverse Event	CML-CP N=318		CML-AP N=120	
	All grades	All grades %	All grades	All grades %
<b>Blood and lymphatic system disorders</b>				
Thrombocytopenia	94	29.6	47	39.2
Anaemia	60	18.9	36	30.0
Neutropenia	53	16.7	27	22.5
Leukopenia	12	3.8	11	9.2
Thrombocythaemia	12	3.8	7	5.8
Leukocytosis	6	1.9	6	5.0
Febrile neutropenia	4	1.3	6	5.0

<b>Gastrointestinal disorders</b>				
Nausea	99	31.1	22	18.3
Diarrhoea	72	22.6	23	19.2
Constipation	66	20.8	22	18.3
Vomiting	67	21.1	12	10.0
Abdominal pain	36	11.3	16	13.3
Abdominal pain upper	32	10.1	11	9.2
Dyspepsia	25	7.9	3	2.5
<b>General disorders and administration site conditions</b>				
Fatigue	90	28.3	19	15.8
Pyrexia	45	14.2	29	24.2
Asthenia	44	13.8	14	11.7
Oedema peripheral	34	10.7	13	10.8
Pain	12	3.8	6	5.0
Chills	10	3.1	6	5.0
<b>Hepatobiliary disorders</b>				
Hyperbilirubinaemia	23	7.2	9	7.5
<b>Infections and infestations</b>				
Nasopharyngitis	50	15.7	13	10.8
Upper respiratory tract infection	27	8.5	7	5.8
Bronchitis	16	5.0	2	1.7
Urinary tract infection	11	3.5	6	5.0
Influenza	5	1.6	7	5.8
Pneumonia	5	1.6	6	5.0
<b>Investigations</b>				
Lipase increased	42	13.2	15	12.5
Alanine aminotransferase increased	30	9.4	5	4.2
Blood bilirubin increased	25	7.9	9	7.5
Weight decreased	22	6.9	5	4.2
Aspartate aminotransferase increased	16	5.0	4	3.3
Haemoglobin decreased	6	1.9	8	6.7
Anorexia	28	8.8	12	10.0
<b>Metabolism and nutrition disorders</b>				
Hypokalaemia	11	3.5	7	5.8
<b>Musculoskeletal and connective tissue disorders</b>				
Arthralgia	58	18.2	19	15.8
Myalgia	46	14.5	18	15.0
Pain in extremity	42	13.2	19	15.8
Bone pain	36	11.3	16	13.3
Muscle spasms	34	10.7	17	14.2
Back pain	33	10.4	14	11.7
Musculoskeletal pain	17	5.3	9	7.5

<b>Nervous system disorders</b>				
Headache	98	30.8	26	21.7
Dizziness	25	7.9	5	4.2
<b>Psychiatric disorders</b>				
Insomnia	30	9.4	8	6.7
Anxiety	16	5.0	2	1.7
<b>Respiratory, thoracic and mediastinal disorders</b>				
Cough	54	17.0	15	12.5
Dyspnoea	36	11.3	9	7.5
Pharyngolaryngeal pain	23	7.2	6	5.0
Dyspnoea exertional	19	6.0	3	2.5
<b>Skin and subcutaneous tissue disorders</b>				
Rash	107	33.6	34	28.3
Pruritus	91	28.6	24	20.0
Alopecia	28	8.8	11	9.2
Night sweats	27	8.5	8	6.7
Erythema	25	7.9	4	3.3
Dry skin	26	8.2	3	2.5
Hyperhidrosis	19	6.0	3	2.5

Source: A\_AEV.xpt

#### 7.1.5.5 Identifying common and drug-related adverse events

The common AEs have been identified in the previous section. The applicant submitted drug-related AEs.

#### 7.1.5.6 Additional analyses and explorations

Not applicable

#### 7.1.6 Less Common Adverse Events

### **120-Day Safety Update**

#### **CML-CP**

In patients with CML-CP, less common adverse events (upto 5%) were mostly grades 1-2. Grade 3/4 AEs which have not been described above included cardiovascular events (coronary artery disease, cardiomegaly, pericarditis, tricuspid valve incompetence and increased troponin); gastrointestinal events (peritonitis, ulcer perforation, chelecystitis); administration site necrosis; infections (bacterial and fungal); subdural hemorrhage and transient ischemic attack; muskuloskeletal disorders (osteoarthritis, flank pain, muscle weakness); reproductive disorders

(pelvic pain, vulvovagial dryness, priapism, testicular swelling); renal failure; interstitial lung disease; and vascular disorders (peripheral arterial occlusive disease, hypertensive crisis, hemorrhagic shock, thrombophlebitis, vascular stenosis, vasculitis).

The tables below list the less common AEs seen in CML-CP.

**Table 62 Adverse events in 1-5% CML-CP (Reviewer's Table)**

Adverse Event	CML-CP N=318							
	All grades	All grades %	Grade 3	Grade 3%	Grade 4	Grade 4%	Grades 3/4	Grades 3/4 %
<b>Blood and lymphatic system disorders</b>								
Leukopenia	12	3.8	8	2.5	0	1.3	8	2.5
Thrombocytopenia	12	3.8	6	1.9	0	0.0	6	1.9
Leukocytosis	6	1.9	1	0.3	1	0.3	2	0.6
Febrile neutropenia	4	1.3	4	1.3	0	0.0	4	1.3
<b>General disorders and administration site conditions</b>								
Pain	12	3.8	1	0.3	0	0.0	1	0.3
Chills	10	3.1	0	0.0	0	0.0	0	0.0
<b>Infections and infestations</b>								
Urinary tract infection	11	3.5	0	0.0	0	0.0	0	0.0
Pneumonia	5	1.6	1	0.3	0	0.9	1	0.3
Influenza	5	1.6	0	0.0	0	0.0	0	0.0
<b>Investigations</b>								
Haemoglobin decreased	6	1.9	0	0.0	0	0.0	0	0.0
<b>Metabolism and nutrition disorders</b>								
Hypokalaemia	11	3.5	1	0.3	0	0.0	1	0.3

**Table 63 Adverse events in < 1% CML-CP (N=318) (Reviewer's Table)**

Adverse Event	CML-CP N=318							
	All grades	All grades %	Grade 3	Grade 3%	Grade 4	Grade 4%	Grades 3/4	Grades 3/4 %
<b>Blood and lymphatic system disorders</b>								
Eosinophilia	1	0.3	0	0.0	0	0.0	0	0.0
Lymphadenitis	1	0.3	0	0.0	0	0.0	0	0.0
Coagulopathy	0	0.0	0	0.0	0	0.0	0	0.0
Microcytic anaemia	0	0.0	0	0.0	0	0.0	0	0.0
<b>Cardiac disorders</b>								

Coronary artery disease	3	0.9	2	0.6	1	0.0	3	0.9
Cardiomegaly	3	0.9	1	0.3	0	0.0	1	0.3
Extrasystoles	3	0.9	0	0.0	0	0.0	0	0.0
Pericarditis	2	0.6	2	0.6	0	0.0	2	0.6
Coronary artery stenosis	2	0.6	0	0.0	1	0.0	1	0.3
Pericardial effusion	2	0.6	0	0.0	1	0.0	1	0.3
Cardiac flutter	2	0.6	0	0.0	0	0.0	0	0.0
Dilatation atrial	2	0.6	0	0.0	0	0.0	0	0.0
Sinus bradycardia	2	0.6	0	0.0	0	0.0	0	0.0
Tachycardia	2	0.6	0	0.0	0	0.0	0	0.0
Ventricular dysfunction	2	0.6	0	0.0	0	0.0	0	0.0
Ventricular extrasystoles	2	0.6	0	0.0	0	0.0	0	0.0
Acute myocardial infarction	1	0.3	0	0.0	1	0.0	1	0.3
Arteriosclerosis coronary artery	1	0.3	0	0.0	1	0.0	1	0.3
Tachyarrhythmia	1	0.3	1	0.3	0	0.0	1	0.3
Tricuspid valve incompetence	1	0.3	1	0.3	0	0.0	1	0.3
Atrial flutter	1	0.3	0	0.0	0	0.0	0	0.0
Atrioventricular block first degree	1	0.3	0	0.0	0	0.0	0	0.0
Bundle branch block right	1	0.3	0	0.0	0	0.0	0	0.0
Cardiac failure congestive	1	0.3	0	0.0	0	0.0	0	0.0
Cardiac valve disease	1	0.3	0	0.0	0	0.0	0	0.0
Dilatation ventricular	1	0.3	0	0.0	0	0.0	0	0.0
Mitral valve incompetence	1	0.3	0	0.0	0	0.0	0	0.0
Myocardial ischaemia	1	0.3	0	0.0	0	0.0	0	0.0
Sinus tachycardia	1	0.3	0	0.0	0	0.0	0	0.0
Cardiac failure	0	0.0	0	0.0	0	0.3	0	0.0
Pericardial disease	0	0.0	0	0.0	0	0.0	0	0.0
Supraventricular tachycardia	0	0.0	0	0.0	0	0.0	0	0.0
<b>Congenital, familial and genetic disorders</b>								
Gilbert's syndrome	1	0.3	0	0.0	0	0.0	0	0.0
Factor XIII deficiency	0	0.0	0	0.0	0	0.0	0	0.0
<b>Ear and labyrinth disorders</b>								
Tinnitus	3	0.9	0	0.0	0	0.0	0	0.0
Cerumen impaction	2	0.6	0	0.0	0	0.0	0	0.0

Deafness	2	0.6	0	0.0	0	0.0	0	0.0
Hearing impaired	1	0.3	0	0.0	0	0.0	0	0.0
Hypoacusis	1	0.3	0	0.0	0	0.0	0	0.0
Ear discomfort	0	0.0	0	0.0	0	0.0	0	0.0
Tympanic membrane perforation	0	0.0	0	0.0	0	0.0	0	0.0
<b>Endocrine disorders</b>								
Hypothyroidism	3	0.9	0	0.0	0	0.0	0	0.0
Hyperthyroidism	2	0.6	0	0.0	0	0.0	0	0.0
Thyroid cyst	0	0.0	0	0.0	0	0.0	0	0.0
Thyroiditis	0	0.0	0	0.0	0	0.0	0	0.0
<b>Eye disorders</b>								
Lacrimation increased	3	0.9	0	0.0	0	0.0	0	0.0
Visual acuity reduced	3	0.9	0	0.0	0	0.0	0	0.0
Blepharitis	2	0.6	0	0.0	0	0.0	0	0.0
Conjunctival haemorrhage	2	0.6	0	0.0	0	0.0	0	0.0
Diplopia	2	0.6	0	0.0	0	0.0	0	0.0
Amaurosis	1	0.3	1	0.3	0	0.0	1	0.3
Cataract	1	0.3	0	0.0	0	0.0	0	0.0
Conjunctival hyperaemia	1	0.3	0	0.0	0	0.0	0	0.0
Eye oedema	1	0.3	0	0.0	0	0.0	0	0.0
Eye swelling	1	0.3	0	0.0	0	0.0	0	0.0
Eyelids pruritus	1	0.3	0	0.0	0	0.0	0	0.0
Foreign body sensation in eyes	1	0.3	0	0.0	0	0.0	0	0.0
Hypermetropia	1	0.3	0	0.0	0	0.0	0	0.0
Maculopathy	1	0.3	0	0.0	0	0.0	0	0.0
Ocular discomfort	1	0.3	0	0.0	0	0.0	0	0.0
Orbital oedema	1	0.3	0	0.0	0	0.0	0	0.0
Panophthalmitis	1	0.3	0	0.0	0	0.0	0	0.0
Papilloedema	1	0.3	0	0.0	0	0.0	0	0.0
Pterygium	1	0.3	0	0.0	0	0.0	0	0.0
Retinal haemorrhage	1	0.3	0	0.0	0	0.0	0	0.0
Scleral haemorrhage	1	0.3	0	0.0	0	0.0	0	0.0
Visual disturbance	1	0.3	0	0.0	0	0.0	0	0.0
Keratoconjunctivitis sicca	0	0.0	0	0.0	0	0.0	0	0.0
Retinal detachment	0	0.0	0	0.0	0	0.0	0	0.0
<b>Gastrointestinal disorders</b>								
Dysphagia	3	0.9	0	0.0	0	0.0	0	0.0
Gastritis	3	0.9	0	0.0	0	0.0	0	0.0
Gingival bleeding	3	0.9	0	0.0	0	0.0	0	0.0
Gingivitis	3	0.9	0	0.0	0	0.0	0	0.0
Pancreatitis	3	0.9	0	0.0	0	0.0	0	0.0

Gastrointestinal haemorrhage	2	0.6	0	0.0	1	0.0	1	0.3
Peritonitis	2	0.6	1	0.3	0	0.0	1	0.3
Epigastric discomfort	2	0.6	0	0.0	0	0.0	0	0.0
Haemorrhoidal haemorrhage	2	0.6	0	0.0	0	0.0	0	0.0
Inguinal hernia	2	0.6	0	0.0	0	0.0	0	0.0
Duodenal ulcer haemorrhage	1	0.3	1	0.3	0	0.0	1	0.3
Gastric ulcer haemorrhage	1	0.3	1	0.3	0	0.0	1	0.3
Gastrointestinal ulcer perforation	1	0.3	0	0.0	1	0.0	1	0.3
Anorectal disorder	1	0.3	0	0.0	0	0.0	0	0.0
Cheilitis	1	0.3	0	0.0	0	0.0	0	0.0
Diarrhoea haemorrhagic	1	0.3	0	0.0	0	0.0	0	0.0
Duodenitis	1	0.3	0	0.0	0	0.0	0	0.0
Erosive oesophagitis	1	0.3	0	0.0	0	0.0	0	0.0
Faeces discoloured	1	0.3	0	0.0	0	0.0	0	0.0
Faeces hard	1	0.3	0	0.0	0	0.0	0	0.0
Food poisoning	1	0.3	0	0.0	0	0.0	0	0.0
Gastric ulcer	1	0.3	0	0.0	0	0.0	0	0.0
Gastrointestinal hypermotility	1	0.3	0	0.0	0	0.0	0	0.0
Gastrointestinal ulcer	1	0.3	0	0.0	0	0.0	0	0.0
Gingival pain	1	0.3	0	0.0	0	0.0	0	0.0
Glossodynia	1	0.3	0	0.0	0	0.0	0	0.0
Haematemesis	1	0.3	0	0.0	0	0.0	0	0.0
Haematochezia	1	0.3	0	0.0	0	0.0	0	0.0
Hyperchlorhydria	1	0.3	0	0.0	0	0.0	0	0.0
Hypoaesthesia oral	1	0.3	0	0.0	0	0.0	0	0.0
Impaired gastric emptying	1	0.3	0	0.0	0	0.0	0	0.0
Intestinal functional disorder	1	0.3	0	0.0	0	0.0	0	0.0
Lip oedema	1	0.3	0	0.0	0	0.0	0	0.0
Lip ulceration	1	0.3	0	0.0	0	0.0	0	0.0
Malocclusion	1	0.3	0	0.0	0	0.0	0	0.0
Melaena	1	0.3	0	0.0	0	0.3	0	0.0
Mucous stools	1	0.3	0	0.0	0	0.0	0	0.0
Oesophagitis ulcerative	1	0.3	0	0.0	0	0.0	0	0.0
Palatal disorder	1	0.3	0	0.0	0	0.0	0	0.0
Pancreatitis chronic	1	0.3	0	0.0	0	0.0	0	0.0
Salivary	1	0.3	0	0.0	0	0.0	0	0.0

hypersecretion								
Stomach discomfort	1	0.3	0	0.0	0	0.0	0	0.0
Subileus	1	0.3	0	0.0	0	0.0	0	0.0
Swollen tongue	1	0.3	0	0.0	0	0.0	0	0.0
Tongue coated	1	0.3	0	0.0	0	0.0	0	0.0
Tongue ulceration	1	0.3	0	0.0	0	0.0	0	0.0
Tooth disorder	1	0.3	0	0.0	0	0.0	0	0.0
Abdominal hernia	0	0.0	0	0.0	0	0.0	0	0.0
Abdominal wall disorder	0	0.0	0	0.0	0	0.0	0	0.0
Anal discomfort	0	0.0	0	0.0	0	0.0	0	0.0
Aphthous stomatitis	0	0.0	0	0.0	0	0.0	0	0.0
Ascites	0	0.0	0	0.0	0	0.0	0	0.0
Dental caries	0	0.0	0	0.0	0	0.0	0	0.0
Enteritis	0	0.0	0	0.0	0	0.0	0	0.0
Gastric disorder	0	0.0	0	0.0	0	0.0	0	0.0
Gastrointestinal disorder	0	0.0	0	0.0	0	0.0	0	0.0
Odynophagia	0	0.0	0	0.0	0	0.0	0	0.0
Oesophageal pain	0	0.0	0	0.0	0	0.0	0	0.0
Oral mucosal petechiae	0	0.0	0	0.0	0	0.0	0	0.0
Proctalgia	0	0.0	0	0.0	0	0.0	0	0.0
Rectal haemorrhage	0	0.0	0	0.0	0	0.0	0	0.0
Retroperitoneal haemorrhage	0	0.0	0	0.0	0	0.0	0	0.0
<b>General disorders and administration site conditions</b>								
Oedema	3	0.9	0	0.0	0	0.0	0	0.0
General physical health deterioration	2	0.6	1	0.3	0	0.3	1	0.3
Feeling cold	2	0.6	0	0.0	0	0.0	0	0.0
Injection site pain	2	0.6	0	0.0	0	0.0	0	0.0
Multi-organ failure	1	0.3	0	0.0	1	0.3	1	0.3
Necrosis	1	0.3	0	0.0	1	0.0	1	0.3
Suprapubic pain	1	0.3	1	0.3	0	0.0	1	0.3
Cyst	1	0.3	0	0.0	0	0.0	0	0.0
Face oedema	1	0.3	0	0.0	0	0.0	0	0.0
Feeling abnormal	1	0.3	0	0.0	0	0.0	0	0.0
Feeling hot	1	0.3	0	0.0	0	0.0	0	0.0
Feeling hot and cold	1	0.3	0	0.0	0	0.0	0	0.0
Gravitational oedema	1	0.3	0	0.0	0	0.0	0	0.0
Hyperpyrexia	1	0.3	0	0.0	0	0.0	0	0.0
Impaired healing	1	0.3	0	0.0	0	0.0	0	0.0
Injection site bruising	1	0.3	0	0.0	0	0.0	0	0.0
Injection site erythema	1	0.3	0	0.0	0	0.0	0	0.0

Irritability	1	0.3	0	0.0	0	0.0	0	0.0
Local swelling	1	0.3	0	0.0	0	0.0	0	0.0
Mass	1	0.3	0	0.0	0	0.0	0	0.0
Mucosal inflammation	1	0.3	0	0.0	0	0.0	0	0.0
Pitting oedema	1	0.3	0	0.0	0	0.0	0	0.0
Sensation of pressure	1	0.3	0	0.0	0	0.0	0	0.0
Axillary pain	0	0.0	0	0.0	0	0.0	0	0.0
Catheter site pain	0	0.0	0	0.0	0	0.0	0	0.0
Inflammation	0	0.0	0	0.0	0	0.0	0	0.0
No adverse effect	0	0.0	0	0.0	0	0.0	0	0.0
Nodule	0	0.0	0	0.0	0	0.0	0	0.0
<b>Hepatobiliary disorders</b>								
Cytolytic hepatitis	2	0.6	1	0.3	0	0.0	1	0.3
Hepatotoxicity	2	0.6	1	0.3	0	0.0	1	0.3
Hepatic steatosis	2	0.6	0	0.0	0	0.0	0	0.0
Cholecystitis acute	1	0.3	1	0.3	0	0.0	1	0.3
Hepatic failure	1	0.3	0	0.0	1	0.0	1	0.3
Hepatic cyst	1	0.3	0	0.0	0	0.0	0	0.0
Hepatitis toxic	1	0.3	0	0.0	0	0.0	0	0.0
Jaundice	1	0.3	0	0.0	0	0.0	0	0.0
Liver disorder	1	0.3	0	0.0	0	0.0	0	0.0
Hepatic pain	0	0.0	0	0.0	0	0.0	0	0.0
<b>Immune system disorders</b>								
Seasonal allergy	2	0.6	0	0.0	0	0.0	0	0.0
Graft versus host disease	1	0.3	0	0.0	1	0.0	1	0.3
Drug hypersensitivity	1	0.3	0	0.0	0	0.0	0	0.0
Rhesus incompatibility	0	0.0	0	0.0	0	0.0	0	0.0
<b>Infections and infestations</b>								
Candidiasis	3	0.9	1	0.3	0	0.0	1	0.3
Cystitis	3	0.9	0	0.0	0	0.0	0	0.0
Ear infection	3	0.9	0	0.0	0	0.0	0	0.0
Gastroenteritis viral	3	0.9	0	0.0	0	0.0	0	0.0
Otitis media	3	0.9	0	0.0	0	0.0	0	0.0
Rash pustular	3	0.9	0	0.0	0	0.0	0	0.0
Tooth abscess	3	0.9	0	0.0	0	0.0	0	0.0
Sepsis	2	0.6	1	0.3	1	0.3	2	0.6
Localised infection	2	0.6	0	0.0	1	0.0	1	0.3
Oral candidiasis	2	0.6	1	0.3	0	0.0	1	0.3
Staphylococcal infection	2	0.6	1	0.3	0	0.0	1	0.3
Fungal infection	2	0.6	0	0.0	0	0.0	0	0.0
Furuncle	2	0.6	0	0.0	0	0.0	0	0.0
Tinea pedis	2	0.6	0	0.0	0	0.0	0	0.0

Tonsillitis	2	0.6	0	0.0	0	0.0	0	0.0
Tooth infection	2	0.6	0	0.0	0	0.0	0	0.0
Vulvovaginal mycotic infection	2	0.6	0	0.0	0	0.0	0	0.0
Appendicitis	1	0.3	1	0.3	0	0.0	1	0.3
Bacterial infection	1	0.3	1	0.3	0	0.0	1	0.3
Bronchopulmonary aspergillosis	1	0.3	1	0.3	0	0.0	1	0.3
Escherichia urinary tract infection	1	0.3	1	0.3	0	0.0	1	0.3
Infection	1	0.3	1	0.3	0	0.0	1	0.3
Lobar pneumonia	1	0.3	1	0.3	0	0.3	1	0.3
Sepsis syndrome	1	0.3	0	0.0	1	0.0	1	0.3
Abscess oral	1	0.3	0	0.0	0	0.0	0	0.0
Bronchitis acute	1	0.3	0	0.0	0	0.0	0	0.0
Cellulitis orbital	1	0.3	0	0.0	0	0.0	0	0.0
Diverticulitis	1	0.3	0	0.0	0	0.0	0	0.0
Fungal rash	1	0.3	0	0.0	0	0.0	0	0.0
Gastrointestinal infection	1	0.3	0	0.0	0	0.0	0	0.0
Genital infection fungal	1	0.3	0	0.0	0	0.0	0	0.0
Herpes ophthalmic	1	0.3	0	0.0	0	0.0	0	0.0
Herpes zoster ophthalmic	1	0.3	0	0.0	0	0.0	0	0.0
Labyrinthitis	1	0.3	0	0.0	0	0.0	0	0.0
Laryngitis	1	0.3	0	0.0	0	0.0	0	0.0
Lung infection	1	0.3	0	0.0	0	0.0	0	0.0
Mastitis	1	0.3	0	0.0	0	0.0	0	0.0
Nipple infection	1	0.3	0	0.0	0	0.0	0	0.0
Oral infection	1	0.3	0	0.0	0	0.0	0	0.0
Osteomyelitis	1	0.3	0	0.0	0	0.0	0	0.0
Otitis externa	1	0.3	0	0.0	0	0.0	0	0.0
Paronychia	1	0.3	0	0.0	0	0.0	0	0.0
Pyelonephritis	1	0.3	0	0.0	0	0.0	0	0.0
Scrotal abscess	1	0.3	0	0.0	0	0.0	0	0.0
Skin candida	1	0.3	0	0.0	0	0.0	0	0.0
Skin infection	1	0.3	0	0.0	0	0.0	0	0.0
Subcutaneous abscess	1	0.3	0	0.0	0	0.0	0	0.0
Tinea infection	1	0.3	0	0.0	0	0.0	0	0.0
Vaginitis bacterial	1	0.3	0	0.0	0	0.0	0	0.0
Viral upper respiratory tract infection	1	0.3	0	0.0	0	0.0	0	0.0
Bacteraemia	0	0.0	0	0.0	0	0.0	0	0.0
Enterococcal	0	0.0	0	0.0	0	0.0	0	0.0

infection								
Hordeolum	0	0.0	0	0.0	0	0.0	0	0.0
Lymph gland infection	0	0.0	0	0.0	0	0.0	0	0.0
Mucocutaneous candidiasis	0	0.0	0	0.0	0	0.0	0	0.0
Nail infection	0	0.0	0	0.0	0	0.0	0	0.0
Necrotising fasciitis	0	0.0	0	0.0	0	0.0	0	0.0
Nocardiosis	0	0.0	0	0.0	0	0.0	0	0.0
Onychomycosis	0	0.0	0	0.0	0	0.0	0	0.0
Perianal abscess	0	0.0	0	0.0	0	0.0	0	0.0
Pneumonia fungal	0	0.0	0	0.0	0	0.0	0	0.0
Scrotal infection	0	0.0	0	0.0	0	0.0	0	0.0
Sexually transmitted disease	0	0.0	0	0.0	0	0.0	0	0.0
Varicella	0	0.0	0	0.0	0	0.0	0	0.0
Wound infection	0	0.0	0	0.0	0	0.0	0	0.0
<b>Injury, poisoning and procedural complications</b>								
Joint injury	2	0.6	1	0.3	0	0.0	1	0.3
Arthropod bite	2	0.6	0	0.0	0	0.0	0	0.0
Joint sprain	2	0.6	0	0.0	0	0.0	0	0.0
Skin laceration	2	0.6	0	0.0	0	0.0	0	0.0
Sunburn	2	0.6	0	0.0	0	0.0	0	0.0
Subdural haemorrhage	1	0.3	1	0.3	0	0.0	1	0.3
Excoriation	1	0.3	0	0.0	0	0.0	0	0.0
Eye burns	1	0.3	0	0.0	0	0.0	0	0.0
Hand fracture	1	0.3	0	0.0	0	0.0	0	0.0
Laceration	1	0.3	0	0.0	0	0.0	0	0.0
Periorbital haematoma	1	0.3	0	0.0	0	0.0	0	0.0
Post procedural nausea	1	0.3	0	0.0	0	0.0	0	0.0
Tendon rupture	1	0.3	0	0.0	0	0.0	0	0.0
Thermal burn	1	0.3	0	0.0	0	0.0	0	0.0
Wound	1	0.3	0	0.0	0	0.0	0	0.0
Allergic transfusion reaction	0	0.0	0	0.0	0	0.0	0	0.0
Post procedural haematoma	0	0.0	0	0.0	0	0.0	0	0.0
<b>Investigations</b>								
Blood phosphorus decreased	3	0.9	2	0.6	1	0.0	3	0.9
Liver function test abnormal	3	0.9	2	0.6	0	0.0	2	0.6
Blood creatine	3	0.9	0	0.0	0	0.0	0	0.0

phosphokinase MB increased								
Electrocardiogram QT prolonged	2	0.6	1	0.3	0	0.0	1	0.3
Blood albumin decreased	2	0.6	0	0.0	0	0.0	0	0.0
Blood cholesterol increased	2	0.6	0	0.0	0	0.0	0	0.0
Blood glucose decreased	2	0.6	0	0.0	0	0.0	0	0.0
Blood lactate dehydrogenase increased	2	0.6	0	0.0	0	0.0	0	0.0
Blood urea increased	2	0.6	0	0.0	0	0.0	0	0.0
Blood uric acid increased	2	0.6	0	0.0	0	0.0	0	0.0
Body temperature increased	2	0.6	0	0.0	0	0.0	0	0.0
Electrocardiogram change	2	0.6	0	0.0	0	0.0	0	0.0
Neutrophil count increased	2	0.6	0	0.0	0	0.0	0	0.0
Blood bilirubin unconjugated increased	1	0.3	1	0.3	0	0.0	1	0.3
Haptoglobin decreased	1	0.3	1	0.3	0	0.0	1	0.3
Troponin increased	1	0.3	0	0.0	1	0.3	1	0.3
Atrial pressure increased	1	0.3	0	0.0	0	0.0	0	0.0
Blood calcium decreased	1	0.3	0	0.0	0	0.0	0	0.0
Blood fibrinogen decreased	1	0.3	0	0.0	0	0.0	0	0.0
Blood iron decreased	1	0.3	0	0.0	0	0.0	0	0.0
Blood magnesium increased	1	0.3	0	0.0	0	0.0	0	0.0
Electrocardiogram QT corrected interval prolonged	1	0.3	0	0.0	0	0.0	0	0.0
Electrocardiogram T wave inversion	1	0.3	0	0.0	0	0.0	0	0.0
Exercise electrocardiogram abnormal	1	0.3	0	0.0	0	0.0	0	0.0
Globulins increased	1	0.3	0	0.0	0	0.0	0	0.0

Heart rate irregular	1	0.3	0	0.0	0	0.0	0	0.0
Lipids increased	1	0.3	0	0.0	0	0.0	0	0.0
Red blood cell count decreased	1	0.3	0	0.0	0	0.0	0	0.0
Urine colour abnormal	1	0.3	0	0.0	0	0.0	0	0.0
Breath sounds abnormal	0	0.0	0	0.0	0	0.0	0	0.0
Haemoglobin increased	0	0.0	0	0.0	0	0.0	0	0.0
Hepatic enzyme increased	0	0.0	0	0.0	0	0.0	0	0.0
Lipase abnormal	0	0.0	0	0.0	0	0.0	0	0.0
Lipase decreased	0	0.0	0	0.0	0	0.0	0	0.0
Monocyte count increased	0	0.0	0	0.0	0	0.0	0	0.0
Troponin T increased	0	0.0	0	0.0	0	0.3	0	0.0
<b>Metabolism and nutrition disorders</b>								
Hypophosphataemia	3	0.9	2	0.6	0	0.0	2	0.6
Hypercalcaemia	3	0.9	1	0.3	0	0.0	1	0.3
Hypoglycaemia	3	0.9	1	0.3	0	0.0	1	0.3
Gout	3	0.9	0	0.0	0	0.0	0	0.0
Fluid retention	2	0.6	1	0.3	0	0.0	1	0.3
Hyperphosphataemia	2	0.6	0	0.0	0	0.0	0	0.0
Hypoalbuminaemia	2	0.6	0	0.0	0	0.0	0	0.0
Hyperlipidaemia	1	0.3	0	0.0	0	0.0	0	0.0
Hypernatraemia	1	0.3	0	0.0	0	0.0	0	0.0
Increased appetite	1	0.3	0	0.0	0	0.0	0	0.0
Mineral deficiency	1	0.3	0	0.0	0	0.0	0	0.0
Podagra	1	0.3	0	0.0	0	0.0	0	0.0
Polydipsia	1	0.3	0	0.0	0	0.0	0	0.0
Vitamin B complex deficiency	1	0.3	0	0.0	0	0.0	0	0.0
Vitamin D deficiency	1	0.3	0	0.0	0	0.0	0	0.0
Acidosis	0	0.0	0	0.0	0	0.0	0	0.0
Osteoarthritis	3	0.9	2	0.6	0	0.0	2	0.6
Buttock pain	3	0.9	1	0.3	0	0.0	1	0.3
Flank pain	3	0.9	1	0.3	0	0.0	1	0.3
Arthritis	3	0.9	0	0.0	0	0.0	0	0.0
Joint swelling	2	0.6	0	0.0	0	0.0	0	0.0
Musculoskeletal discomfort	2	0.6	0	0.0	0	0.0	0	0.0
Musculoskeletal stiffness	2	0.6	0	0.0	0	0.0	0	0.0
Spinal osteoarthritis	2	0.6	0	0.0	0	0.0	0	0.0
Muscular weakness	1	0.3	1	0.3	0	0.0	1	0.3

Axillary mass	1	0.3	0	0.0	0	0.0	0	0.0
Bursitis	1	0.3	0	0.0	0	0.0	0	0.0
Groin pain	1	0.3	0	0.0	0	0.0	0	0.0
Intervertebral disc disorder	1	0.3	0	0.0	0	0.0	0	0.0
Intervertebral disc protrusion	1	0.3	0	0.0	0	0.0	0	0.0
Joint effusion	1	0.3	0	0.0	0	0.0	0	0.0
Kyphosis	1	0.3	0	0.0	0	0.0	0	0.0
Muscle contracture	1	0.3	0	0.0	0	0.0	0	0.0
Muscle fibrosis	1	0.3	0	0.0	0	0.0	0	0.0
Osteoporosis	1	0.3	0	0.0	0	0.0	0	0.0
Polyarthritis	1	0.3	0	0.0	0	0.0	0	0.0
Polymyositis	1	0.3	0	0.0	0	0.0	0	0.0
Soft tissue disorder	1	0.3	0	0.0	0	0.0	0	0.0
Spinal column stenosis	1	0.3	0	0.0	0	0.0	0	0.0
Tendon disorder	1	0.3	0	0.0	0	0.0	0	0.0
Tendonitis	1	0.3	0	0.0	0	0.0	0	0.0
Torticollis	1	0.3	0	0.0	0	0.0	0	0.0
Joint range of motion decreased	0	0.0	0	0.0	0	0.0	0	0.0
Mobility decreased	0	0.0	0	0.0	0	0.0	0	0.0
Pain in jaw	0	0.0	0	0.0	0	0.0	0	0.0
Sacroiliitis	0	0.0	0	0.0	0	0.0	0	0.0
<b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b>								
Skin papilloma	3	0.9	0	0.0	0	0.0	0	0.0
Basal cell carcinoma	1	0.3	1	0.3	0	0.0	1	0.3
Fibrous histiocytoma	1	0.3	0	0.0	0	0.0	0	0.0
Lipoma	1	0.3	0	0.0	0	0.0	0	0.0
Seborrheic keratosis	1	0.3	0	0.0	0	0.0	0	0.0
Skin cancer	1	0.3	0	0.0	0	0.0	0	0.0
Testis cancer	1	0.3	0	0.0	0	0.0	0	0.0
Thyroid neoplasm	1	0.3	0	0.0	0	0.0	0	0.0
Metastatic malignant melanoma	0	0.0	0	0.0	0	0.3	0	0.0
<b>Nervous system disorders</b>								
Syncope vasovagal	3	0.9	2	0.6	0	0.0	2	0.6
Hyperaesthesia	3	0.9	0	0.0	0	0.0	0	0.0
Migraine	3	0.9	0	0.0	0	0.0	0	0.0
Neuropathy	3	0.9	0	0.0	0	0.0	0	0.0
Neuropathy peripheral	3	0.9	0	0.0	0	0.0	0	0.0
Restless legs syndrome	3	0.9	0	0.0	0	0.0	0	0.0
Syncope	2	0.6	2	0.6	0	0.0	2	0.6

Amnesia	2	0.6	0	0.0	0	0.0	0	0.0
Dizziness postural	2	0.6	0	0.0	0	0.0	0	0.0
Hypersomnia	2	0.6	0	0.0	0	0.0	0	0.0
Memory impairment	2	0.6	0	0.0	0	0.0	0	0.0
Sinus headache	2	0.6	0	0.0	0	0.0	0	0.0
Piriformis syndrome	1	0.3	1	0.3	0	0.0	1	0.3
Transient ischaemic attack	1	0.3	1	0.3	0	0.0	1	0.3
Balance disorder	1	0.3	0	0.0	0	0.0	0	0.0
Cognitive disorder	1	0.3	0	0.0	0	0.0	0	0.0
Convulsion	1	0.3	0	0.0	0	0.0	0	0.0
Disturbance in attention	1	0.3	0	0.0	0	0.0	0	0.0
Dysarthria	1	0.3	0	0.0	0	0.0	0	0.0
Facial palsy	1	0.3	0	0.0	0	0.0	0	0.0
Hypertonia	1	0.3	0	0.0	0	0.0	0	0.0
Hypokinesia	1	0.3	0	0.0	0	0.0	0	0.0
Loss of consciousness	1	0.3	0	0.0	0	0.0	0	0.0
Neuromuscular blockade	1	0.3	0	0.0	0	0.0	0	0.0
Optic neuritis	1	0.3	0	0.0	0	0.0	0	0.0
Parkinsonism	1	0.3	0	0.0	0	0.0	0	0.0
Parosmia	1	0.3	0	0.0	0	0.0	0	0.0
Poor quality sleep	1	0.3	0	0.0	0	0.0	0	0.0
Post herpetic neuralgia	1	0.3	0	0.0	0	0.0	0	0.0
Sensory disturbance	1	0.3	0	0.0	0	0.0	0	0.0
Sensory loss	1	0.3	0	0.0	0	0.0	0	0.0
Somnolence	1	0.3	0	0.0	0	0.0	0	0.0
Trigeminal neuralgia	1	0.3	0	0.0	0	0.0	0	0.0
Visual field defect	1	0.3	0	0.0	0	0.0	0	0.0
Aphasia	0	0.0	0	0.0	0	0.0	0	0.0
Brain oedema	0	0.0	0	0.0	0	0.0	0	0.0
Cervical root pain	0	0.0	0	0.0	0	0.0	0	0.0
Dysstasia	0	0.0	0	0.0	0	0.0	0	0.0
Haemorrhage intracranial	0	0.0	0	0.0	0	0.3	0	0.0
Muscle contractions involuntary	0	0.0	0	0.0	0	0.0	0	0.0
<b>Psychiatric disorders</b>								
Nervousness	3	0.9	0	0.0	0	0.0	0	0.0
Panic attack	3	0.9	0	0.0	0	0.0	0	0.0
Depressed mood	2	0.6	0	0.0	0	0.0	0	0.0
Restlessness	2	0.6	0	0.0	0	0.0	0	0.0
Abnormal dreams	1	0.3	0	0.0	0	0.0	0	0.0
Loss of libido	1	0.3	0	0.0	0	0.0	0	0.0

Stress	1	0.3	0	0.0	0	0.0	0	0.0
Disorientation	0	0.0	0	0.0	0	0.0	0	0.0
Nightmare	0	0.0	0	0.0	0	0.0	0	0.0
<b>Renal and urinary disorders</b>								
Micturition urgency	3	0.9	0	0.0	0	0.0	0	0.0
Renal failure	2	0.6	0	0.0	1	0.0	1	0.3
Chromaturia	2	0.6	0	0.0	0	0.0	0	0.0
Polyuria	2	0.6	0	0.0	0	0.0	0	0.0
Renal pain	2	0.6	0	0.0	0	0.0	0	0.0
Haematuria	1	0.3	0	0.0	0	0.0	0	0.0
Leukocyturia	1	0.3	0	0.0	0	0.0	0	0.0
Micturition disorder	1	0.3	0	0.0	0	0.0	0	0.0
Nephrolithiasis	1	0.3	0	0.0	0	0.0	0	0.0
Renal disorder	1	0.3	0	0.0	0	0.0	0	0.0
Urinary incontinence	1	0.3	0	0.0	0	0.0	0	0.0
Urine odour abnormal	1	0.3	0	0.0	0	0.0	0	0.0
<b>Reproductive system and breast disorders</b>								
Pelvic pain	3	0.9	1	0.3	0	0.0	1	0.3
Gynaecomastia	2	0.6	0	0.0	0	0.0	0	0.0
Vulvovaginal dryness	2	0.6	0	0.0	0	0.0	0	0.0
Endometrial hyperplasia	1	0.3	0	0.0	1	0.0	1	0.3
Priapism	1	0.3	1	0.3	0	0.0	1	0.3
Testicular swelling	1	0.3	1	0.3	0	0.0	1	0.3
Benign prostatic hyperplasia	1	0.3	0	0.0	0	0.0	0	0.0
Breast enlargement	1	0.3	0	0.0	0	0.0	0	0.0
Breast swelling	1	0.3	0	0.0	0	0.0	0	0.0
Breast tenderness	1	0.3	0	0.0	0	0.0	0	0.0
Genital rash	1	0.3	0	0.0	0	0.0	0	0.0
Menorrhagia	1	0.3	0	0.0	0	0.0	0	0.0
Nipple swelling	1	0.3	0	0.0	0	0.0	0	0.0
Ovarian cyst	1	0.3	0	0.0	0	0.0	0	0.0
Prostatic obstruction	1	0.3	0	0.0	0	0.0	0	0.0
Testicular pain	1	0.3	0	0.0	0	0.0	0	0.0
Uterine polyp	1	0.3	0	0.0	0	0.0	0	0.0
Vulvovaginal discomfort	1	0.3	0	0.0	0	0.0	0	0.0
Breast cyst	0	0.0	0	0.0	0	0.0	0	0.0
Prostatic disorder	0	0.0	0	0.0	0	0.0	0	0.0
<b>Respiratory, thoracic and mediastinal disorders</b>								
Pleural effusion	3	0.9	1	0.3	0	0.0	1	0.3
Pleuritic pain	3	0.9	1	0.3	0	0.0	1	0.3
Asthma	3	0.9	0	0.0	0	0.0	0	0.0
Paranasal sinus hypersecretion	3	0.9	0	0.0	0	0.0	0	0.0

Pulmonary hypertension	3	0.9	0	0.0	0	0.0	0	0.0
Sinus congestion	3	0.9	0	0.0	0	0.0	0	0.0
Interstitial lung disease	2	0.6	2	0.6	0	0.0	2	0.6
Pleurisy	2	0.6	2	0.6	0	0.0	2	0.6
Pulmonary oedema	2	0.6	2	0.6	0	0.3	2	0.6
Lung infiltration	2	0.6	1	0.3	0	0.0	1	0.3
Hiccups	2	0.6	0	0.0	0	0.0	0	0.0
Productive cough	2	0.6	0	0.0	0	0.0	0	0.0
Rales	2	0.6	0	0.0	0	0.0	0	0.0
Throat irritation	2	0.6	0	0.0	0	0.0	0	0.0
Allergic cough	1	0.3	0	0.0	0	0.0	0	0.0
Bronchospasm	1	0.3	0	0.0	0	0.0	0	0.0
Chronic obstructive pulmonary disease	1	0.3	0	0.0	0	0.0	0	0.0
Diaphragmatic hernia	1	0.3	0	0.0	0	0.0	0	0.0
Dry throat	1	0.3	0	0.0	0	0.0	0	0.0
Nasal discomfort	1	0.3	0	0.0	0	0.0	0	0.0
Pharyngeal erythema	1	0.3	0	0.0	0	0.0	0	0.0
Pharyngolaryngeal discomfort	1	0.3	0	0.0	0	0.0	0	0.0
Respiration abnormal	1	0.3	0	0.0	0	0.0	0	0.0
Respiratory tract congestion	1	0.3	0	0.0	0	0.0	0	0.0
Rhinitis allergic	1	0.3	0	0.0	0	0.0	0	0.0
Sinus disorder	1	0.3	0	0.0	0	0.0	0	0.0
Upper respiratory tract congestion	1	0.3	0	0.0	0	0.0	0	0.0
Increased upper airway secretion	0	0.0	0	0.0	0	0.0	0	0.0
Pneumonia aspiration	0	0.0	0	0.0	0	0.0	0	0.0
Pneumonitis	0	0.0	0	0.0	0	0.0	0	0.0
Pulmonary artery wall hypertrophy	0	0.0	0	0.0	0	0.0	0	0.0
Respiratory failure	0	0.0	0	0.0	0	0.6	0	0.0
Sleep apnoea syndrome	0	0.0	0	0.0	0	0.0	0	0.0
<b>Skin and subcutaneous tissue disorders</b>								
Ecchymosis	3	0.9	0	0.0	0	0.0	0	0.0
Hypotrichosis	3	0.9	0	0.0	0	0.0	0	0.0
Rash macular	3	0.9	0	0.0	0	0.0	0	0.0
Rash maculo-papular	3	0.9	0	0.0	0	0.0	0	0.0
Exfoliative rash	2	0.6	1	0.3	0	0.0	1	0.3
Ingrowing nail	2	0.6	1	0.3	0	0.0	1	0.3
Palmar-plantar	2	0.6	1	0.3	0	0.0	1	0.3

erythrodysesthesia syndrome								
Swelling face	2	0.6	1	0.3	0	0.0	1	0.3
Generalised erythema	2	0.6	0	0.0	0	0.0	0	0.0
Hair texture abnormal	2	0.6	0	0.0	0	0.0	0	0.0
Heat rash	2	0.6	0	0.0	0	0.0	0	0.0
Photosensitivity reaction	2	0.6	0	0.0	0	0.0	0	0.0
Dermatitis allergic	1	0.3	1	0.3	0	0.0	1	0.3
Acne	1	0.3	0	0.0	0	0.0	0	0.0
Acne pustular	1	0.3	0	0.0	0	0.0	0	0.0
Acrodermatitis	1	0.3	0	0.0	0	0.0	0	0.0
Actinic keratosis	1	0.3	0	0.0	0	0.0	0	0.0
Blister	1	0.3	0	0.0	0	0.0	0	0.0
Dermatitis	1	0.3	0	0.0	0	0.0	0	0.0
Dermatitis acneiform	1	0.3	0	0.0	0	0.0	0	0.0
Dermatitis atopic	1	0.3	0	0.0	0	0.0	0	0.0
Erythema nodosum	1	0.3	0	0.0	0	0.0	0	0.0
Fat atrophy	1	0.3	0	0.0	0	0.0	0	0.0
Hair colour changes	1	0.3	0	0.0	0	0.0	0	0.0
Hair growth abnormal	1	0.3	0	0.0	0	0.0	0	0.0
Hyperkeratosis	1	0.3	0	0.0	0	0.0	0	0.0
Increased tendency to bruise	1	0.3	0	0.0	0	0.0	0	0.0
Leukoplakia	1	0.3	0	0.0	0	0.0	0	0.0
Lipodystrophy acquired	1	0.3	0	0.0	0	0.0	0	0.0
Nail discolouration	1	0.3	0	0.0	0	0.0	0	0.0
Piloerection	1	0.3	0	0.0	0	0.0	0	0.0
Prurigo	1	0.3	0	0.0	0	0.0	0	0.0
Pruritus generalised	1	0.3	0	0.0	0	0.0	0	0.0
Psoriasis	1	0.3	0	0.0	0	0.0	0	0.0
Rash follicular	1	0.3	0	0.0	0	0.0	0	0.0
Seborrhoeic dermatitis	1	0.3	0	0.0	0	0.0	0	0.0
Skin burning sensation	1	0.3	0	0.0	0	0.0	0	0.0
Skin depigmentation	1	0.3	0	0.0	0	0.0	0	0.0
Skin discolouration	1	0.3	0	0.0	0	0.0	0	0.0
Skin hyperpigmentation	1	0.3	0	0.0	0	0.0	0	0.0
Skin ulcer	1	0.3	0	0.0	0	0.0	0	0.0
Toxic skin eruption	1	0.3	0	0.0	0	0.0	0	0.0
Trichorrhexis	1	0.3	0	0.0	0	0.0	0	0.0
Drug eruption	0	0.0	0	0.0	0	0.0	0	0.0
Skin inflammation	0	0.0	0	0.0	0	0.0	0	0.0

Skin odour abnormal	0	0.0	0	0.0	0	0.0	0	0.0
Skin toxicity	0	0.0	0	0.0	0	0.0	0	0.0
<b>Surgical and medical procedures</b>								
Intervertebral disc operation	1	0.3	0	0.0	1	0.0	1	0.3
Toe amputation	1	0.3	1	0.3	0	0.0	1	0.3
Tooth extraction	1	0.3	0	0.0	0	0.0	0	0.0
<b>Vascular disorders</b>								
Hypertensive crisis	3	0.9	1	0.3	0	0.0	1	0.3
Phlebitis superficial	2	0.6	0	0.0	0	0.0	0	0.0
Venous insufficiency	2	0.6	0	0.0	0	0.0	0	0.0
Peripheral arterial occlusive disease	1	0.3	1	0.3	0	0.0	1	0.3
Shock haemorrhagic	1	0.3	0	0.0	1	0.0	1	0.3
Thrombophlebitis	1	0.3	1	0.3	0	0.0	1	0.3
Vascular stenosis	1	0.3	1	0.3	0	0.0	1	0.3
Vasculitis	1	0.3	1	0.3	0	0.0	1	0.3
Arterial occlusive disease	1	0.3	0	0.0	0	0.0	0	0.0
Arterial stenosis	1	0.3	0	0.0	0	0.0	0	0.0
Arteriosclerosis	1	0.3	0	0.0	0	0.0	0	0.0
Deep vein thrombosis	1	0.3	0	0.0	0	0.0	0	0.0
Pallor	1	0.3	0	0.0	0	0.0	0	0.0
Phlebitis	1	0.3	0	0.0	0	0.0	0	0.0
Raynaud's phenomenon	1	0.3	0	0.0	0	0.0	0	0.0
Erythromelalgia	0	0.0	0	0.0	0	0.3	0	0.0
Thrombosis	0	0.0	0	0.0	0	0.0	0	0.0

## CML-AP

In patients with CML-AP, less common adverse events (upto 5%) were mostly grades 1-2. Grade 3/4 AEs which have not been described above included cardiovascular events (angina pectoris and myocardial infarction); gastrointestinal events (gastric disorder, toothache and stomatitis); infections; osteoarthritis; respiratory failure; thrombosis; and psychiatry disorders (confusional state, sleep disorder and disorientation); coagulopathy; renal failure; factor XIII deficiency; retinal detachment; dental caries; metastatic malignant melanoma; pneumonitis and nervous system disorders (aphasia, convulsion, lethargy, brain edema and intracranial hemorrhage).

The tables below list the less common AEs seen in CML-AP.

**Table 64 Adverse events in 1-5% CML-AP (Reviewer's Table)**

Adverse Event	CML-AP N=120							
	All grades	All grades %	Grade 3	Grade 3%	Grade 4	Grade 4%	Grade 3/4	Grade 3/4%
<b>Cardiac disorders</b>								
Palpitations	5	4.2	0	0.0	0	0.0	0	0.0
Atrial fibrillation	3	2.5	1	0.8	0	0.0	1	0.8
Angina pectoris	2	1.7	1	0.8	1	0.8	2	1.7
Myocardial infarction	2	1.7	0	0.0	1	0.8	1	0.8
<b>Ear and labyrinth disorders</b>								
Vertigo	3	2.5	0	0.0	0	0.0	0	0.0
Conjunctivitis	3	2.5	0	0.0	0	0.0	0	0.0
Lacrimation increased	3	2.5	0	0.0	0	0.0	0	0.0
Vision blurred	2	1.7	0	0.0	0	0.0	0	0.0
Visual acuity reduced	2	1.7	0	0.0	0	0.0	0	0.0
<b>Gastrointestinal disorders</b>								
Haemorrhoids	4	3.3	0	0.0	0	0.0	0	0.0
Dyspepsia	3	2.5	0	0.0	0	0.0	0	0.0
Abdominal discomfort	3	2.5	0	0.0	0	0.0	0	0.0
Flatulence	3	2.5	0	0.0	0	0.0	0	0.0
Gastric disorder	3	2.5	1	0.8	0	0.0	1	0.8
Toothache	2	1.7	1	0.8	0	0.0	1	0.8
Stomatitis	2	1.7	0	0.0	1	0.8	1	0.8
Abdominal distension	2	1.7	0	0.0	0	0.0	0	0.0
Aphthous stomatitis	2	1.7	0	0.0	0	0.0	0	0.0
Gingivitis	2	1.7	0	0.0	0	0.0	0	0.0
Haemorrhoidal haemorrhage	2	1.7	0	0.0	0	0.0	0	0.0
<b>General disorders and administration site conditions</b>								
Non-cardiac chest pain	3	2.5	0	0.0	1	0.8	1	0.8
Chest pain	2	1.7	0	0.0	0	0.0	0	0.0
General physical health deterioration	2	1.7	0	0.0	1	0.8	1	0.8
Inflammation	2	1.7	0	0.0	0	0.0	0	0.0
<b>Immune system disorders</b>								
Seasonal allergy	2	1.7	0	0.0	0	0.0	0	0.0
<b>Infections and infestations</b>								
Herpes simplex	4	3.3	0	0.0	0	0.0	0	0.0
Sinusitis	4	3.3	0	0.0	0	0.0	0	0.0
Lower respiratory tract infection	3	2.5	1	0.8	0	0.0	1	0.8
Cellulitis	3	2.5	2	1.7	0	0.0	2	1.7
Furuncle	3	2.5	0	0.0	0	0.0	0	0.0
Pharyngitis	3	2.5	0	0.0	0	0.0	0	0.0
Rhinitis	3	2.5	0	0.0	0	0.0	0	0.0
Bacterial infection	2	1.7	1	0.8	0	0.0	1	0.8
Bronchitis	2	1.7	0	0.0	0	0.0	0	0.0
Ear infection	2	1.7	0	0.0	0	0.0	0	0.0

Rash pustular	2	1.7	0	0.0	0	0.0	0	0.0
Skin infection	2	1.7	0	0.0	0	0.0	0	0.0
Tooth abscess	2	1.7	0	0.0	0	0.0	0	0.0
Tooth infection	2	1.7	0	0.0	0	0.0	0	0.0
<b>Injury, poisoning and procedural complications</b>								
Arthropod bite	4	3.3	0	0.0	0	0.0	0	0.0
Procedural pain	3	2.5	0	0.0	0	0.0	0	0.0
<b>Investigations</b>								
Alanine aminotransferase increased	5	4.2	0	0.0	0	0.0	0	0.0
Blood amylase increased	5	4.2	3	2.5	0	0.0	3	2.5
Weight decreased	5	4.2	0	0.0	0	0.0	0	0.0
Aspartate aminotransferase increased	4	3.3	0	0.0	0	0.0	0	0.0
Electrocardiogram QT corrected interval prolonged	4	3.3	0	0.0	0	0.0	0	0.0
Platelet count decreased	3	2.5	2	1.7	1	0.8	3	2.5
Neutrophil count decreased	3	2.5	1	0.8	2	1.7	3	2.5
White blood cell count decreased	3	2.5	0	0.0	0	0.0	0	0.0
White blood cell count increased	3	2.5	2	1.7	0	0.0	2	1.7
Blood creatinine increased	3	2.5	0	0.0	0	0.0	0	0.0
Blood creatine phosphokinase increased	2	1.7	1	0.8	0	0.0	1	0.8
Blood glucose increased	2	1.7	0	0.0	0	0.0	0	0.0
Blood alkaline phosphatase increased	2	1.7	0	0.0	0	0.0	0	0.0
Troponin increased	2	1.7	0	0.0	1	0.8	1	0.8
Blood potassium decreased	2	1.7	1	0.8	0	0.0	1	0.8
Blood urea increased	2	1.7	0	0.0	0	0.0	0	0.0
Body temperature increased	2	1.7	0	0.0	0	0.0	0	0.0
Cardiac murmur	2	1.7	0	0.0	0	0.0	0	0.0
<b>Metabolism and nutrition disorders</b>								
Hyperkalaemia	5	4.2	2	1.7	0	0.0	2	1.7
Hyperuricaemia	4	3.3	0	0.0	0	0.0	0	0.0
Hypocalcaemia	4	3.3	0	0.0	1	0.8	1	0.8
Hypophosphataemia	3	2.5	2	1.7	0	0.0	2	1.7
Dehydration	3	2.5	1	0.8	0	0.0	1	0.8
Gout	3	2.5	0	0.0	0	0.0	0	0.0
Hypomagnesaemia	3	2.5	0	0.0	0	0.0	0	0.0
Hyperglycaemia	2	1.7	0	0.0	0	0.0	0	0.0
<b>Musculoskeletal and connective tissue disorders</b>								
Musculoskeletal chest pain	5	4.2	2	1.7	0	0.0	2	1.7
Osteoarthritis	4	3.3	1	0.8	0	0.0	1	0.8
Joint swelling	3	2.5	0	0.0	0	0.0	0	0.0
Neck pain	3	2.5	0	0.0	0	0.0	0	0.0
Buttock pain	2	1.7	1	0.8	0	0.0	1	0.8
Muscular weakness	2	1.7	0	0.0	0	0.0	0	0.0
Intervertebral disc protrusion	2	1.7	0	0.0	0	0.0	0	0.0

Musculoskeletal stiffness	2	1.7	0	0.0	0	0.0	0	0.0
<b>Nervous system disorders</b>								
Dizziness	5	4.2	0	0.0	0	0.0	0	0.0
Syncope	3	2.5	1	0.8	0	0.0	1	0.8
Sciatica	3	2.5	0	0.0	0	0.0	0	0.0
Tremor	3	2.5	0	0.0	0	0.0	0	0.0
Dysgeusia	2	1.7	0	0.0	0	0.0	0	0.0
Haemorrhage intracranial	2	1.7	1	0.8	1	0.8	2	1.7
Migraine	2	1.7	0	0.0	0	0.0	0	0.0
<b>Psychiatric disorders</b>								
Depression	4	3.3	0	0.0	0	0.0	0	0.0
Anxiety	2	1.7	0	0.0	0	0.0	0	0.0
Confusional state	2	1.7	1	0.8	0	0.0	1	0.8
Sleep disorder	2	1.7	1	0.8	0	0.0	1	0.8
Disorientation	2	1.7	1	0.8	0	0.0	1	0.8
<b>Renal and urinary disorders</b>								
Dysuria	3	2.5	0	0.0	0	0.0	0	0.0
Micturition urgency	3	2.5	0	0.0	0	0.0	0	0.0
Pollakiuria	2	1.7	0	0.0	0	0.0	0	0.0
Haematuria	2	1.7	0	0.0	0	0.0	0	0.0
Nocturia	2	1.7	0	0.0	0	0.0	0	0.0
<b>Respiratory, thoracic and mediastinal disorders</b>								
Epistaxis	5	4.2	1	0.8	0	0.0	1	0.8
Dysphonia	4	3.3	0	0.0	0	0.0	0	0.0
Dyspnoea exertional	3	2.5	0	0.0	0	0.0	0	0.0
Productive cough	3	2.5	0	0.0	0	0.0	0	0.0
Respiratory failure	3	2.5	0	0.0	2	1.7	2	1.7
Pleural effusion	2	1.7	0	0.0	0	0.0	0	0.0
Throat irritation	2	1.7	0	0.0	0	0.0	0	0.0
<b>Skin and subcutaneous tissue disorders</b>								
Erythema	4	3.3	0	0.0	0	0.0	0	0.0
Dry skin	3	2.5	0	0.0	0	0.0	0	0.0
Hyperhidrosis	3	2.5	0	0.0	0	0.0	0	0.0
Rash papular	3	2.5	0	0.0	0	0.0	0	0.0
Urticaria	3	2.5	0	0.0	0	0.0	0	0.0
Rash pruritic	2	1.7	0	0.0	0	0.0	0	0.0
Acne	2	1.7	0	0.0	0	0.0	0	0.0
Skin lesion	2	1.7	0	0.0	0	0.0	0	0.0
Skin odour abnormal	2	1.7	0	0.0	0	0.0	0	0.0
<b>Vascular disorders</b>								
Hypertension	5	4.2	0	0.0	0	0.0	0	0.0
Haematoma	3	2.5	0	0.0	0	0.0	0	0.0
Hot flush	3	2.5	0	0.0	0	0.0	0	0.0
Thrombosis	3	2.5	1	0.8	0	0.0	1	0.8
Hypotension	2	1.7	0	0.0	0	0.0	0	0.0
Flushing	2	1.7	0	0.0	0	0.0	0	0.0

**Table 65 Adverse Reactions in < 1% AP (N=120) (Reviewer's Table)**

Adverse Event	CML-AP N=120							
	All grades	All grades %	Grade 3	Grade 3%	Grade 4	Grade 4%	Grades 3/4	Grade 3/4%
<b>Blood and lymphatic system disorders</b>								
Lymphopenia	1	0.8	1	0.8	0	0.0	1	0.8
Pancytopenia	1	0.8	0	0.0	0	0.0	0	0.0
Coagulopathy	1	0.8	1	0.8	0	0.0	1	0.8
Lymphadenopathy	1	0.8	0	0.0	0	0.0	0	0.0
Microcytic anaemia	1	0.8	0	0.0	0	0.0	0	0.0
Splenomegaly	1	0.8	0	0.0	0	0.0	0	0.0
<b>Cardiac disorders</b>								
Cardiomegaly	1	0.8	0	0.0	0	0.0	0	0.0
Cardiac failure	1	0.8	0	0.0	1	0.8	1	0.8
Pericardial disease	1	0.8	0	0.0	0	0.0	0	0.0
Supraventricular tachycardia	1	0.8	0	0.0	0	0.0	0	0.0
Ventricular dysfunction	1	0.8	1	0.8	0	0.0	1	0.8
Coronary artery disease	0	0.0	0	0.0	0	0.0	0	0.0
Pericarditis	0	0.0	0	0.0	0	0.0	0	0.0
Acute myocardial infarction	0	0.0	0	0.0	0	0.0	0	0.0
<b>Congenital, familial and genetic disorders</b>								
Factor XIII deficiency	1	0.8	1	0.8	0	0.0	1	0.8
Gilbert's syndrome	1	0.8	0	0.0	0	0.0	0	0.0
Ear and labyrinth disorders								
Ear discomfort	1	0.8	0	0.0	0	0.0	0	0.0
Hypoacusis	1	0.8	0	0.0	0	0.0	0	0.0
Tinnitus	1	0.8	0	0.0	0	0.0	0	0.0
Tympanic membrane perforation	1	0.8	0	0.0	0	0.0	0	0.0
<b>Endocrine disorders</b>								
Hyperthyroidism	1	0.8	0	0.0	0	0.0	0	0.0
Thyroid cyst	1	0.8	0	0.0	0	0.0	0	0.0
Thyroiditis	1	0.8	0	0.0	0	0.0	0	0.0
<b>Eye disorders</b>								
Blepharitis	1	0.8	0	0.0	0	0.0	0	0.0
Conjunctival	1	0.8	0	0.0	0	0.0	0	0.0

hyperaemia								
Dry eye	1	0.8	0	0.0	0	0.0	0	0.0
Eye haemorrhage	1	0.8	0	0.0	0	0.0	0	0.0
Eye irritation	1	0.8	0	0.0	0	0.0	0	0.0
Eye swelling	1	0.8	0	0.0	0	0.0	0	0.0
Keratoconjunctivitis sicca	1	0.8	0	0.0	0	0.0	0	0.0
Photophobia	1	0.8	0	0.0	0	0.0	0	0.0
Retinal detachment	1	0.8	1	0.8	0	0.0	1	0.8
Visual disturbance	1	0.8	0	0.0	0	0.0	0	0.0
<b>Gastrointestinal disorders</b>								
Abdominal hernia	1	0.8	0	0.0	0	0.0	0	0.0
Abdominal pain lower	1	0.8	0	0.0	0	0.0	0	0.0
Abdominal wall disorder	1	0.8	0	0.0	0	0.0	0	0.0
Anal discomfort	1	0.8	0	0.0	0	0.0	0	0.0
Anal fissure	1	0.8	0	0.0	0	0.0	0	0.0
Ascites	1	0.8	0	0.0	0	0.0	0	0.0
Dental caries	1	0.8	1	0.8	0	0.0	1	0.8
Dry mouth	1	0.8	0	0.0	0	0.0	0	0.0
Enteritis	1	0.8	0	0.0	0	0.0	0	0.0
Faeces discoloured	1	0.8	0	0.0	0	0.0	0	0.0
Gastrointestinal disorder	1	0.8	0	0.0	0	0.0	0	0.0
Gingival bleeding	1	0.8	0	0.0	0	0.0	0	0.0
Gingival pain	1	0.8	0	0.0	0	0.0	0	0.0
Glossodynia	1	0.8	0	0.0	0	0.0	0	0.0
Haematochezia	1	0.8	0	0.0	0	0.0	0	0.0
Hyperchlorhydria	1	0.8	0	0.0	0	0.0	0	0.0
Melaena	1	0.8	0	0.0	1	0.8	1	0.8
Mouth ulceration	1	0.8	0	0.0	0	0.0	0	0.0
Odynophagia	1	0.8	0	0.0	0	0.0	0	0.0
Oesophageal pain	1	0.8	0	0.0	0	0.0	0	0.0
Oral mucosal petechiae	1	0.8	0	0.0	0	0.0	0	0.0
Pancreatitis	1	0.8	0	0.0	0	0.0	0	0.0
Proctalgia	1	0.8	0	0.0	0	0.0	0	0.0
Rectal haemorrhage	1	0.8	0	0.0	0	0.0	0	0.0
Retroperitoneal haemorrhage	1	0.8	1	0.8	0	0.0	1	0.8
Stomach discomfort	1	0.8	0	0.0	0	0.0	0	0.0
<b>General disorders and administration site conditions</b>								
Multi-organ failure	1	0.8	0	0.0	1	0.8	1	0.8
Axillary pain	1	0.8	0	0.0	0	0.0	0	0.0
Catheter site pain	1	0.8	0	0.0	0	0.0	0	0.0

Chest discomfort	1	0.8	0	0.0	0	0.0	0	0.0
Face oedema	1	0.8	0	0.0	0	0.0	0	0.0
Gait disturbance	1	0.8	0	0.0	0	0.0	0	0.0
Gravitational oedema	1	0.8	0	0.0	0	0.0	0	0.0
Influenza like illness	1	0.8	0	0.0	0	0.0	0	0.0
Nodule	1	0.8	0	0.0	0	0.0	0	0.0
<b>Hepatobiliary disorders</b>								
Cholelithiasis	1	0.8	0	0.0	0	0.0	0	0.0
Hepatotoxicity	1	0.8	1	0.8	0	0.0	1	0.8
Hepatic pain	1	0.8	1	0.8	0	0.0	1	0.8
<b>Immune system disorders</b>								
Drug hypersensitivity	1	0.8	0	0.0	0	0.0	0	0.0
Rhesus incompatibility	1	0.8	0	0.0	0	0.0	0	0.0
Graft versus host disease	0	0.0	0	0.0	0	0.0	0	0.0
<b>Infections and infestations</b>								
Sepsis	1	0.8	0	0.0	1	0.8	1	0.8
Candidiasis	1	0.8	0	0.0	0	0.0	0	0.0
Lobar pneumonia	1	0.8	0	0.0	1	0.8	1	0.8
Localised infection	1	0.8	0	0.0	0	0.0	0	0.0
Oral candidiasis	1	0.8	0	0.0	0	0.0	0	0.0
Bacteraemia	1	0.8	1	0.8	0	0.0	1	0.8
Cystitis	1	0.8	0	0.0	0	0.0	0	0.0
Enterococcal infection	1	0.8	1	0.8	0	0.0	1	0.8
Folliculitis	1	0.8	0	0.0	0	0.0	0	0.0
Fungal infection	1	0.8	0	0.0	0	0.0	0	0.0
Fungal skin infection	1	0.8	0	0.0	0	0.0	0	0.0
Gastroenteritis viral	1	0.8	0	0.0	0	0.0	0	0.0
Herpes zoster	1	0.8	0	0.0	0	0.0	0	0.0
Hordeolum	1	0.8	0	0.0	0	0.0	0	0.0
Lung infection	1	0.8	1	0.8	0	0.0	1	0.8
Lymph gland infection	1	0.8	0	0.0	0	0.0	0	0.0
Mucocutaneous candidiasis	1	0.8	0	0.0	0	0.0	0	0.0
Nail infection	1	0.8	1	0.8	0	0.0	1	0.8
Necrotising fasciitis	1	0.8	1	0.8	0	0.0	1	0.8
Nocardiosis	1	0.8	1	0.8	0	0.0	1	0.8
Onychomycosis	1	0.8	0	0.0	0	0.0	0	0.0
Oral infection	1	0.8	0	0.0	0	0.0	0	0.0
Otitis externa	1	0.8	0	0.0	0	0.0	0	0.0
Otitis media	1	0.8	0	0.0	0	0.0	0	0.0

Paronychia	1	0.8	0	0.0	0	0.0	0	0.0
Perianal abscess	1	0.8	0	0.0	0	0.0	0	0.0
Pneumonia fungal	1	0.8	1	0.8	0	0.0	1	0.8
Scrotal infection	1	0.8	0	0.0	0	0.0	0	0.0
Sexually transmitted disease	1	0.8	0	0.0	0	0.0	0	0.0
Tinea pedis	1	0.8	0	0.0	0	0.0	0	0.0
Tonsillitis	1	0.8	0	0.0	0	0.0	0	0.0
Varicella	1	0.8	1	0.8	0	0.0	1	0.8
Wound infection	1	0.8	0	0.0	0	0.0	0	0.0
<b>Injury, poisoning and procedural complications</b>								
Allergic transfusion reaction	1	0.8	0	0.0	0	0.0	0	0.0
Excoriation	1	0.8	0	0.0	0	0.0	0	0.0
Fall	1	0.8	1	0.8	0	0.0	1	0.8
Joint sprain	1	0.8	0	0.0	0	0.0	0	0.0
Post procedural haematoma	1	0.8	0	0.0	0	0.0	0	0.0
<b>Investigations</b>								
Blood phosphorus decreased	1	0.8	0	0.0	0	0.0	0	0.0
Platelet count increased	1	0.8	1	0.8	0	0.0	1	0.8
Blood bilirubin unconjugated increased	1	0.8	1	0.8	0	0.0	1	0.8
Electrocardiogram QT prolonged	1	0.8	0	0.0	0	0.0	0	0.0
Blood creatine phosphokinase MB increased	1	0.8	1	0.8	0	0.0	1	0.8
Breath sounds abnormal	1	0.8	0	0.0	0	0.0	0	0.0
Haemoglobin increased	1	0.8	0	0.0	0	0.0	0	0.0
Hepatic enzyme increased	1	0.8	0	0.0	0	0.0	0	0.0
Lipase abnormal	1	0.8	0	0.0	0	0.0	0	0.0
Lipase decreased	1	0.8	0	0.0	0	0.0	0	0.0
Monocyte count increased	1	0.8	0	0.0	0	0.0	0	0.0
Troponin T increased	1	0.8	0	0.0	1	0.8	1	0.8
Weight increased	1	0.8	0	0.0	0	0.0	0	0.0
Metabolism and nutrition disorders								

Hyponatraemia	1	0.8	0	0.0	0	0.0	0	0.0
Fluid retention	1	0.8	0	0.0	0	0.0	0	0.0
Hypoglycaemia	1	0.8	0	0.0	0	0.0	0	0.0
Acidosis	1	0.8	0	0.0	0	0.0	0	0.0
Decreased appetite	1	0.8	0	0.0	0	0.0	0	0.0
Hyperphosphataemia	1	0.8	1	0.8	0	0.0	1	0.8
Hypoalbuminaemia	1	0.8	0	0.0	0	0.0	0	0.0
Increased appetite	1	0.8	0	0.0	0	0.0	0	0.0
<b>Musculoskeletal and connective tissue disorders</b>								
Arthritis	1	0.8	0	0.0	0	0.0	0	0.0
Joint range of motion decreased	1	0.8	0	0.0	0	0.0	0	0.0
Mobility decreased	1	0.8	0	0.0	0	0.0	0	0.0
Pain in jaw	1	0.8	0	0.0	0	0.0	0	0.0
Sacroiliitis	1	0.8	0	0.0	0	0.0	0	0.0
Tendonitis	1	0.8	0	0.0	0	0.0	0	0.0
<b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b>								
Metastatic malignant melanoma	1	0.8	0	0.0	1	0.8	1	0.8
Seborrhoeic keratosis	1	0.8	0	0.0	0	0.0	0	0.0
<b>Nervous system disorders</b>								
Hypoaesthesia	1	0.8	0	0.0	0	0.0	0	0.0
Aphasia	1	0.8	1	0.8	0	0.0	1	0.8
Brain oedema	1	0.8	1	0.8	0	0.0	1	0.8
Cervical root pain	1	0.8	0	0.0	0	0.0	0	0.0
Convulsion	1	0.8	1	0.8	0	0.0	1	0.8
Disturbance in attention	1	0.8	1	0.8	0	0.0	1	0.8
Dizziness postural	1	0.8	0	0.0	0	0.0	0	0.0
Dysstasia	1	0.8	1	0.8	0	0.0	1	0.8
Lethargy	1	0.8	1	0.8	0	0.0	1	0.8
Muscle contractions involuntary	1	0.8	0	0.0	0	0.0	0	0.0
Paraesthesia	1	0.8	0	0.0	0	0.0	0	0.0
Restless legs syndrome	1	0.8	0	0.0	0	0.0	0	0.0
Sinus headache	1	0.8	0	0.0	0	0.0	0	0.0
Somnolence	1	0.8	0	0.0	0	0.0	0	0.0
<b>Psychiatric disorders</b>								
Loss of libido	1	0.8	0	0.0	0	0.0	0	0.0
Nightmare	1	0.8	0	0.0	0	0.0	0	0.0
Restlessness	1	0.8	0	0.0	0	0.0	0	0.0
<b>Renal and urinary disorders</b>								
Renal failure	1	0.8	1	0.8	0	0.0	1	0.8
Chromaturia	1	0.8	0	0.0	0	0.0	0	0.0

Urinary incontinence	1	0.8	0	0.0	0	0.0	0	0.0
<b>Reproductive system and breast disorders</b>								
Breast cyst	1	0.8	0	0.0	0	0.0	0	0.0
Breast pain	1	0.8	0	0.0	0	0.0	0	0.0
Erectile dysfunction	1	0.8	0	0.0	0	0.0	0	0.0
Gynaecomastia	1	0.8	0	0.0	0	0.0	0	0.0
Menorrhagia	1	0.8	1	0.8	0	0.0	1	0.8
Metrorrhagia	1	0.8	0	0.0	0	0.0	0	0.0
Nipple swelling	1	0.8	0	0.0	0	0.0	0	0.0
Ovarian cyst	1	0.8	0	0.0	0	0.0	0	0.0
Prostatic disorder	1	0.8	0	0.0	0	0.0	0	0.0
Testicular pain	1	0.8	0	0.0	0	0.0	0	0.0
<b>Respiratory, thoracic and mediastinal disorders</b>								
Interstitial lung disease	1	0.8	0	0.0	0	0.0	0	0.0
Pleurisy	1	0.8	0	0.0	0	0.0	0	0.0
Pulmonary oedema	1	0.8	0	0.0	1	0.8	1	0.8
Pleuritic pain	1	0.8	0	0.0	0	0.0	0	0.0
Hiccups	1	0.8	0	0.0	0	0.0	0	0.0
Increased upper airway secretion	1	0.8	0	0.0	0	0.0	0	0.0
Pneumonia aspiration	1	0.8	0	0.0	0	0.0	0	0.0
Pneumonitis	1	0.8	1	0.8	0	0.0	1	0.8
Pulmonary artery wall hypertrophy	1	0.8	1	0.8	0	0.0	1	0.8
Rales	1	0.8	0	0.0	0	0.0	0	0.0
Rhinorrhoea	1	0.8	0	0.0	0	0.0	0	0.0
Sleep apnoea syndrome	1	0.8	0	0.0	0	0.0	0	0.0
Wheezing	1	0.8	0	0.0	0	0.0	0	0.0
<b>Skin and subcutaneous tissue disorders</b>								
Rash generalised	1	0.8	0	0.0	0	0.0	0	0.0
Exfoliative rash	1	0.8	0	0.0	0	0.0	0	0.0
Swelling face	1	0.8	0	0.0	0	0.0	0	0.0
Blister	1	0.8	0	0.0	0	0.0	0	0.0
Dermatitis	1	0.8	0	0.0	0	0.0	0	0.0
Drug eruption	1	0.8	0	0.0	0	0.0	0	0.0
Ecchymosis	1	0.8	0	0.0	0	0.0	0	0.0
Heat rash	1	0.8	0	0.0	0	0.0	0	0.0
Periorbital oedema	1	0.8	0	0.0	0	0.0	0	0.0
Pruritus generalised	1	0.8	0	0.0	0	0.0	0	0.0
Rash erythematous	1	0.8	0	0.0	0	0.0	0	0.0
Rash macular	1	0.8	0	0.0	0	0.0	0	0.0
Skin burning sensation	1	0.8	0	0.0	0	0.0	0	0.0

Skin discolouration	1	0.8	0	0.0	0	0.0	0	0.0
Skin exfoliation	1	0.8	0	0.0	0	0.0	0	0.0
Skin inflammation	1	0.8	0	0.0	0	0.0	0	0.0
Skin toxicity	1	0.8	0	0.0	0	0.0	0	0.0
<b>Vascular disorders</b>								
Hypertensive crisis	1	0.8	0	0.0	0	0.0	0	0.0
Erythromelalgia	1	0.8	0	0.0	1	0.8	1	0.8

### 7.1.7 Laboratory Findings

Laboratory abnormalities were reviewed in all patients eligible for the safety evaluation. Differences with the applicant was due to the patients removed by the applicant from the denominator and numerator. In the FDA analyses, only patients who had an abnormality at baseline was not included in the numerator for that abnormality with the same grade or lower.

According to the applicant, these overlap with the adverse events. They state that the only laboratory abnormalities that appear in the AEV dataset are those which required medical intervention and was therefore considered to be an AE. According to the applicant, the data in Table 3 have been derived from the datasets LRS (1) (2) (3).xpt. Table 3 includes all lab abnormalities including any that are also reported as an adverse event (lab abnormalities that required a medical intervention). The lab abnormalities reported as an adverse event also appear in the AEV dataset. Therefore there is some duplication between the adverse event data and the laboratory abnormalities data.

### 120-Day Safety Update

In patients with CML-CP, the common clinically relevant grade 3/4 newly occurring or worsening laboratory abnormalities were neutropenia (28%), thrombocytopenia (27%), elevated lipase (14%), hyperglycemia (11%), hypophosphatemia (10%), elevated bilirubin (8.8%) and anemia (8.5%). Electrolyte abnormalities were also seen.

In patients with CML-AP, the common clinically relevant grade 3/4 newly occurring or worsening laboratory abnormalities were thrombocytopenia (40%), neutropenia (37.5%), anemia (27.5%), elevated lipase (15.8%), hypophosphatemia (12.5%), elevated bilirubin (10%) and hyperglycemia (5%). Electrolyte abnormalities were also seen.

The table below shows the newly occurring or worsening laboratory abnormalities in patients with CML-CP and CML-AP.

**Table 66 Newly Occurring or Worsening Laboratory Abnormalities in CML-CP and CML-AP**  
(Reviewer's Table)

Laboratory Test	CML-CP N=318				CML-AP N=120			
	All grades	All grades %	Grade 3/4	Grade 3/4 %	All grades	All grade %	Grade 3/4	Grade 3/4 %
<b>Hematology</b>								
Thrombocytopenia	173	54.4	86	27.0	78	65.0	48	40.0
Anemia	164	51.6	27	8.5	77	64.2	33	27.5
Neutropenia	156	49.1	89	28.0	67	55.8	45	37.5
<b>Biochemistry</b>								
Hypophosphatemia	136	42.8	32	10.1	48	40.0	15	12.5
Hypocalcemia	130	40.9	2	0.6	63	52.5	5	4.2
Hyponatremia	70	22.0	10	3.1	31	25.8	3	2.5
Decreased albumin	65	20.4	4	1.3	29	24.2	1	0.8
Hypokalemia	59	18.6	4	1.3	27	22.5	6	5.0
Hypomagnesemia	41	12.9	0	0.0	17	14.2	0	0.0
Hypoglycemia	39	12.3	1	0.3	7	5.8	0	0.0
Elevated bilirubin (total)	222	69.8	28	8.8	79	65.8	12	10.0
Hyperglycemia	212	66.7	35	11.0	65	54.2	6	5.0
Elevated SGPT	197	61.9	12	3.8	62	51.7	3	2.5
Elevated SGOT	147	46.2	4	1.3	43	35.8	1	0.8
Elevated lipase	128	40.3	46	14.5	43	35.8	19	15.8
Elevated alkaline phosphatase	91	28.6	2	0.6	43	35.8	3	2.5
Hyperkalemia	82	25.8	13	4.1	29	24.2	4	3.3
Hypernatremia	57	17.9	4	1.3	16	13.3	0	0.0
Elevated creatinine	56	17.6	2	0.6	21	17.5	0	0.0
Elevated amylase	53	16.7	5	1.6	16	13.3	2	1.7
Hypermagnesemia	48	15.1	5	1.6	9	7.5	1	0.8
Hypercalcemia	33	10.4	4	1.3	9	7.5	0	0.0

Source: A\_LRS.xpt

The table below shows the newly occurring or worsening laboratory abnormalities in patients with CML-CP and CML-AP with the grades 3 and 4 shown separately. In the CML-CP population, grade 3 thrombocytopenia was 9.7% and grade 4 thrombocytopenia was 17.3%. In the CML-AP population, grade 3 thrombocytopenia was 10.8 % and grade 4 thrombocytopenia was 29.2%; grade 3 neutropenia was 12.5% and grade 4 neutropenia was 25%.

**Table 67 Grade 3 and 4 Newly Occurring or Worsening Laboratory Abnormalities in CML-CP and CML-AP (Reviewer's Table)**

Laboratory Test	CML-CP N=318				CML-AP N=120			
	Grade 3	Grade 3 %	Grade 4	Grade 4 %	Grade 3	Grade 3 %	Grade 4	Grade %
<b>Hematology</b>								
Thrombocytopenia	31	9.7	55	17.3	13	10.8	35	29.2
Anemia	23	7.2	4	1.3	27	22.5	6	5.0
Neutropenia	46	14.5	43	13.5	15	12.5	30	25.0
<b>Biochemistry</b>								
Hypophosphatemia	29	9.1	3	0.9	13	10.8	2	1.7
Hypocalcemia	0	0.0	2	0.6	3	2.5	2	1.7
Hyponatremia	9	2.8	1	0.3	3	2.5	0	0.0
Decreased albumin	4	1.3	0	0.0	1	0.8	0	0.0
Hypokalemia	3	0.9	1	0.3	5	4.2	1	0.8
Hypomagnesemia	0	0.0	0	0.0	0	0.0	0	0.0
Hypoglycemia	1	0.3	0	0.0	0	0.0	0	0.0
Elevated bilirubin (total)	26	8.2	2	0.6	11	9.2	1	0.8
Hyperglycemia	32	10.1	3	0.9	6	5.0	0	0.0
Elevated SGPT	12	3.8	0	0.0	3	2.5	0	0.0
Elevated SGOT	4	1.3	0	0.0	1	0.8	0	0.0
Elevated lipase	39	12.3	7	2.2	16	13.3	3	2.5
Elevated alkaline phosphatase	2	0.6	0	0.0	3	2.5	0	0.0
Hyperkalemia	11	3.5	2	0.6	3	2.5	1	0.8
Hypernatremia	2	0.6	2	0.6	0	0.0	0	0.0
Elevated creatinine	0	0.0	2	0.6	0	0.0	0	0.0
Elevated amylase	5	1.6	0	0.0	2	1.7	0	0.0
Hypermagnesemia	5	1.6	0	0.0	1	0.8	0	0.0
Hypercalcemia	1	0.3	3	0.9	0	0.0	0	0.0

Source: A\_LRS.xpt

*Reviewer's Comments:*

*There was a large difference between the laboratory AE rate based on the AE dataset and LRS datasets. The applicant was queried and they stated that laboratory abnormalities that required a medical intervention were also reported as an adverse event. The laboratory datasets were used to derive the laboratory abnormalities.*

*In both CML-CP and CML-AP populations, grade 4 thrombocytopenia was higher than the grade 3 thrombocytopenia. In the CML-AP patient population, grade 4 neutropenia was higher than grade 3 neutropenia. This information should be included in the label to help physicians in monitoring the patients. Our consultant agreed.*

#### 7.1.7.1 Overview of laboratory testing in the development program

The summary of laboratory evaluations was presented with respect to three groups of laboratory tests (hematology, serum chemistry, and cardiac enzymes). Laboratory values were converted to SI units and analyzed using NCI CTC grades version 3. Notably abnormal laboratory values (new or worsening from baseline based on CTC grades) were summarized by laboratory parameters for hematology, biochemistry and cardiac enzymes. Shift tables are presented comparing baseline laboratory result (CTC grade) with the worst result (expressed in NCI CTC grades) during study for hematology, biochemistry and cardiac enzymes. Patient with abnormal laboratory values were listed and values outside the normal ranges were flagged.

Times to grade 3 or 4 neutropenia, thrombocytopenia, leucopenia, anemia or liver toxicity were calculated as well as the duration (time since grade 3 or 4 until grade = 2 occurred again) of all episodes of these grade 3 or 4 laboratory abnormalities.

#### 7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Assessment of adverse events related to laboratory abnormalities was performed using the safety population of Study 2101. Arms 3 and 4, Group A were the arms that enrolled imatinib-resistant or –intolerant CML patients in the chronic phase and accelerated phase at the proposed dose for marketing. This was a single-arm trial and there was no control arm. These two arms were not pooled due to the variable populations in the two indications.

#### 7.1.7.3 Standard analyses and explorations of laboratory data

At baseline, more than 95% of patients in each treatment arm had potentially clinically important laboratory abnormalities.

As discussed in the analyses of common and grade 3/4 TEAEs above, certain laboratory abnormalities, including decreased lymphocyte count, decreased platelet count, decreased neutrophil count, decreased hemoglobin, increased glucose elevated lipase, increased blood bilirubin and abnormal electrolytes occurred more commonly. The relative incidence of selected potentially clinically important changes in laboratory parameters is shown in the table in Section 7.1.7.

#### 7.1.7.4 Additional analyses and explorations

See Section 7.2.2.

#### 7.1.7.5 Special assessments

In a pharmacogenetic analysis of UGT1A1 polymorphism and hyperbilirubinemia, it was observed that patients with UGT1A1 7/7 genotype treated with nilotinib were observed to have increased elevations in bilirubin relative to the 6/6 or 6/7 patients. Large increases in  $\geq$  grade 3 hyperbilirubinemia were seen in the 7/7 genotype (58%) relative to 6/7 (4.5%) or 6/6 (4.9%) genotypes. Only slight increases were seen for  $\geq$  grade 3 ALT increases. Other transaminases (AST or ALP) did not recapitulate the changes observed for ALT.

The study results indicate that UGT1A1 7/7 genotype patients are at an increased risk for hyperbilirubinemia.

#### 7.1.8 Vital Signs

##### 7.1.8.1 Overview of vital signs testing in the development program

Vital signs which were considered abnormal by the investigator were graded as per NCI CTC AE version 3.0.

##### 7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

No applicable.

##### 7.1.8.3 Standard analyses and explorations of vital signs data

Summary analyses of vital signs and body weight were not provided by the applicant.

##### 7.1.8.4 Additional analyses and explorations

Not applicable.

#### 7.1.9 Electrocardiograms (ECGs)

##### 7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

The applicant submitted ECGs to the ECG Warehouse. Due to the prolongation of QTc interval caused by nilotinib, the QT-Interdisciplinary review Team was consulted who reviewed the ECGs submitted. Quantitative ECG variables were summarized using descriptive statistics at each time point.

#### 7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Not applicable.

#### 7.1.9.3 Standard analyses and explorations of ECG data

The number and percentage of patients who had an increase from baseline in QTc interval (using Fridericia's formula) of > 30 msec and > 60 msec were presented. The number and percentage of patients with any post-baseline QTc values of > 480 msec and > 500 msec were also presented. These are shown in the table below.

A relatively high number of patients experienced QTcF prolongations from baseline of > 30 msec (33.0% of CML-CP patients, 40.8% of CML-AP patients). QTcF increases of > 60 msec were reported in 1.9% of CML-CP and 2.5% of CML-AP patients. The incidence of absolute QTcF values > 500 msec was < 1%.

**Table 68 Patients with QTcF intervals, CML-CP and CML-AP (Applicant's Table)**

ECG Parameter	CML-CP (2101E2)	CML-AP (2101E1)	Total
	N = 318 n (%)	N = 120 n (%)	N = 438 n (%)
Increase from baseline > 30 msec	105 (33.0)	49 (40.8)	154 (35.2)
Increase from baseline > 60 msec	6 (1.9)	3 (2.5)	9 (2.1)
Absolute value > 450 msec	38 (11.9)	14 (11.7)	52 (11.9)
Absolute value > 480 msec	5 (1.6)	0	5 (1.1)
Absolute value > 500 msec	3 (0.9)	0	3 (0.7)

n = number of patients who meet the criterion for at least one post-baseline value.

Source: Table 6-2, 120-day Safety Update

#### 7.1.9.4 Additional analyses and explorations

Not applicable.

#### 7.1.10 Immunogenicity

Immunogenicity studies have not been performed with nilotinib.

#### 7.1.11 Human Carcinogenicity

No animal carcinogenicity study has been conducted with nilotinib.

#### 7.1.12 Special Safety Studies

A phase 1 study in healthy volunteers to assess the effect of nilotinib on QT/QTc interval was initiated shortly after the reporting of sudden deaths. Nilotinib was found to significantly prolong the QT/QTc interval.

#### 7.1.13 Withdrawal Phenomena and/or Abuse Potential

Nilotinib is not associated with withdrawal or abuse potential.

#### 7.1.14 Human Reproduction and Pregnancy Data

Nilotinib can cause fetal harm when administered to a pregnant woman. In a study where male and female rats were treated with nilotinib at oral doses 20-180 mg/kg/day (approximately 1.6-6.6 fold the AUC in patients at the recommended human dose) during the pre-mating and mating periods and then mated, and dosing of pregnant rats continued through gestation day (GD) 6, nilotinib increased post-implantation loss and early resorption, and decreased the number of viable fetuses and litter size at all doses tested.

Nilotinib was studied for effects on embryo-fetal development in pregnant rats (GD 6-17) and rabbits (GD 7-20) given oral doses of 10, 30, 100 mg/kg, and 30, 100, 300 mg/kg/day, respectively. In rats, nilotinib at doses of 100 mg/kg/day (approximately 5.7 fold the AUC in patients at the recommended human dose) was associated with maternal toxicity (decreased gestation weight, gravid uterine weight, net weight gain, and food consumption). Nilotinib at doses  $\geq 30$  mg/kg/day resulted in embryo-fetal toxicity as shown by increased resorption and post-implantation loss, and at 100 mg/kg/day a decrease in viable fetuses. Skeletal malformations and variations were also observed at doses  $\geq 30$  mg/kg/day (approximately 2-fold the AUC in patients at the recommended human dose). In rabbits, maternal toxicity at 300 mg/kg/day (0.48 fold the AUC in patients at the recommended human dose) was associated with mortality abortion, decreased gestation weights and decreased food consumption. Embryonic toxicity (increased resorption) and minor skeletal anomalies were observed at a dose of 300 mg/kg/day. Nilotinib is not considered teratogenic.

There are no adequate and well-controlled studies with nilotinib in pregnant women. Women of childbearing potential should be advised to avoid becoming pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential risk to the fetus.

#### 7.1.15 Assessment of Effect on Growth

Not applicable.

#### 7.1.16 Overdose Experience

There is no specific treatment for nilotinib overdose. Nilotinib has been administered to patients with cancer in phase 1 trials with repeated doses as high as 1200 mg per day. The risk of several serious adverse events, including hepatotoxicity, hyperbilirubinemia and myelosuppression is increased with doses of nilotinib greater than 2400 mg bid.

#### 7.1.17 Postmarketing Experience

Not applicable. Nilotinib has not been marketed before in any country.

### 7.2 Adequacy of Patient Exposure and Safety Assessments

#### 7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

##### 7.2.1.1 Study type and design/patient enumeration

The primary data sources for evaluating safety was the single Study 2101 including the treatment arms in CML-CP and CML-AP patients. There were no randomized controlled trials. This study is therefore inadequate to provide useful comparative data. The safety database therefore consists of approximately 438 patients who had received nilotinib at the phase 2 dose and schedule.

See Sections 4.1, 4.2.

##### 7.2.1.2 Demographics

The age and gender distributions of patients were appropriate to the disease under study. Almost all patients across the clinical program were Caucasian. Conclusions about the safety of dasatinib in races other than Caucasian cannot be drawn from this database.

See Section 6.1.

##### 7.2.1.3 Extent of exposure (dose/duration)

There were 438 patients with CML-CP and CML-AP studied and are included in the safety analysis. About 42% patients on the study in these two arms had received between 6-12 months of nilotinib at the time of the 120-day safety update, about 12% had received less than 3 months and 15.8% had received greater than 6 months of nilotinib.

## CML-CP

14 patients received a treatment duration of < 30 days (range: 3-27 days). Dose interruption occurred in 6/14 patients, dose reduction in 3/14 patients and either occurred in 7/14 patients.

15 /132 patients received a dose of > 400 bid. Dose interruption occurred in 4/15 patients, dose reduction in 2/15 patients and either in 5/15 patients.

Common Grade 3/4 AEs that lead to dose adjustments and interruptions suspected related to nilotinib were thrombocytopenia (15%) and neutropenia (6.4%).

The table below shows the other AEs leading to dose adjustments and interruptions suspected related to nilotinib treatment.

**Table 69 Adverse events Leading to Dose Adjustments or Interruptions Suspected treatment related CML-CP N=282 (Reviewer's Table)**

Adverse Event	All grades	All grades %	Grades 3/4	Grades 3/4 %
<b>Blood and lymphatic system disorders</b>				
Thrombocytopenia	45	16.0	43	15.2
Neutropenia	19	6.7	18	6.4
Leukopenia	3	1.1	2	0.7
Pancytopenia	2	0.7	1	0.4
Anaemia	1	0.4	0	0.0
<b>Cardiac disorders</b>				
Angina pectoris	1	0.4	1	0.4
Atrial fibrillation	1	0.4	1	0.4
Pericardial effusion	1	0.4	1	0.4
Pericarditis	1	0.4	1	0.4
Ventricular extrasystoles	1	0.4	0	0.0
<b>Eye disorders</b>				
Diplopia	1	0.4	0	0.0
Visual acuity reduced	1	0.4	0	0.0
<b>Gastrointestinal disorders</b>				
Nausea	4	1.4	1	0.4
Vomiting	4	1.4	1	0.4
Diarrhoea	2	0.7	2	0.7
Abdominal discomfort	1	0.4	0	0.0
Abdominal distension	1	0.4	0	0.0
Pancreatitis	1	0.4	0	0.0
<b>General disorders and administration site conditions</b>				

Asthenia	1	0.4	0	0.0
Fatigue	1	0.4	0	0.0
Mass	1	0.4	0	0.0
Pyrexia	1	0.4	0	0.0
<b>Hepatobiliary disorders</b>				
Hyperbilirubinaemia	4	1.4	3	1.1
<b>Infections and infestations</b>				
Oral candidiasis	1	0.4	1	0.4
<b>Injury, poisoning and procedural complications</b>				
Subdural haemorrhage	1	0.4	1	0.4
<b>Investigations</b>				
Lipase increased	7	2.5	7	2.5
Blood bilirubin increased	6	2.1	3	1.1
Platelet count decreased	5	1.8	4	1.4
Blood amylase increased	3	1.1	2	0.7
Alanine aminotransferase increased	2	0.7	1	0.4
Blood creatine phosphokinase increased	1	0.4	1	0.4
Haptoglobin decreased	1	0.4	1	0.4
Liver function test abnormal	1	0.4	1	0.4
Neutrophil count decreased	1	0.4	1	0.4
<b>Metabolism and nutrition disorders</b>				
Dehydration	1	0.4	0	0.0
<b>Musculoskeletal and connective tissue disorders</b>				
Arthralgia	4	1.4	2	0.7
Bone pain	2	0.7	2	0.7
Musculoskeletal stiffness	1	0.4	0	0.0
Pain in extremity	1	0.4	1	0.4
<b>Nervous system disorders</b>				
Headache	4	1.4	1	0.4
Hyperaesthesia	1	0.4	0	0.0
Optic neuritis	1	0.4	0	0.0
Tremor	1	0.4	0	0.0
<b>Respiratory, thoracic and mediastinal disorders</b>				
Cough	1	0.4	1	0.4
Dyspnoea	1	0.4	1	0.4
Pleural effusion	1	0.4	0	0.0
<b>Skin and subcutaneous tissue disorders</b>				
Rash	8	2.8	4	1.4
Pruritus	2	0.7	1	0.4
Dry skin	1	0.4	1	0.4
Ecchymosis	1	0.4	0	0.0
Erythema	1	0.4	1	0.4

Exfoliative rash	1	0.4	1	0.4
Generalised erythema	1	0.4	0	0.0
Palmar-plantar erythrodysesthesia syndrome	1	0.4	1	0.4
Rash generalised	1	0.4	1	0.4
Rash pruritic	1	0.4	1	0.4
Skin burning sensation	1	0.4	0	0.0
Toxic skin eruption	1	0.4	0	0.0
Vascular disorders				
Flushing	1	0.4	0	0.0

Source: AE\_AEV.xpt

### CML-AP

9/64 patients received > 600 bid. 3/9 had dose interruptions, 4/9 dose reductions and 5 either.

4/64 patients had a treatment duration 2-7 days. All neither had dose interruptions or reductions.

Common Grade 3/4 AEs that lead to dose adjustments and interruptions suspected related to nilotinib were thrombocytopenia (19%), neutropenia (15%).

The table below shows the other AEs leading to dose adjustments and interruptions suspected related to nilotinib treatment.

**Table 70 Adverse events Leading to Dose Adjustments or Interruptions Suspected treatment related CML-AP N=89 (Reviewer's Table)**

Adverse Event	All grades	All grades %	grades 3/4	Grades 3/4 %
<b>Blood and lymphatic system disorders</b>				
Thrombocytopenia	18	20.2	17	19.1
Neutropenia	14	15.7	13	14.6
Leukopenia	3	3.4	2	2.2
Febrile neutropenia	2	2.2	1	1.1
Anaemia	1	1.1	1	1.1
Pancytopenia	1	1.1	0	0.0
<b>Endocrine disorders</b>				
Hyperthyroidism	1	1.1	0	0.0
<b>General disorders and administration site conditions</b>				
Pyrexia	2	2.2	1	1.1
<b>Hepatobiliary disorders</b>				
Hyperbilirubinaemia	1	1.1	0	0.0

<b>Infections and infestations</b>				
Influenza	1	1.1	0	0.0
<b>Investigations</b>				
Lipase increased	5	5.6	5	5.6
Platelet count decreased	3	3.4	3	3.4
Blood amylase increased	2	2.2	2	2.2
Neutrophil count decreased	2	2.2	2	2.2
Blood bilirubin increased	1	1.1	0	0.0
Blood bilirubin unconjugated increased	1	1.1	1	1.1
Blood creatine phosphokinase increased	1	1.1	1	1.1
Haemoglobin decreased	1	1.1	1	1.1
Troponin increased	1	1.1	1	1.1
White blood cell count decreased	1	1.1	0	0.0
<b>Musculoskeletal and connective tissue disorders</b>				
Musculoskeletal chest pain	1	1.1	1	1.1
Myalgia	1	1.1	1	1.1
<b>Nervous system disorders</b>				
Migraine	1	1.1	0	0.0
<b>Skin and subcutaneous tissue disorders</b>				
Rash	1	1.1	0	0.0

Source: AE\_AEV.xpt

### 120-Day Update

#### **CML-CP**

The average daily dose of nilotinib for CML-CP patients in the two enrollments is similar as shown in the applicant's table below.

**Table 71 Average Daily Dose CML-CP (Applicant's Table)**

No prior TKI except imatinib	Primary enrollment	Additional enrollment	Total
<b>Actual average dose intensity (mg/days)</b>			
N	132	148	280
mean ± SD	689.5 ± 215.20	704.7 ± 191.08	697.5
Median	798.1	793.6	796.6
Range	151.0 – 1106.2	191.9 – 1111.5	151.0 – 1111.5

The duration of exposure to nilotinib in the CML-CP patients (regardless of dose reduction or interruption) is presented in the table below for the primary and additional enrollments and overall. As of the cut-off date for the 120-day update, the median duration of exposure to nilotinib was 355.0 days in the primary enrollment, 244.5 days in the additional enrollment, and 260.5 days overall. Fifty-two (46.8%) of patients in the primary enrollment received nilotinib for 12 months or more and 101 (78.3%) of patients in the additional enrollment received nilotinib for 6 to <12 months. The shorter duration of exposure to nilotinib in the additional enrollment is consistent with the shorter duration of efficacy follow-up for these patients (6 months or more, compared with 10 months or more for the primary enrollment).

**Table 72 Duration of Exposure CML-CP (Applicant's Table)**

No prior TKI except imatinib	Primary enrollment	Additional enrollment	Total
<b>Duration of exposure (days)</b>			
N	132	148	280
Mean ±SD	287.7 ± 157.02	215.4 ± 95.57	249.5 ± 133.02
Median	355.0	244.5	260.5
Range	3.0 – 502.0	1.0 – 323.0	1.0 – 502.0
< 1 month	13 (9.8)	12 (8.1)	25 (8.9)
1 - < 3 months	15 (11.4)	12 (8.1)	27 (9.6)
3 - < 6 months	14 (10.6)	11 (7.4)	25 (8.9)
6 - < 12 months	33 (25.0)	113 (76.4)	146 (52.1)
≥ 12 months	57 (43.2)	0 (0.0)	57 (20.4)

Source: Table 4-4, SCE, 120-DayUpdate

### CML-AP

The median daily dose of nilotinib for CML-AP patients in the two enrollments is shown in the table below.

**Table 73 Average Daily Dose CML-AP (Applicant's Table)**

No prior TKI except imatinib	Primary enrollment	Additional enrollment	Total
<b>Actual average dose intensity (mg/days)</b>			
N	64	41	105
Mean± SD	676.3 ± 205.70	713.1 ± 228.13	690.7 ± 214.41
Median	786.8	790.0	790.0
Range	247.0 – 1149.0	145.4 – 1098.3	145.4 – 1149.0

Source: Table 4-10, SCE, 120-Day Update

The duration of exposure to nilotinib in CML-AP patients (regardless of dose reduction or interruption) is presented in the table below for the primary and additional enrollments and overall. As of the cut-off date for the 12-month day update, the median duration of exposure to nilotinib was 207.5 days in the primary enrollment, 136.0 days in the additional enrollment, and 169.0 days overall. Nine (17.6%) of the patients in the primary enrollment received nilotinib for 12 months or more and 11 (36.7%) of the patients in the additional enrollment received nilotinib for >6 to <12 months. The shorter duration of exposure to nilotinib in the additional enrollment is consistent with the shorter duration of efficacy follow-up for these patients (4 months or more, compared with 8 months or more for the primary enrollment).

**Table 74 Duration of Exposure CML-CP (Applicant's Table)**

No prior TKI except imatinib	Primary enrollment	Additional enrollment	Total
<b>Duration of exposure (days)</b>			
N	64	41	105
Mean ±SD	221.6 ± 137.21	133.3 ± 74.87	187.1 ± 124.24
Median	207.5	136.0	169.0
Range	2.0 – 503.0	4.0 – 249.0	503.0
< 1 month	4 (6.3)	5 (12.2)	9 (8.6)
1 - < 3 months	8 (12.5)	7 (17.1)	15 (14.3)
3 - < 6 months	17 (26.6)	15 (36.6)	32 (30.5)
6 - < 12 months	23 (35.9)	14 (34.1)	37 (35.2)
≥ 12 months	12 (18.8)	0 (0.0)	12 (11.4)

## 7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

### 7.2.2.1 Other studies

The primary safety review has been limited to data from the two populations of the single-arm phase 2 trial and limited to the imatinib-resistant or –intolerant CML-CP and CML-AP populations. The phase 1 trial used varying doses and there were no appropriate controls in this or other studies of nilotinib included in the safety database. The other clinical studies included in the safety database have been used for investigation of rare, serious toxicities such as sudden deaths.

### 7.2.2.2 Postmarketing experience

Not applicable. Nilotinib has not been marketed before in any country.

### 7.2.2.3 Literature

See Section 8.6.

## 7.2.3 Adequacy of Overall Clinical Experience

The overall clinical experience with nilotinib is sufficient to perform the safety review. The registration trial was a single-arm, open-label, trial with two populations, CML-CP and CML-AP. The dose and duration of exposure are detailed in the tables incorporated in Section 7.2.1.3. The design and exposure were adequate to assess safety in the intended treatment population of patients with imatinib-resistant or-intolerant CML-CP and CML-AP.

### *Reviewer Comment:*

*The study eligibility criteria selected for patients who were imatinib resistant or –intolerant is likely to be representative of the patient population who will receive nilotinib once marketed.*

## 7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Special animal and in vitro testing was adequate.

## 7.2.5 Adequacy of Routine Clinical Testing

The nature and timing of clinical and laboratory monitoring of patients for adverse event data collection are detailed in Section 7.1 and were adequate for the expected toxicities of treatment with nilotinib.

#### 7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Overall, the metabolic, clearance and interaction workup was adequate. One outstanding clinical pharmacology study will be the subject of a phase 4 commitment: submission of the ongoing hepatic impairment study.

#### 7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

A cardiac safety study in healthy volunteers to assess the effect of nilotinib on QT/QTc interval was initiated shortly after sudden deaths were reported. Nilotinib prolongs QT interval. Administration of Tasigna was associated with concentration-dependent QT prolongation. At exposures that were 26% lower than the therapeutic exposures observed in patients, the maximum mean placebo-adjusted QTcF change from baseline was 18 msec (1-sided 95% upper CI: 26 msec).

The applicant has appropriately identified the following potential safety concerns in the nilotinib development program: risk of QT/QTc prolongation, CYP drug-drug interactions, drug-food interactions, myelosuppression, elevated lipase, and fluid retention. A pharmacovigilance and risk minimization plan for the risk of QT prolongation, drug-drug interaction and drug-food interaction has been submitted by the applicant. A medication guide for these risks have been submitted by the applicant.

In addition to the risks identified by the applicant, risks of sudden deaths, hyperbilirubinemia and hepatic transaminase elevations and electrolyte abnormalities should also be included in the pharmacovigilance and risk minimization plan.

A study of nilotinib in patients with hepatic impairment will be requested.

Caution is recommended in patients with hepatic impairment and patients with a history of pancreatitis.

See section 7.1.9.

#### 7.2.8 Assessment of Quality and Completeness of Data

The quality and completeness of data for Study 2101 in CML-CP and CML-AP were adequate for the review. AEs were reported for 317 out of 318 patients in the 120-day updated safety population for CML-CP. AEs were reported for 118 out of 120 patients in the 120-day updated safety population for CML-AP. Reported AEs had been converted into preferred terms for most total AEs on study and CTC grading assigned.

Laboratory values were reported for all the 318 CML-CP patients and 120 CML-AP patients. Among the 13600 clinically relevant laboratory abnormalities reviewed, seventy one albumin values and one platelet count value were not assigned a CTC grade.

Thus, missing data were few and felt unlikely by the reviewer to alter the safety conclusions in a meaningful way.

### 7.2.9 Additional Submissions, Including Safety Update

The 120-day Safety Update submitted by the applicant on 01/26/2007 included safety analyses from Study 2101 for CML-CP patients that became available after the original data cutoff of 07/04//2006 through the safety update data cutoff date of 09/04/2006. The 120-day Safety Update submitted on 01/26/2007 also included safety data from Study 2101 for CML-AP patients that became available after the original data cutoff of 07/23//2006 through the safety update data cutoff date of 09/23/2006. The 120-day Safety Update submission did not provide any datasets for review. Upon request by the Agency, the 120-day Update safety datasets were subsequently submitted on 03/13/2007. Case report forms were provided for any patients who newly met a criterion of death, discontinuation due to an adverse event, or occurrence of an SAE.

#### *Reviewer's Comments:*

*Due to the inclusion in the 120-day Safety Update of the primary as well a significant number of additional patients enrolled, the 120-day Safety Update datasets were reviewed in detail. Details are presented in the relevant sections above.*

## **7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions**

Adverse events which were most likely to be disease related included myelosuppression (neutropenia, thrombocytopenia, and anemia), QT interval prolongation, elevated lipase, elevated bilirubin and hypophosphatemia. Other events which may be related to nilotinib use include cardiac events such as arrhythmias, gastrointestinal events such as diarrhea, nausea, abdominal pain and vomiting, bleeding events and infections. The ability to assess causality of adverse events in this application is limited by the lack of randomized data.

## **7.4 General Methodology**

### 7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Data from the two arms were not pooled for the safety analysis because of the different variable patient populations, and lack of appropriate controls, particularly given the high background rate of adverse events in patients with imatinib-resistant or -intolerant CML-CP and CML-AP.

#### 7.4.1.1 Pooled data vs. individual study data

Not applicable. See Section 7.1.

#### 7.4.1.2 Combining data

Not applicable. See Section 7.1.

### 7.4.2 Explorations for Predictive Factors

In the CML-CP population in this study, 49 (15.4%) patients were given red blood cells, 28 (8.8%) patients received platelets or human blood, and three (0.9%) patients received blood or related products (WBC). In the CML-AP population in this study, 55 (45.8%) patients were given red blood cells, 37 (30.8%) patients received platelets or human blood, and one (0.8%) patient received blood or related products (WBC).

See also Section 7.1.7.

#### 7.4.2.1 Explorations for dose dependency for adverse findings

Only the 400 mg bid dose was thoroughly evaluated with respect to adverse events as there were insufficient numbers of patients treated at other doses to perform an adequate safety evaluation.

#### 7.4.2.2 Explorations for time dependency for adverse findings

Evaluations for adverse events occurring with long term administration (> 6 months) could not be performed due to the limited duration of exposure in the submitted study.

#### 7.4.2.3 Explorations for drug-demographic interactions

The distribution of patients aged < 65 years were greater than patients > 65 years in both the CML-CP and CML-AP populations. There were no apparent differences in the safety profile of nilotinib based on patient age or gender. There were too few non-Caucasian patients to perform a comparative evaluation of safety.

#### 7.4.2.4 Explorations for drug-disease interactions

All patients evaluated had CML-CP or CML-AP. Most adverse events were expected based on the disease and phase of disease with AEs more common in advanced CML-AP. No further evaluation of drug-disease interaction was examined.

#### 7.4.2.5 Explorations for drug-drug interactions

No formal analyses of drug-drug interactions were performed as part of the clinical review. Patients were often receiving multiple concomitant medications.

See the clinical pharmacology review for information regarding interactions with medications which induce, inhibit or are metabolized by the CYP 3A4, food effects and drugs which prolong QT interval.

#### 7.4.3 Causality Determination

All the adverse event data was obtained from a single-arm trial, complicating the issue of determining causality. Myelosuppression, QT interval prolongation including sudden deaths, elevated lipase, elevated bilirubin, elevated hepatic transaminases, rash and hypophosphatemia appear to be caused by nilotinib. Cardiac events, fluid retention and gastrointestinal events may also be related to nilotinib and may be class effects. Given the nature of the disease, it is difficult to ascertain whether drug or disease is responsible for the high incidence of bleeding events, and infections. However, since these events are associated with myelosuppression, it is likely that some of these events are caused by nilotinib.

## 8 ADDITIONAL CLINICAL ISSUES

### 8.1 Dosing Regimen and Administration

In the phase 1 study, dose escalation was conducted on a q.d. continuous dosing regimen from 50 mg to 1200 mg/day. When PK data suggested that there was a plateau in C<sub>max</sub> and AUC 0-24 starting at the q.d. doses of 400 mg and which was maintained to 1200 mg, b.i.d. dose escalation was started. For determination of MTD, the two sample MCRM model was performed twice: the first time at the completion of the initial dose-escalation phase including the initial enrollment to the two b.i.d. cohorts (400 mg and 600 mg b.i.d) for a total of 84/91 evaluable patients, and the second time at the completion of additional enrollment (28 patients) to the two b.i.d. cohorts, for further expansion of safety data for lower grade toxicities, for a total of 110/119 evaluable patients. The second two sample MCRM model confirmed that 600 mg b.i.d. was the MTD dose level. Dose-limiting toxicities occurring during cycle 1 for the initial dose escalation cohort and the expanded cohort were primarily related to hematologic and hepatic toxicities including transaminase elevations, hyperbilirubinemia, increased lipases, neutropenia and thrombocytopenia which occurred at doses starting at 600 mg q.d. MTD was determined to be 600 mg b.i.d by a two stage MCRM model, The 400 mg b.i.d. dose regimen was selected for evaluation in the Phase II component of the study according to criteria based on safety, PK and preliminary efficacy.

Since intra-patient dose escalation was permitted to treat disease that was persistent after > 14 days of nilotinib therapy, the initial dose assignment may not be reflective of the nilotinib dose received throughout the study, and makes dose-response conclusions for safety and efficacy difficult. However, a separate analysis on CML-AP patients, which represented the largest group of patients in one classification of CML who were similarly distributed across the total q.d. and b.i.d. initial dose cohorts and for whom inpatient dose escalation was less frequently used prior to the completion of cycles 1 and 2, revealed a dose-response for patients on q.d. doses of 40 to 200, q.d. doses of 400 to 1200, and 400 and 600 mg b.i.d. doses.

Pharmacokinetic profile of nilotinib revealed that steady state conditions were achieved by day 8, t<sub>max</sub> was 3 hours and elimination t<sub>1/2</sub> was 16 hours. The accumulation ratio of nilotinib was 2.0 for q.d. dosing, consistent with the observed half life. With q.d. dosing, AUC 0-24 increased with increasing dose from 50 mg to 400 mg, and appeared to plateau at dose levels starting at 400 mg to 1200 mg q.d. The 400 mg b.i.d. dosing schedule resulted in exposures that were 35% higher than with 800 mg q.d.; however, there was no further increase in exposure to nilotinib when given at the 600 mg b.i.d. dose. Interpatient variability in drug exposure was moderate to high, with coefficients of variation for AUC, C<sub>max</sub>, and C<sub>min</sub> of 33-64%, 34-73%, and 36-72%, respectively. The trough levels followed the same trend as in C<sub>max</sub> and AUC (i.e., increased up to 400 mg, then no increase at higher dose levels). Expectedly, twice daily dosing showed a lower peak to trough fluctuation compared to once daily dosing, with an average C<sub>max</sub>/C<sub>min</sub> ratio of 2.39 for 400 mg b.i.d. and 4.36 for 800 mg q.d. dosing.

The bioavailability of nilotinib was increased when given with a meal. Compared to the fasted state, the systemic exposure (AUC) increased by 15% (drug administered 2 hours after a light meal), 29% (30 minutes after a light meal), or 82% (30 minutes after a high fat meal), and the C<sub>max</sub> increased by 33% (2 hours after a light meal), 55% (30 minutes after a light meal), or 112% (30 minutes after a high fat meal).

The dose and dosing regimen were selected based upon safety, PK and efficacy response. Based on the exposure response for efficacy, a higher nilotinib exposure may have better response rate; however, there was no further increase in exposure of the 600 mg BID dose as compared to the 400 mg BID dose.

*Reviewer's Comments:*

*The recommended dose level declared was 600 mg b.i.d. However, the 400 mg b.i.d. dose regimen was selected for evaluation supported by safety, PK and preliminary efficacy. The 400 mg BID dosing regimen appears reasonable.*

## **8.2 Drug-Drug Interactions**

Nilotinib undergoes extensive metabolism by CYP3A4, and concomitant administration of strong inhibitors or inducers of CYP3A4 alter nilotinib concentrations significantly. In healthy

subjects, co-administration of nilotinib with ketoconazole, a strong inhibitor of CYP3A4, increased nilotinib C<sub>max</sub> by 80% and AUC by 3-fold on average. Therefore, patients who take strong CYP3A4 inhibitors concomitantly with nilotinib are likely to attain nilotinib exposure that is associated with an increased risk for QT interval prolongation.

### 8.3 Special Populations

Based on the sponsor's population PK analysis, age, body weight, or ethnic origin were not found to significantly affect the pharmacokinetics of nilotinib, whereas there is an effect of gender, with exposure to nilotinib in female patients being approximately 12% greater than in male patients. It also appears that female patients had a slightly higher response rate than male patients (55 vs 45% for cytogenetic response in CML-CP patients; 60 vs 50% for the confirmed HR response in the CML-AP patients), which seems to be consistent with the finding that the exposure to nilotinib in female patients is slightly greater than in male patients.

Safety and effectiveness have not been established in pediatric patients.

Based on the sponsor's population PK analysis, ethnic origin was not found to affect the pharmacokinetics of nilotinib.

Approximately 30% of subjects in clinical studies were 65 or over. No major differences were observed for safety and efficacy in patients  $\geq 65$  years of age as compared to adults 18 to 65 years.

Clinical studies have not been performed in patients with impaired renal function. Clinical studies have excluded patients with serum creatinine concentration  $>1.5$  times the upper limit of the normal range.

Nilotinib has not been investigated in patients with hepatic impairment. Clinical studies have excluded patients with ALT and/ or AST  $>2.5$  (or  $>5$ , if related to disease) times the upper limit of the normal range and/or total bilirubin  $>1.5$  times the upper limit of the normal range.

Metabolism of nilotinib is mainly hepatic. A hepatic impairment study is underway. Caution is recommended in patients with hepatic impairment.

A pharmacogenetic analysis examining the polymorphism of UGT1A1 and its potential association with hyperbilirubinemia during nilotinib treatment was conducted (Study CAMN107A2101). In this study, The (TA)<sub>7</sub>/(TA)<sub>7</sub> genotype was associated with a statistically significant increase in risk of hyperbilirubinemia relative to the (TA)<sub>6</sub>/(TA)<sub>6</sub> and (TA)<sub>6</sub>/(TA)<sub>7</sub> genotypes.

In CML-CP patients aged  $< 65$  years had a higher MCyR response (68/92, 73.9%) than patients  $\geq 65$  years (25/92, 27.2%). Female patients had a slightly higher response rate (47/92, 51.1% )

than male patients (45/93, 48.9%). Most of the responders were of Caucasian race (85/92, 92.4%).

In CML-AP patients, the incidence of major hematologic response was higher in patients < 65 years of age (21/26, 80.8 %) than in patients ≥ 65 years (5/26, 19.2 %). The incidence was slightly higher in males (14/26, 53.8 %) than females (12/26, 46.2 %).

#### **8.4 Pediatrics**

Nilotinib has not been studied in pediatric populations.

#### **8.5 Advisory Committee Meeting**

No advisory committee meeting was held to discuss this application.

Discussions were held with two ODAC consultants during the course of the review.

#### **8.6 Literature Review**

A literature review was performed on the natural history of CML, available treatments for CML, published efficacy trials for CML, and any studies published using nilotinib. The literature was also reviewed for safety reports in pharmacologically related drugs.

CML is a clonal myeloproliferative disorder of the hematopoietic stem cell, characterized by a reciprocal translocation t(9;22) which forms the Philadelphia chromosome (Ph<sup>+</sup>) and creates a novel fusion gene *bcr-abl*. CML accounts for approximately 15 to 20 percent of cases of leukemia in adults. It has an annual incidence of 1 to 2 cases per 100,000, with a slight male predominance. The median age at presentation is approximately 50 years for patients enrolled on clinical studies, but the actual median age from cancer registry data may be 60 years of age or older [7].

CML has a triphasic clinical course: an initial indolent chronic phase (CP), which is present at the time of diagnosis in approximately 85 percent of patients; an accelerated phase (AP), in which neutrophil differentiation becomes progressively impaired and leukocyte counts are more difficult to control with myelosuppressive medications; and a terminal blast crisis (BC), a condition resembling acute leukemia in which myeloid or lymphoid blasts fail to differentiate. CML inevitably progresses to blast crisis within an average of three to five years after diagnosis, and three to eighteen months after onset of the accelerated phase. Median survival is 4 to 6 years, with a range of less than 1 year to more than 10 years.

Imatinib resistance can be defined as lack of a complete hematologic response in patients with CP-CML or as a failure to return to CP for patients with CML in AP or BP. The majority of patients with imatinib-resistant CML have secondary *bcr-abl* mutations which either impair the

ability of the kinase to adopt the closed conformation to which imatinib binds or directly interfere with drug binding. The estimated 2-year incidence of imatinib resistance is 10 to 20% in CML-CP post-interferon- $\alpha$  failure and 40 to 50% in CML-AP. Drug resistance is associated with the reactivation of BCR-ABL signal transduction [8].

Relapse with imatinib frequently depends not only on re-emergence of BCR-ABL kinase activity but may also indicate BCR-ABL-independent disease progression not amenable to imatinib inhibition. Results from phase 2/3 trials suggest that rates of resistance and relapse correlate with the stage of disease and with the monitoring parameters – hematologic, cytogenetic and molecular response [9].

Imatinib mesylate, an inhibitor of the BCR-ABL tyrosine kinase, received FDA approval in May 2001 for the treatment of CML in CML-CP, CML-AP and CML-BC [1].

Dasatinib (Sprycel®) was approved in June 2006 as a treatment for patients with imatinib-resistant CML-CP, AP, BC and Ph<sup>+</sup> ALL [10].

The results of the phase 1 dose-escalation study of nilotinib in patients with CML whose disease was resistant to imatinib was reported in 2006 [11]. The results from the interim analysis conducted on the first 280 patients consecutively enrolled patients with at least 6 months of follow-up was reported in 2007 [12].

## **8.7 Postmarketing Risk Management Plan**

This drug will be prescribed by physicians familiar with the management of toxicity associated with the use of anti-neoplastic agents. Drug-drug interactions are seen with nilotinib and will be described in the labeling. The applicant will conduct post-marketing pharmacovigilance activities to evaluate safety signals associated with nilotinib including QT interval prolongation and sudden deaths, drug interactions with QT prolonging drugs, CYP3A4 inhibitors, food effects with high fat meals and hepatic impairment.

## **8.8 Other Relevant Materials**

None

# **9 OVERALL ASSESSMENT**

## **9.1 Conclusions**

## **Efficacy**

The efficacy data demonstrate that nilotinib treatment results in cytogenetic and hematologic responses in patients with CML-CP and CML-AP who are imatinib-resistant or intolerant on imatinib. Most responses occurred within 3 months of initiation of therapy. The number of patients in the population who received prior dasatinib and imatinib were too small for interpretation. There were only slight age and gender-related response differences apparent in both the CML-CP and CML-AP populations except for hematologic response in the AP population, which seemed to be higher in patients less than 65 years of age.

The trial was conducted per protocol except for certain eligibility criteria. The trial appears to have been well conducted. The largest accruing groups and those with the most responses were not found to have potentially confounding deficiencies on FDA site inspection.

The results of the trial provide evidence that nilotinib is effective as a single agent in CML-CP and CML-AP groups who are imatinib-resistant or –intolerant to prior imatinib. The primary analysis is conservative, since patients who were not assessable for response were counted as non-responders.

Cytogenetic and hematologic responses in imatinib resistant or intolerant CML-CP and CML-AP patients respectively, who have limited treatment options, are reasonably likely to predict clinical benefit and therefore support accelerated approval

## **Safety**

Four hundred and thirty eight patients comprised the safety population including 318 patients with CML-CP and 120 patients with CML-AP. All patients were treated with a starting dose of 400 mg orally twice daily.

The median duration of exposure to nilotinib in CML-CP patients was 245 days. Fifty-two percent were treated for 6 - 12 months, while 19% were treated for less than 3 months and 20% were treated for more than 12 months.

The median duration of exposure to nilotinib in CML-AP patients was 138 days. Thirty-five percent were treated for 6 - 12 months, while 23% were treated for less than 3 months and 11% were treated for more than 12 months.

In CML-CP patients, the most commonly reported drug-related adverse reactions (>10%) were rash, pruritis, nausea, fatigue, headache, constipation, diarrhea and vomiting. The common serious drug-related adverse reactions were thrombocytopenia and neutropenia.

In CML-AP patients, the most commonly reported drug-related adverse reactions (>10%) were rash, pruritus and constipation. The common serious drug-related adverse reactions were thrombocytopenia, neutropenia, pneumonia, febrile neutropenia, leukopenia, intracranial hemorrhage, elevated lipase and pyrexia.

Treatment-emergent grade 3/4 thrombocytopenia occurred in 28% of CML-CP patients and 37% of CML-AP patients. Grade 3/4 neutropenia occurred in 28% of CML-CP patients and 37% of CML-AP patients. Grade 3/4 anemia occurred in 8% of CML-CP patients and 28% of CML-CP patients.

Other treatment-emergent grade 3/4 laboratory abnormalities occurring in CML patients receiving nilotinib included:

*greater than 5% incidence* : elevated lipase, hyperglycemia, hypophosphatemia, elevated bilirubin

*less than 5%* : elevated SGOT or SGPT, hyperkalemia, hyponatremia, hypokalemia, decreased albumin, hypocalcemia, elevated alkaline phosphatase, and elevated creatinine

A relatively high number of patients experienced QTcF prolongations from baseline of > 30 msec (33.0% of CML-CP patients, 40.8% of CML-AP patients). QTcF increases of > 60 msec were reported in 1.9% of CML-CP and 2.5% of CML-AP patients. The incidence of absolute QTcF values > 500 msec was < 1%. There were ten sudden deaths reported. Six sudden deaths occurred in the ongoing phase 1/2 study (an additional death was reported after database lock but appeared to be possibly related to cardiac surgery and other morbidity) ; 4 deaths occurred in the expanded access program or with single patient use. Syncope occurred in 2% of CML-CP and 2.5 % of CML-AP patients.

The following wording is recommended for the black box warning:

**Tasigna prolongs the QT interval. Sudden deaths have been reported in patients receiving nilotinib. Tasigna should not be used in patients with hypokalemia, hypomagnesemia, or long QT syndrome. Hypokalemia or hypomagnesemia must be corrected prior to Tasigna administration and should be periodically monitored. Drugs known to prolong the QT interval and strong CYP3A4 inhibitors should be avoided. Patients should avoid food 2 hours before and 1 hour after taking dose. Use with caution in patients with hepatic impairment. ECGs should be obtained to monitor the QTc at baseline, seven days after initiation, and periodically thereafter, as well as following any dose adjustments.**

## 9.2 Recommendation on Regulatory Action

The reviewers recommend that accelerated approval should be granted for nilotinib for use in the treatment of adults with chronic myeloid leukemia (CML) in chronic phase (CML-CP) and accelerated phase (CML-AP), with resistance or intolerance to prior imatinib mesylate therapy.

## 9.3 Recommendation on Postmarketing Actions

### 9.3.1 Risk Management Activity

The sponsor should provide periodic safety reporting and continue post-marketing surveillance activities. The applicant will conduct post-marketing pharmacovigilance activities to evaluate safety signals associated with nilotinib including QT interval prolongation and sudden deaths, drug interactions with QT prolonging drugs, CYP3A4 inhibitors, food effects with high fat meals and hepatic impairment.

### 9.3.2 Required Phase 4 Commitments

The reviewers recommend the following commitment under subpart H (accelerated approval):

To submit the complete study report (at least 24 months follow-up in all patients) and data from study 2101, a phase 2 multi-center study of nilotinib in patients with imatinib resistant or intolerant chronic myeloid leukemia.

### 9.3.3 Other Phase 4 Requests

The following additional post-marketing commitments are recommended:

To submit the completed report and datasets for the hepatic impairment study.

To submit the completed report and datasets for the absolute bioavailability study.

To conduct clinical study(ies) to evaluate if multiple doses of nilotinib alter the metabolism of a sensitive CYP2C9 substrate (for example, S-warfarin). If a significant interaction is demonstrated, additional clinical studies to evaluate if multiple doses of nilotinib alter the metabolism of a sensitive CYP2C8 substrate (for example, repaglinide) and/or a sensitive CYP3A4 substrate (for example, midazolam) may be needed.

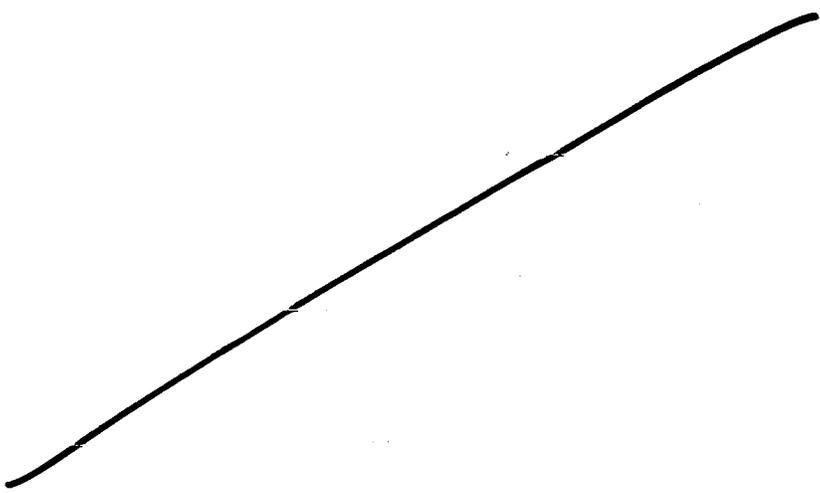
To conduct clinical study(ies) to evaluate if antacids and H2 blockers/proton pump inhibitors alter the pharmacokinetics of nilotinib.

#### 9.4 Labeling Review

The submitted product labeling was extensively revised. The labeling is not finalized at the time of filing of this review.

The label of a previously approved drug, dasatinib, was considered in the labeling review.

Although the patient populations and primary endpoints were similar in the approvals for imatinib and dasatinib, the label contains different descriptions. The major cytogenetic responses are confirmed responses in the imatinib package insert (PI) but are unconfirmed in the dasatinib PI. The hematologic response in the imatinib PI includes return to chronic phase along with complete hematologic response and no evidence of leukemia. The dasatinib PI has the category of major hematologic response which includes complete hematologic response and no evidence of leukemia categories. A comparison table is shown below followed by the relevant table of the PI of dasatinib showing the efficacy data are shown below.



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## **9.5 Comments to Applicant**

Comments will be sent with the action letter.

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On Original**

## 10 APPENDICES

### 10.1 Review of Individual Study Reports

None.

### 10.2 Line-by-Line Labeling Review

Currently ongoing.

### 10.3 References

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BIOMETRICS

Rajeshwari Sridhara  
10/22/2007 05:12:00 PM  
BIOMETRICS



# Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: August 16, 2007

From: Stephen M. Grant, M.D.  
Scientific Lead, Interdisciplinary Review Team for QT Studies  
Division of Cardiovascular and Renal Products

Through: Norman Stockbridge, M.D., Ph.D.  
Division Director  
Division of Cardiovascular and Renal Products

To: Janet Jamison, R.N.  
Regulatory Project Manager  
Division of Drug Oncology Products

Subject: Sudden deaths after administration of nilotinib during clinical development

This memo responds to your consult to us dated 16 July 2007 to evaluate sponsor identified sudden deaths that have occurred after administration of nilotinib during clinical development. The QT-IRT received and reviewed the following materials:

- Your consult
- Our consult dated 28 Feb 2007
- The clinical Summary of Clinical Safety in NDA 22068 (CTD 2.7.4) along with sponsor narratives and MedWatch reports.

## **Background**

Almost all cases of chronic myelogenous leukemia (CML) can be linked to a mutated chromosome in the blood-forming cells of the bone marrow. Called the Philadelphia (Ph) chromosome, it produces an abnormal protein (BCR-ABL protein) that leads to the overproduction of immature, poorly functioning white blood cells. The current approved first line therapy is imatinib, a tyrosine kinase inhibitor which inhibits the BCR-ABL protein, and has limited effects on normal cells. However, CML can become resistant to imatinib due to the emergence of imatinib-resistant point mutations within the BCR-ABL tyrosine kinase domain. Nilotinib is another tyrosine kinase inhibitor, which was designed to overcome imatinib resistance due to higher affinity for the tyrosine kinase domain of the BCR-ABL protein. Nilotinib is being developed by Novartis Pharmaceuticals as a treatment for chronic

myelogenous leukemia (CML), Ph-positive acute lymphocytic leukemia (Ph+ALL), hypereosinophilic syndrome, systemic mastocytosis, and gastrointestinal stromal tumors (GIST). Novartis has submitted an NDA to market nilotinib as treatment for patients with Ph+ CML in chronic phase (CML-CP) or accelerated phase (CML-AP) and who are intolerant or resistant to imatinib.

### **Clinical Pharmacology**

Nilotinib has a half-life of about 17 hours, requiring five to seven days to reach steady state. At the proposed dose of 400 mg po bid, the mean  $C_{max}$  is 2210 ng/mL. Factors that increase plasma concentrations include 1) co-administration of drugs that inhibit the CYP3A4 system, 2) administration with a high fat meal, and 3) probably hepatic dysfunction.

### **Nonclinical Evaluation**

Nilotinib's effect on the hERG ion channel was evaluated in an assay in which hERG was expressed in a human embryonic kidney cell line. Over the concentration range of 0.01 -1.0  $\mu$ M (n=3/conc.), AMN107 dose-dependently inhibited hERG peak tail current (over 2 sec. at clamped -50 mV) up to 90%, with an  $IC_{25}$  and  $IC_{50}$  of 0.04 and 0.13  $\mu$ M, respectively.

*Reviewer comment: An  $IC_{50}$  in the sub-micromolar range suggests that a product is likely to prolong the QT interval significantly.*

### **Dedicated QT Study**

Novartis conducted single-blind, randomized, placebo-controlled parallel group study of the effect of nilotinib on the QT interval in healthy male subjects (CAMN107A2119). In the relevant part of the study, subjects were randomized to either a single dose of 800 mg of nilotinib with a high fat meal or placebo. The data demonstrated a mean nilotinib effect on the QTc of 14.5 ms with an upper 90% CI of 21 ms and that this effect was concentration dependent. However, the mean nilotinib concentration achieved in this study was only 1669 ng/ml well below the expected steady state concentration of 2210 ng/mL at a dose of 400 mg bid.

*Reviewer comments:*

- 1. The increase in QTc associated with nilotinib administration is well above the level identified as of regulatory concern in the ICH E14 guideline.*
- 2. The actual mean QTc prolongation that will be observed in clinical practice if nilotinib is approved for marketing at a dose of 400 mg bid is expected to be greater than 14.5 ms not only because of higher serum concentration but also because of the inevitable occurrence of factors that further increase its concentration (listed in the Clinical Pharmacology section above).*
- 3. The probability that serious ventricular arrhythmias will occur after nilotinib administration is further increased by factors likely to be prevalent in the CML population, e.g., left ventricular dysfunction, older age, female gender, co-administration of other QT-prolonging drugs, and hypokalemia / hypomagnesemia.*

### **Brief Review of individual subject sudden deaths**

The following subjects have been identified by Novartis as dying suddenly either during a clinical trial of nilotinib, in an expanded access protocol, or as part of a compassionate use protocol.

1. Subject **0304/04010** was 73 year old (yo) male with hypertension. Concomitant medications are not mentioned. Baseline echocardiogram was normal. He had CML-CP and was administered nilotinib 400 mg bid. ECG on day 246 is reported as normal. He complained of left shoulder pain on day 264. He was found dead on day 265. Autopsy on 267 demonstrated extensive coronary artery disease and ventricular rupture.
2. Subject **0304/05001** was 66 yo male with hypertension on lasix and verapamil and a history of myocardial infarction. He had chronic eosinophilic leukemia and was administered nilotinib 400 mg bid. On day 14 he developed fever and was admitted to hospital. He had cardiac arrest on day 15. Autopsy indicated aseptic endocarditis and Loeffler's syndrome.

*Reviewer's comment: Verapamil inhibits CYP 3A4, which increases serum concentrations of nilotinib.*

3. Subject **0502/00122** was 31 yo male with a history of smoking. He had CML-AP and was administered nilotinib 400 mg bid. He had a pulmonary embolism on day 44. On day 177 he was found dead with a needle and tourniquet nearby. Autopsy revealed high levels of methadone.

*Reviewer's comment: Methadone is associated with torsade de pointes.*

4. Subject **0303/01001** was a 75 yo female with a history of hypertension on ramipril. Baseline echocardiography revealed left ventricular dilatation and inferior wall motion abnormality. Baseline potassium level was 3.5  $\mu\text{mol/L}$ . Baseline QTcF was 410 ms. She had Ph+ALL and was administered nilotinib 400 mg bid. On day 2 QTcF is reported to be 484 ms. On day 7 she died suddenly.

*Reviewer's comment: This subject had several risk factors for torsade including female gender, LV dysfunction, and hypokalemia. The increase in QTcF on day should have been concerning. Further, nilotinib serum concentration probably did not peak until about the day of her death.*

5. Subject **0501/00103** was a 52 yo male whose past medical history and concomitant medications are not mentioned. He had CML-CP and was administered nilotinib 400 mg bid. In the sponsor-supplied narrative it states he presented to hospital complaining of left arm pain. In the Summary of Clinical Safety section of the NDA it states he was found unresponsive and found to be in ventricular fibrillation.
6. Subject **0505/04001** was a 69 yo male with a history of coronary artery disease. Concomitant medications are not mentioned. He had CML-CP and was administered nilotinib 400 mg bid. Day 8 ECG demonstrated first degree AV block. He died suddenly on day 20. Autopsy demonstrated coronary artery disease.
7. Subject **0514/00015** was a 65 yo female with left bundle branch block. She had CML-AP and was administered nilotinib 400 mg bid in hospital. She was also administered fluconazole. On day 5 she died suddenly. No autopsy was performed.

*Reviewer's comment: Fluconazole prolongs the QT interval and inhibits CYP 3A4, which increases serum concentrations of nilotinib.*

8. Subject **PHHO2006US20288** was a 49 yo male with a history of coronary artery stent placement and cocaine abuse. He had CML-CP and was administered nilotinib (dose not disclosed). He is reported to have not taken nilotinib regularly. Approximately three months after beginning nilotinib he was found dead.

9. Subject **PHHO2007DE05370** was a 78 yo female with CML-CP and was administered nilotinib 800 mg qd. ECGs are reported to have been normal. On day 132 she began moxifloxacin 400 mg qd. On day 140 she died suddenly.

*Reviewer's comment: Moxifloxacin prolongs the QT interval and is associated with torsade de pointes.*

10. Subject **PHHO2007CA06532** was a 46 yo female with hypertension, diabetes, and deep venous thrombosis. She had CML-CP and was administered nilotinib 800 mg qd. On day 49 she developed blast crisis and nilotinib was discontinued. Three days later she had a cardiorespiratory arrest.

#### **QT-IRT COMMENTS:**

1. This reviewer was unable to determine the actual total number of patients who have been exposed to nilotinib or the total exposure (i.e., dose x duration). Hence trying to determine a meaningful rate of sudden death is not possible. Sudden death is not unexpected in an older population with serious underlying disease.
2. Novartis has not conducted any controlled studies of nilotinib so contemporary randomized controls for comparison are not available.
3. The actual mode of death is unclear for all of these patients so the question of whether QT prolongation due to nilotinib played a role can not be answered definitively.
4. Nonetheless in three of the cases the timing and circumstances suggest that nilotinib administration may have been related to death. These three are
  - **0303/01001**, an older female left ventricular dysfunction and hypokalemia, whose demonstrated prolonged QTc on the second day of nilotinib therapy and then died on day 7, which is approximately the time of  $C_{max}$  was reached.
  - **0514/00015**, an older female with abnormal baseline ECG co-administered fluconazole (a QT prolonger as well as a CYP3A4 inhibitor) who died on day 5, which is approximately the time the new  $C_{max}$  was attained.
  - **PHHO2007DE05370**, an older female who was co-administered moxifloxacin (a QT-prolonger), and then died eight days later.

These three cases suggest a concentration dependent relation of nilotinib to sudden death.

5. The causes of sudden death are many and none of these the deaths may be due to prolongation of the QT interval by nilotinib. Therefore, measures taken to minimize or mitigate QT prolongation may not affect the rate of sudden death, if related, after nilotinib administration.

Thank you for requesting our input into the evaluation of this product. We welcome more discussion with you now and in the future.

Please feel free to contact us via email at [cdcrdcrpqt@fda.hhs.gov](mailto:cdcrdcrpqt@fda.hhs.gov)

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8/16/2007 12:13:38 PM  
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# Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: June 12, 2007

From: Stephen M. Grant, M.D.  
Scientific Lead, Interdisciplinary Review Team for QT Studies  
Division of Cardiovascular and Renal Products /CDER

Through: Norman Stockbridge, M.D., Ph.D.  
Division Director, DCRP

To: Janet Jamison, R.N.  
Regulatory Project Manager  
Division of Drug Oncology Products

Subject: QT-IRT consult to review proposed labeling for Tasigna, an anti-neoplastic agent which prolongs the QT interval

This memo responds to your consult to us dated 23 Mar 2007 regarding the proposed labeling for Tasigna (nilotinib), an antineoplastic agent for which Novartis has submitted NDA 22-068. The QT-IRT received and reviewed the following materials:

- Your consult
- Sponsor's proposed label

## Background

Please refer to the previous QT-IRT consult dated 28 Feb 2007 for background and our assessment of the effect of Tasigna administration on the QT interval.

## QT-IRT COMMENTS:

The following are our suggestions for revisions to Novartis' proposed label (proposed language that we do not recommend changing is in black, proposed language we recommend deleting is in red with a strikeout line, and our proposed additional language is in blue):

## **HIGHLIGHTS OF PRESCRIBING INFORMATION**

QT Prolongation: ~~\_\_\_\_\_~~ Tasigna prolongs the QT interval. Use with caution in patients ~~\_\_\_\_\_~~ Avoid CYP3A4 inhibitors. Hypokalemia or hypomagnesemia must be corrected prior to Tasigna

administration and should be periodically monitored.

## WARNINGS AND PRECAUTIONS

### 5.2 QT Prolongation

Tasigna has been shown to prolong cardiac ventricular repolarization as measured by the QT interval on the surface ECG in a concentration-dependent manner. Prolongation of the QT interval can result in a type of ventricular tachycardia called Torsade de pointes, which may result in syncope, seizure, and death.

### Drug Interactions

The administration of Tasigna with agents that are strong CYP3A4-inhibitors

should be avoided. Should treatment with any of these agents be required, it is recommended that therapy with Tasigna be interrupted. If interruption of treatment with Tasigna is not possible, patients who require treatment with a drug that strongly inhibits CYP3A4 should be closely monitored for prolongation of the QT interval. [See Drug Interactions]

### 5.9 Hepatic Impairment

Tasigna has not been investigated in patients with hepatic impairment. Clinical studies have excluded patients with ALT and/ or AST >2.5 (or >5, if related to disease) times the upper limit of the normal range and/or total bilirubin >1.5 times the upper limit of the normal range. Metabolism of nilotinib is mainly hepatic. Caution is recommended in patients with hepatic impairment. These patients should be closely monitored for QT interval prolongation. [See Dosing and Administration (2) and Use in Specific Populations (8.7)].

## 6 ADVERSE REACTIONS

### 6.1 Clinical — Experience

Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

## CLINICAL PHARMACOLOGY

### 12.4 QT/QTc Prolongation

In a healthy volunteer study designed to assess the effects of Tasigna on the QT interval, administration of Tasigna was associated with concentration-dependent QT prolongation. — the maximum mean placebo-adjusted QTcF change from baseline was 18 msec (1-sided 95% Upper CI: 26 msec). A positive control was not included in the study.

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future.

Please feel free to contact us via email at [cdcrdcrpqt@fda.hhs.gov](mailto:cdcrdcrpqt@fda.hhs.gov)

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