Gilteritinib for the Treatment of FMS-like tyrosine kinase 3 (FLT3) Mutation Positive Acute Myeloid Leukemia (AML)

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Astellas

Including, but not limited to, Astellas Pharma Global Development, Inc., Astellas Pharma Europe B.V., and Astellas Pharma Inc.

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List of Abbreviations

AE	adverse event
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
APGD	Astellas Pharma Global Development
APL	acute promyelocytic leukemia
AST	aspartate aminotransferase
AXL	AXL receptor tyrosine kinase
BSA	body surface area
Ca^{2+}	calcium ion
CK	creatine kinase
CNS	central nervous system
CR	complete remission
CRc	composite complete remission
CRi	complete remission with incomplete hematologic recovery
CRp	complete remission with incomplete platelet recovery
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
ECG	electrocardiogram
EFS	event free survival
FLA	fludarabine and cytarabine
FLAG-DNX	fludarabine, cytarabine, granulocyte colony-stimulating factor and liposomal daunorubicin
FLT3	Fms-like tyrosine kinase 3
FLT3/ITD	FLT3/internal tandem duplication
GCSF	granulocyte colony-stimulating factor
GVHD	graft-versus-host disease
hERG	human ether-a-go-go related gene
HLA	human leukocyte antigen
HSC	hematopoietic stem cell
HSCT	hematopoietic stem cell transplant
IC_{50}	half maximal inhibitory concentration
ITD	internal tandem duplication
LTK	leukocyte tyrosine kinase
MATE1	multidrug and toxin extrusion protein 1
MRD	Minimal Residual Disease
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute-Common Criteria for Adverse Events
NOAEL	no observed adverse effect level

OS	overall survival
PFS	progression free survival
PIA	plasma inhibitory activity
PR	partial response
QTcF	Fridericia-corrected QT interval
RP2D	recommended Phase 2 dose
RP3D	recommended Phase 3 dose
R/R	relapsed/refractory
TdP	torsades de pointes
$5HT_{2B}$	5-Hydroxytryptamine receptor 2B

1 INTRODUCTION

The purpose of this Pediatric Subcommittee Meeting of the Oncology Drug Advisory Committee is to discuss and receive feedback on the proposed pediatric investigational program for gilteritinib. Gilteritinib is a new chemical entity under development by Astellas Pharma Inc. for the treatment of acute myeloid leukemia (AML). Astellas is currently developing a pediatric investigation plan for gilteritinib, which is presented herein.

2 ACUTE MYELOID LEUKEMIA

AML is a cancer of the blood cells, generally characterized by aberrant differentiation and proliferation of malignantly transformed myeloid progenitor cells. AML results in the accumulation of these transformed cells within the bone marrow, suppression of the production of normal blood cells (resulting in severe neutropenia and/or thrombocytopenia), as well as infiltration of these cells into other organs and tissues. When untreated or refractory to available treatments, AML can be rapidly fatal.

First-line treatment for AML in both adults and children has traditionally been administered in stages: induction chemotherapy (to reduce blast cells/achieve remission) followed by postremission or consolidation therapy (to destroy any remaining leukemia cells and prevent relapse) [National Comprehensive Cancer Network (NCCN), 2015; American Cancer Society, 2014]. Standard chemotherapy is associated with complete remission (CR) in approximately 70% of younger adult patients and 85% of pediatric patients [NCCN, 2015]. However, approximately 30% of adult AML patients and 20% of children are refractory to induction therapy. Furthermore, of those who achieve CR, approximately 75% of adults and 20% to 40% of children will relapse [Zwaan et al, 2015]. Survival after first relapse can be low (5-year survival of 11% for adult patients under 55 years, 6% for those over 55 years), demonstrating the lack of effective cure for patients in relapsed AML [Rowe et al, 2010]. Patients who are in second relapse or refractory to first line therapy have an extremely poor prognosis, with survival often measured in weeks (n = 594 patients, CR rate for patients in second relapse was 13%, with a median survival of nearly 6 weeks) [Giles et al, 2005].

An estimated 500 new cases of AML are diagnosed annually (2014) in children 0 to 14 years of age and another 230 new cases are diagnosed in adolescents 15 to 19 years of age [American Cancer Society, 2014]. Between 1975 and 2011, the incidence rates increased for childhood and adolescent AML [Leukemia and Lymphoma Society, 2014-2015]. The 5-year survival rate for AML for children diagnosed in 2003 through 2009 was 64% [American Cancer Society, 2014]. These data indicate that pediatric AML is a rare but life-threatening cancer, representing a significant unmet medical need.

3 FMS-LIKE TYROSINE KINASE 3 (FLT3) MUTATION POSITIVE AML

Certain genetic factors appear to predispose AML patients to poorer outcomes. Mutational status of FMS-like tyrosine kinase 3 (FLT3), a member of the class III receptor tyrosine kinase, is now well recognized as delineating a subtype of leukemia with poor prognosis in both adults and in children. The most common FLT3 mutation is a self-activating internal tandem duplication (FLT3/ITD) in the juxtamembrane domain of FLT3, which is oncogenic and shows transforming activity in cells [Yamamoto et al, 2001].

Adult patients with FLT3/ITD AML show poor prognosis in clinical studies, with a higher relapse rate, a shorter duration of remission from initial therapy, as well as reduced disease-free survival and overall survival (OS) [Patel et al, 2012; Gale et al, 2008; Yanada et al, 2005; Tiesmeier et al, 2004; Moreno et al, 2003]. In the only published randomized study in relapsed AML patients with FLT3/ITD mutations [Levis et al, 2011], 112 patients in first relapse in the control arm who received either mitoxantrone, etoposide and cytarabine or high dose cytarabine as salvage treatment had a CR/complete remission with incomplete platelet recovery (CRp) rate of 21% and a median survival of 4.3 months, which included 22 patients undergoing allogeneic hematopoietic stem cell transplant (HSCT) on study. Patients in second relapse demonstrated a median survival of less than 8 weeks.

Similar to adults, FLT3/ITD positive AML in children is a well-established prognostic factor for poorer outcomes, regardless of diagnostic white blood cells, cytogenetic markers, or induction regimen used [Meshinchi et al, 2001; Pratz & Levis, 2008; Govedarovic & Marjanovic, 2011; Puumala et al, 2013; Bachas et al, 2014]. Pediatric patients with FLT3/ITD AML are more likely to be refractory to primary induction therapy, demonstrate lower rates of progression free survival (PFS) and OS after CR, and experience higher rates of relapse and subsequent death even if they achieve remission [Meshinchi et al, 2001].

Based on available clinical trial data [Table 1], the rates of induction failure and disease relapse in pediatric AML patients with FLT3/ITD mutations range from 10% to 30% and 27% to 65%, respectively.

Table 1 Relapse and Induction Chemotherapy Failure Rates in Pediatric Patients with FLT3/ITD Mutation as Reported in Clinical Trials

Study	Country	Age group (yrs)	Induction Failure	Relapse (Cumulative Incidence for patients in CR)
Meshinchi et al, 2001	US	3-19	40%	Data not given
Zwaan et al, 2003	Germany, Netherlands	0-18	30%	47% §
Meshinchi et al, 2006	US, Germany, Netherlands	0-20	19%	65% ‡
Masetti et al, 2014; Pession et al, 2013	Italy	< 1	14%	31.3%†
		1	6%	25.7%†
		2-9	11%	30.5%†
		10-18	9%	22.9%†
		Overall	10%	27%†
Overall Range			**10-30%**	**27-65%**

CR: complete remission; US: United States, † 8 year cumulative incidence , ‡ 4 year cumulative incidence, § 5 year cumulative incidence

Based on data from population-based observational studies [Table 2], the reported estimated prevalence of FLT3/ITD mutations in pediatric patients with AML ranges from 6.6% to 22.5%. The prevalence of the FLT3/ITD mutation subgroup is lower in children than in adults, is rare in infants (0% to 2%) and increases with increasing age [Zwaan et al, 2003; Meshinchi et al, 2006; Govedarovic and Marjanovic, 2011; Schneider et al, 2012; Masetti et al, 2014].

Table 2 Prevalence of Pediatric FLT3/ITD Mutation as Reported in Population-based Studies

Study	Country	Duration (year)	n	Age group (yrs)	Prevalence (%)
Xu et al, 1999	Japan	NA	87	<18	13.8%
Kondo et al, 1999	Japan	1985-1997	64	0-9	5%
				10-16	21%
				Overall	11%
Arrigoni et al, 2003	Italy	1985-2000	45	≤10	9.4%
				>10	53.8%
				Overall	22.2%
Liang et al, 2003	China	NA	91	0-18	15.4%
Kang et al, 2005	Korea	1996-2003	61	0-17	6.6% 9.8% (total FLT3)
Andersson et al, 2008	Sweden	1995-2004	34	0-17	12% 21% (total FLT3)
Hollink et al, 2009	Germany	1982-2005	276	NA	19.2%
Chang et al, 2010	US	1995-2002	73	0-14	8.2% 12.3% (total FLT3)
Chauhan et al, 2011	India	2005-2009	38	0-14	13%
Karabacak et al, 2011	Turkey	2000-2010	40	0-16 Mean=7.2	22.5%
Chauhan et al, 2013	India	2006-2010	45	1-15 Median=10	8%
Yatsenko et al, 2013	Russia	2006-2010	186	0-16	8.9% 12.1% (total FLT3)
Overall Range					**6.6%-22.5%**

NA: not applicable; US: United States

In summary, FLT3/ITD mutation is present in approximately 10% to 20% of pediatric AML cases, and appears to predispose patients to poorer responses to induction therapy, shorter durations of remission, lower rates of overall survival and higher rates of relapse.

4 DESCRIPTION OF MOLECULE AND RATIONALE FOR THE DEVELOPMENT OF GILTERITINIB FOR THE TREATMENT OF PEDIATRIC FLT3/ITD POSITIVE AML

Inhibition of FLT3 has been demonstrated to have anti-leukemic activity in cellular and animal models of AML, and is hypothesized to improve outcomes in patients that are positive for FLT3 mutation. Gilteritinib is a new chemical entity discovered by Astellas Pharma Inc. in collaboration with Kotobuki Pharmaceutical Co., Ltd and is under development for the treatment of AML. Gilteritinib has an inhibitory effect on tyrosine kinases, mainly FLT3, AXL, leukocyte receptor tyrosine kinase (LTK) and anaplastic lymphoma kinase (ALK) [Table 3]. Gilteritinib has inhibitory effects on mutated FLT3 (FLT3/ITD, FLT3 with tyrosine kinase domain mutation [FLT3/D835]) at concentrations that can be achieved clinically. Additionally, gilteritinib has activity in cell lines and animal models of FLT3/ITD positive AML.

Figure 1 Chemical Structure of Gilteritinib

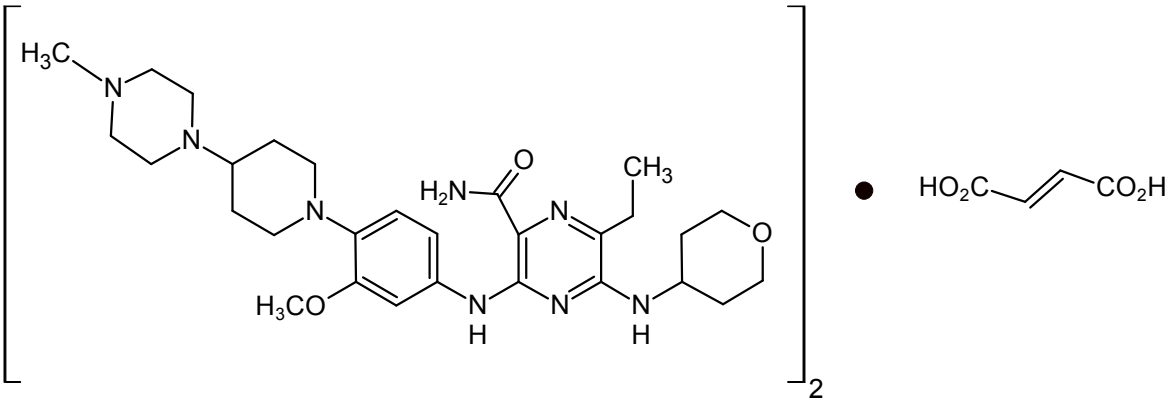


Table 3 Gilteritinib Pharmacology

Target	IC_{50} nmol/L
FLT3	0.291
LTK	0.350
AXL	0.726
EML4-ALK	1.2
c-KIT	230

AXL: AXL receptor tyrosine kinase; EML4-ALK: echinoderm microtubule-associated protein-like 4- anaplastic lymphoma kinase; FLT3: FMS-like tyrosine kinase 3; LTK: leukocyte receptor tyrosine kinase

In vitro studies, kinase activity assayed by ELISA or off-chip mobility shift assay

Definitive nonclinical toxicology and safety pharmacology studies have been completed for gilteritinib and supported phase 1 clinical investigation in humans. A brief summary of the results of the nonclinical safety pharmacology and toxicology studies conducted for gilteritinib is provided in as an appendix in [Section 10].

The primary analysis of Study 2215-CL-0101, a first-in-human phase 1/2 open-label, dose-escalation clinical study investigating the safety, tolerability, pharmacokinetics and pharmacodynamics of gilteritinib in adult patients with relapsed or refractory (R/R) AML, was completed in 2016. Data from Study 2215-CL-0101 demonstrated anti-leukemic activity in FLT3 mutation positive patients with R/R AML, with a tolerable safety profile. The details of this clinical study are presented in [Section 6]. Although the incidence of FLT3/ITD positive AML is lower in children than in adults, children with FLT3/ITD positive AML has an underlying biology and clinical course similar to adults, with high relapse rate and poor survival. Therefore, it is expected that the potential clinical efficacy and tolerability of gilteritinib should be similar in both adult and pediatric patients with FLT3/ITD positive AML.

5 GILTERITINIB CLINICAL DEVELOPMENT IN ADULT AML

The clinical development plan for gilteritinib currently includes four phase 3 studies and one phase 2/3 study for adult FLT3 mutation positive AML patient populations. [Table 4]

displays the current global clinical development plan for gilteritinib. As of April 2017, 179 healthy volunteers and 564 patients have received at least 1 dose of gilteritinib.

Study 2215-CL-0101 is a phase 1 (dose-finding) / phase 2 (safety and efficacy) study in adult patients with relapsed or refractory AML. The primary analysis of this study are available, and represent the most relevant data set to understand the pharmacokinetics, safety and potential anti-leukemic activity of gilteritinib to date. A data summary of Study 2215-CL-0101 is presented in [Section 6].

Study 2215-CL-0301, a phase 3 study of gilteritinib in FLT3 mutated AML subjects who are refractory to or have relapsed after first-line therapy, will be the first pivotal study to be completed. If successful, this study may provide the basis for a new drug application for gilteritinib.

Table 4 Gilteritinib Clinical Development Plan for Adult Acute Myeloid Leukemia

Study Number Country/Region	Study Phase	Planned Sample Size	Therapy	Population	Purpose	Study Status
2215-CL-0101 US, Italy, France and Germany	1/2	270	Monotherapy	Patients with R/R AML	Safety/MTD/PK/Efficacy/DDI¶	Enrollment complete, study on-going
2215-CL-0102 Japan	1	36	Monotherapy	Japanese patients with R/R AML	Safety/MTD/ Efficacy/PK/ PD	Complete
2215-CL-0103 US	1	44	Combination w/ chemotherapy	Patients w/ newly diagnosed AML	Safety/MTD/PK/ Efficacy/PD	Ongoing
2215-CL-0104 Japan	1	6	Combination w/ chemotherapy	Japanese patients w/ newly diagnosed AML	Safety/MTD/PK/ Efficacy/PD	Ongoing
2215-CL-0105 US	1	8§	Monotherapy	Patients with solid tumors	Mass balance/PK/ Safety	Ongoing
2215-CL-0106 US	1	24	Monotherapy	Subjects with normal hepatic function and mild/moderate hepatic impairment	Safety/PK (Hepatic impairment)	Complete
2215-CL-0108 US	1	80	Monotherapy	Healthy subjects	Safety/PK/ DDI††	Complete
2215-CL-0109 North America, Europe and Asia	1/2	120	Monotherapy and combination w/ chemotherapy	Patients from Studies 2215-CL-0101, -0301, -0201 and -0105	Safety (Rollover study)	Ongoing
2215-CL-0110 US	1	40	Monotherapy	Healthy subjects	rBA	Complete
2215-CL-0113 US	1	32	Monotherapy	Healthy subjects	Safety/PK (Food effect)	Ongoing
2215-CL-0201 North America, EU, Asia	2/3	528 (12 patients in safety cohort)	Monotherapy and combination w/ chemotherapy	Patients w/newly diagnosed FLT3 mutation positive AML who are not eligible for intensive induction chemotherapy	Safety/ Efficacy/ Population PK	Ongoing
2215-CL-0301 North America, EU, Asia	3	369	Monotherapy	Patients with first R/R FLT3 mutation positive AML	Efficacy/ Safety/ Population PK/PD	Ongoing

Study Number Country/Region	Study Phase	Planned Sample Size	Therapy	Population	Purpose	Study Status
2215-CL-0302 North America, EU, Asia, Central and South America and rest of world	3	354	Monotherapy compared against placebo	Patients with FLT3/ITD AML in CR1 following induction/ consolidation therapy	Efficacy/ Safety/ Population PK	Ongoing
2215-CL-0303 Asia and Russia	3	318	Monotherapy compared against salvage therapy	Patients with R/R FLT3 mutation positive AML	Efficacy/ Safety/ Population PK	Planned
2215-CL-0304 North America, EU, Asia	3	346	Monotherapy compared against placebo	Post-transplant patients with FLT3/ITD AML (received transplant after first-line chemotherapy)	Efficacy/ Safety/ Population PK	Ongoing

AML: acute myeloid leukemia; DDI: drug-drug interaction; FLT3: FMS-like tyrosine kinase 3; ITD: internal tandem duplication; MTD: maximum tolerated dose; PD: pharmacodynamics; PK: pharmacokinetics; rBA: relative bioavailability; R/R: relapsed/refractory

¶ Includes DDI with a cytochrome P450 3A4 (CYP3A4) substrate (midazolam), and with a multidrug and toxin extrusion protein 1 substrate (cephalexin)

§ Up to 8 subjects can be enrolled to ensure at least 4 evaluable subjects

†† DDI with a strong (itraconazole)/moderate (fluconazole) CYP3A4 inhibitor or inducer (rifampin)

6 STUDY 2215-CL-0101: A PHASE 1/2 CLINICAL STUDY OF GILTERITINIB IN ADULT PATIENTS WITH RELAPSED/REFRACTORY AML

Study 2215-CL-0101 was a first-in-human phase 1/2 open-label, dose-escalation study investigating the safety, tolerability, pharmacokinetics and pharmacodynamics of gilteritinib monotherapy in patients with relapsed or refractory AML. The primary objectives of this study were to assess the safety and tolerability, including determination of the maximum tolerated dose (MTD), of oral gilteritinib in patients with relapsed or treatment-refractory AML and to determine the pharmacokinetic parameters of gilteritinib. Secondary objectives were to investigate the anti-leukemic activity of various doses of gilteritinib in patients with AML, to evaluate the effect of strong or moderate cytochrome P450 3A4 (CYP3A4) inhibitors on the pharmacokinetics of gilteritinib and to evaluate the potential induction of CYP3A4 by gilteritinib by assessment of midazolam pharmacokinetics and to evaluate the effect of gilteritinib on multidrug and toxin extrusion protein 1 (MATE1) substrates by assessment of cephalexin pharmacokinetics. The study was initiated in October 2013, and enrolled patients at 24 centers in the United States, 3 centers in Germany and 1 center in Italy. The primary analysis for the study was conducted for the safety analysis set of 252 patients that received at least one dose of gilteritinib, including data from all subject visits as of 24 Nov 2015 (data cut-off date); 9 patients currently remain on treatment.

6.1 Study 2215-CL-0101: Baseline Demographics

Baseline patient demographics for the study are displayed in [Table 5]. Of the 252 patients that received at least one dose of gilteritinib, a total of 191 patients had FLT3 mutations. Of these patients, 178 patients had FLT3/ITD mutations, with 162 patients (64% overall) with FLT3/ITD alone, and 16 patients (6%) with both FLT3/ITD and FLT3/D835 mutations. Additionally, there were 13 patients (5%) with FLT3/D835 mutation only. Among all the patients enrolled, approximately 70% of patients had received 2 or more lines of therapy prior to enrollment. Besides standard chemotherapy, 63 patients (25%) had received a prior tyrosine kinase inhibitor (most commonly sorafenib) and 73 patients (29%) had received allogeneic HSCT.

Table 5 Study 2215-CL-0101: Patient Baseline Demographics

Parameter Category/Statistics	Total (N = 252)
Age, years Median (min, max)	62 (21, 90)
Sex, n (%)	
Male	129 (51)
Female	123 (49)
Cytogenetic risk status, n (%)	
Favorable	7 (2.8)
Intermediate	143 (57)
Unfavorable	56 (22)
AML Disease History, duration of disease, months	
Median (min, max)	9.1 (0.3, 133)
Prior hematopoietic stem cell transplant, n (%)	
0	179 (71)
1	67 (27)
≥ 2	6 (2)
Prior lines of AML therapy, n (%)	
1	75 (30)
2	66 (26)
≥ 3	111 (44)
Prior tyrosine kinase inhibitor therapy, n (%)	
No	189 (75)
Yes‡	63 (25)
FLT3 mutation type, n (%)§	
FLT3/ITD	162 (64)
FLT3/D835	13 (5)
FLT3/ITD and FLT3/D835	16 (6)

Safety Analysis Set: All patients that received at least 1 dose of study drug

AML: acute myeloid leukemia; D835: missense mutation at aspartic acid residue 835; FLT3: FMS-related tyrosine kinase 3; ITD: internal tandem duplication.

‡ Patients may have received more than 1 prior tyrosine kinase inhibitor

§ FLT3 mutation status was determined by a local laboratory.

6.2 Study 2215-CL-0101: Gilteritinib Pharmacokinetics

Gilteritinib exhibited linear, dose-proportional pharmacokinetics at doses ranging from 20 to 450 mg administered once daily. Median t_{max} was observed between 2 and 6 hours following single and multiple dosing, and the estimated $t_{1/2}$ ranged from 45 to 159 hours. Overall, the pharmacokinetics of gilteritinib appear suitable for once daily dosing.

6.3 Study 2215-CL-0101: Anti-leukemic Response

Clinical response to gilteritinib in FLT3 mutation positive patients is shown by initially assigned dose group in [Table 6]. The observed composite complete remission (CRc) rate at the end of treatment for FLT3 mutation positive patients in dose groups of ≥ 80 mg was 40.8%, with an additional 11.3% of patients achieving partial response (PR). Median duration of response for these patients was 112 days, median OS was 214 days, with survival

probabilities of 56.6% at 26 weeks and 21.7% at 1 year. Response rates in FLT3 mutation negative patients were low (8.6% across dose groups).

Table 6 Study 2215-CL-0101: Clinical Response to Gilteritinib (20 to 450 mg) by Dose in FLT3 Mutation Positive Patients

Clinical Response	Number of FLT3 Mutation Positive Patients n (%) [95% CI] †,‡							
	20 mg (N = 14)	40 mg (N = 8)	80 mg (N = 12)	120 mg (N = 56)	200 mg (N = 89)	300 mg (N = 10)	450 mg (N = 2)	Total (N = 191)
End of Treatment								
CR	0	0	2 (16.7) [2.1, 48.4]	7 (12.5) [5.2, 24.1]	8 (9.0) [4.0, 16.9]	1 (10.0) [0.3, 44.5]	0	18 (9.4) [5.7, 14.5]
CRp	0	0	0	2 (3.6) [0.4, 12.3]	7 (7.9) [3.2, 15.5]	1 (10.0) [0.3, 44.5]	0	10 (5.2) [2.5, 9.4]
CRi	1 (7.1) [0.2, 33.9]	0	3 (25.0) [5.5, 57.2]	17 (30.4) [18.8, 44.1]	20 (22.5) [14.3, 32.6]	1 (10.0) [0.3, 44.5]	0	42 (22.0) [16.3, 28.5]
PR	1 (7.1) [0.2, 33.9]	3 (37.5) [8.5, 75.5]	3 (25.0) [5.5, 57.2]	5 (8.9) [3.0, 19.6]	7 (7.9) [3.2, 15.5]	3 (30.0) [6.7, 65.2]	1 (50.0) [1.3, 98.7]	23 (12.0) [7.8, 17.5]
CRc rate	1 (7.1) [0.2, 33.9]	0	5 (41.7) [15.2, 72.3]	26 (46.4) [33.0, 60.3]	35 (39.3) [29.1, 50.3]	3 (30.0) [6.7, 65.2]	0	70 (36.6) [29.8, 43.9]
Response rate	2 (14.3) [1.8, 42.8]	3 (37.5) [8.5, 75.5]	8 (66.7) [34.9, 90.1]	31 (55.4) [41.5, 68.7]	42 (47.2) [36.5, 58.1]	6 (60.0) [26.2, 87.8]	1 (50.0) [1.3, 98.7]	93 (48.7) [41.4, 56.0]

Full Analysis Set: All patients who were enrolled and received at least 1 dose of study drug and who had at least 1 posttreatment data point.

Patients are included in the dose group of the initial dose received prior to any dose increase or decrease.
CRc rate = CR + CRp + CRi. Response rate = CRc + PR.

CI: confidence interval; CR: complete remission; CRc: composite CR; CRi: CR with incomplete hematological recovery; CRp: CR with incomplete platelet recovery; FLT3: FMS-like tyrosine kinase 3; PR: partial remission.

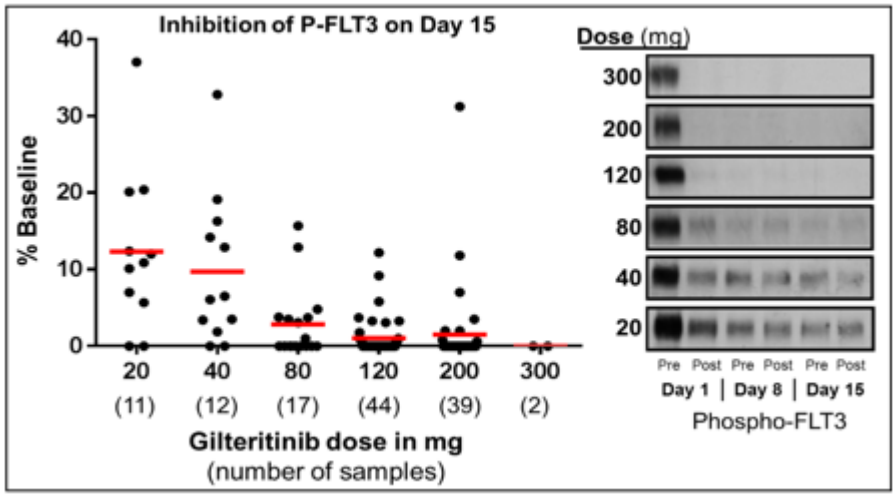
† Exact 95% CI was estimated using the binomial distribution.

‡ Based on local FLT3 mutation testing.

At present, 9 FLT3 mutation positive patients remain on study drug in Study 2215-CL-0101. All 9 of these patients have been durably on treatment for more than 1 year, with 6 patients on treatment for more than 2 years; the range for study treatment at present for these patients is 1.6 to 2.9 years.

CRc occurred more commonly in patients with gilteritinib steady-state trough concentrations ≥ 100 ng/mL which can be achieved at once-daily gilteritinib doses of 80 mg or greater. Gilteritinib exhibited rapid and sustained inhibition of FLT3 phosphorylation, with greater than 90% inhibition of FLT3 phosphorylation observed by cycle 1 day 8 at gilteritinib doses of ≥ 80 mg (ex vivo plasma inhibitory activity [PIA] assay, [Figure 2]).

Figure 2 Study 2215-CL-0101: Plasma Inhibitory Assay



An ad hoc analysis of minimal residual disease in patients receiving 120 mg and 200 mg demonstrated that 25% of evaluable patients achieved an ITD signal ratio of 10^{-2} or less (signal ratio is defined as FLT3/ITD to Total FLT3). This molecular response was associated with clinical response. Furthermore, the depth of the molecular response correlated with OS, as patients who achieved an ITD signal ratio of 10^{-2} or lower demonstrated longer OS, even with censoring at the time of HSCT.

6.4 Study 2215-CL-0101: Safety

An overview of adverse events (AE) for the safety analysis set are shown in [Table 7]. Overall, 249 patients (98.8%) experienced at least one AE during the treatment period, with 188 patients (74.6%) experiencing at least one drug-related AE during the treatment period (drug-related AEs were defined as events assessed by the investigator to be probably or possibly attributable to gilteritinib). Two-hundred-and-twenty-seven patients (90.1%) experienced an AE with a National Cancer Institute-Common Criteria for Adverse Events (NCI-CTCAE) Grade ≥ 3, with 124 patients (49.2%) experiencing a drug-related AE NCI-CTCAE Grade ≥ 3. Two-hundred-and-seven patients (82.1%) experienced a serious AE, with 72 patients (28.6%) experiencing a drug-related serious AE.

Table 7 Study 2215-CL-0101: Overview of Adverse Events

Safety Overview	Safety Analysis Set (N = 252)	
	n	%
Treatment-emergent AEs	249	98.8%
Drug-related treatment-emergent AEs	188	74.6%
Treatment-emergent AEs leading to discontinuation	76	30.2%
Drug-related treatment-emergent AEs leading to discontinuation	25	9.9%
Treatment-emergent AEs, NCI-CTCAE, Grade ≥ 3	227	90.1%
Drug-related treatment-emergent AEs, NCI-CTCAE, Grade ≥ 3	124	49.2%
Serious treatment-emergent AEs	207	82.1%
Drug-related treatment-emergent serious AEs	72	28.6%
Treatment-emergent AEs leading to death	95	37.7%

AE: adverse events; NCI-CTCAE: National Cancer Institute-Common Criteria for Adverse Events

Seventy-six patients (30.2%) experienced an AE leading to permanent discontinuation of study drug, The most common events (at least 1.5% of patients) leading to discontinuation were acute myeloid leukemia (15 patients, 6.0%), sepsis (7 patients, 2.8%) and respiratory failure (4 patients, 1.6%) [Table 8]. Twenty-five patients (9.9%) experienced events leading to discontinuation that were considered drug-related, none of these drug-related events led to treatment discontinuation in more than one patient.

Table 8 Study 2215-CL-0101: Most Common Adverse Events Leading to Discontinuation

Adverse Events Leading to Discontinuation (at least 1.5% of patients), MedDRA (V 16.0), Preferred Term	Safety Analysis Set (N = 252)	
	n	%
Total	**76**	**30.2%**
Acute myeloid leukemia	15	6.0%
Sepsis	7	2.8%
Respiratory failure	4	1.6%

The most common events AEs of NCI-CTCAE Grade ≥ 3 (those occurring in at least 10% of patients) were febrile neutropenia (98 patients, 38.9%), anemia (62 patients, 24.6%), acute myeloid leukemia (43 patients, 17.1%), platelet count decreased (37 patients, 14.7%), sepsis (35 patients, 13.9%), thrombocytopenia (33 patients, 13.1%) and pneumonia (31 patients, 12.3%) [Table 9]. These reflect events that are commonly observed among patients undergoing treatment for AML. Drug-related AEs of NCI-CTCAE Grade ≥ 3 occurring in greater than 5% of patients were anemia (21 patients, 8.3%), platelet count decreased (17 patients, 6.7%) and thrombocytopenia (14 patients, 5.6%).

Table 9 Study 2215-CL-0101: Most Common Adverse Events, National Cancer Institute-Common Criteria for Adverse Events (NCI-CTCAE) Grade ≥ 3

Adverse Events NCI-CTCAE Grade ≥ 3 (at least 10% of patients), MedDRA (V 16.0), Preferred Term	Safety Analysis Set (N = 252)	
	n	%
Total	**227**	**90.1%**
Febrile neutropenia	98	38.9%
Anemia	62	24.6%
Acute myeloid leukemia	43	17.1%
Platelet count decreased	37	14.7%
Sepsis	35	13.9%
Thrombocytopenia	33	13.1%
Pneumonia	31	12.3%

A total of 207 (82.1%) patients experienced a serious AE; the most common events again reflect events that are commonly observed among patients undergoing treatment for AML. [Table 10].

Table 10 Study 2215-CL-0101: Most Common Serious Adverse Events

Serious Adverse Events (at least 5% of patients), MedDRA (V 16.0), Preferred Term	Safety Analysis Set (N = 252)	
	n	%
Total	**207**	**82.1%**
Febrile neutropenia	78	31.0%
Acute myeloid leukemia	43	17.1%
Sepsis	36	14.3%
Pneumonia	27	10.7%
Acute renal failure	25	9.9%
Pyrexia	21	8.3%
Bacteremia	14	5.6%
Respiratory Failure	14	5.6%

The majority of serious AEs were considered by the investigator to be not related to the study drug, with 28.6% of patients overall experiencing a drug-related serious AE [Table 11]. The most frequent drug-related serious AEs were acute renal failure (5 patients, 2.0%), blood creatine phosphokinase increased (5 patients, 2.0%), febrile neutropenia (5 patients, 2.0%) and aspartate aminotransferase (AST) increased (4 patients, 1.6%).

Table 11 Study 2215-CL-0101: Most Common Drug-related Serious Adverse Events

Serious Adverse Events (greater than 1% of patients), MedDRA (V 16.0), Preferred Term	Safety Analysis Set (N = 252)	
	n	%
Total	**72**	**28.6%**
Acute renal failure	5	2.0%
Blood creatine phosphokinase increased	5	2.0%
Febrile neutropenia	5	2.0%
Aspartate aminotransferase increased	4	1.6%
Blood bilirubin increased	3	1.2%
Diarrhoea	3	1.2%
Gastrointestinal haemorrhage	3	1.2%
Hypotension	3	1.2%
Pyrexia	3	1.2%

Ninety-five patients (37.7%) experienced an AE that resulted in death [Table 12]; disease progression was the most commonly reported AE with fatal outcome (16.3%). Six AEs resulting in death were assessed by the investigator to be possibly attributable to gilteritinib administration (1 case each of intracranial hemorrhage, pulmonary embolism, hemoptysis, septic shock, neutropenia and ventricular fibrillation), and 1 AE resulting in death was assessed as probably attributed to gilteritinib administration (respiratory failure). Additional information regarding these events is provided as an appendix in [Section 11, Table 14].

Table 12 Study 2215-CL-0101: Most Common Adverse Events Leading to Death

Adverse Events Leading to Death, MedDRA (V 16.0), Preferred Term	Safety Analysis Set (N = 252)	
	n	%
Total	**95**	**37.7%**
Disease progression	41	16.3%
Multiple organ failure	7	2.8%
Sepsis	7	2.8%
Respiratory failure	7	2.8%
Pneumonia	4	1.6%
Septic shock	4	1.6%

The following are risks identified as associated with gilteritinib treatment in Study 2215-CL-0101:

Posterior Reversible Encephalopathy Syndrome (PRES)

- Two patients (1 in the 120 mg dose group, 1 in the 200 mg dose group) developed PRES, a serious neurologic condition. Symptoms included seizure, altered mental status and MRI findings consistent with PRES. Both patients were discontinued from gilteritinib treatment, and the patients' altered mental status returned to baseline with no other episodes of seizure.

QT Prolongation

- Ten percent of patients experienced a QT interval (Fridericia's correction, QTcF) of > 480 msec and 8.8% experienced a maximal QTcF change from baseline of > 30 msec; the majority of these patients were concurrently taking at least one concomitant medication with a known risk of QT prolongation.
- In Study 2215-CL-0101, there was 1 serious AE of sudden death (assessed by the investigator as not drug-related), 1 serious AE of ventricular tachycardia (assessed by the investigator as not drug-related) and 1 serious AE of ventricular fibrillation (assessed by the investigator as possibly drug-related). Additional information regarding these events is provided as an appendix in [Section 11, Table 15].
- Overall, there have been no reported cases of torsades de pointes across the clinical development program.
- A concentration-related increase in ΔQTcF was observed across gilteritinib doses ranging from 20 to 450 mg. The predicted mean ΔQTcF at the mean gilteritinib steady-state C_{max} (282.0 ng/mL) was 5.70 msec with an upper 1-sided 95% CI = 7.41 msec. As the predicted upper limit of the mean change from baseline is less than 10 msec, this effect is not considered clinically significant.
- Gilteritinib clinical studies exclude patients with a baseline QTc of greater than 450 ms, or a history of long QT syndrome, hypokalemia or hypomagnesemia. Additionally, all gilteritinib studies include ECG monitoring at multiple study timepoints.

Elevated Creatine Kinase (CK)

- The incidence of higher CTCAE grades of elevated creatine kinase (CK) laboratory values appeared to increase with increasing gilteritinib dose. However, almost all of the observed elevations in CK laboratory values were grade 1 and grade 2.
- PK/PD modelling demonstrated a statistically significant, exposure-related increase in CK with increasing gilteritinib plasma concentrations across gilteritinib doses ranging from 20 to 450 mg.
- Four patients (1.6%) experienced muscle related serious AEs (1 myopathy, 1 myositis, 2 muscle weakness). An additional patient in the 300 mg dose group developed rhabdomyolysis, which resolved after gilteritinib discontinuation.
- Gilteritinib clinical studies include routine laboratory monitoring CK elevation.

Elevated Liver Transaminases

- Grade 3 or higher increases in laboratory values (26 patients, 10.4%) and/or ≥ grade 3 AEs (15 patients, 6.0%) for AST were low. Similar results were seen for ALT (26 patients, 10.4%; 13 patients, 5.2%, respectively).

- The incidence of ALT and/or AST elevations > 3x ULN was 30.1% (75 patients); ALT > 10x ULN was 2.4% (6 patients); and AST > 10x ULN was 0.8% (2 patients). The incidence of total bilirubin elevations > 2x ULN was 4.8% (12 patients).
- Three patients (1.2%) experienced increases in total bilirubin > 2x ULN concurrent with ALT and/or AST > 3x ULN. None of these cases were confirmed as Hy's Law cases. Additional information regarding these cases is provided as an appendix in [Section 11, Table 16].
- There were no reported events of liver failure or Drug-Induced Liver Injury.
- An exposure-related, statistically significant increase was observed between gilteritinib plasma concentration and ΔAST across gilteritinib doses ranging from 20 to 450 mg. A similar relationship was observed for gilteritinib plasma concentration and ΔALT.
- Gilteritinib clinical studies include routine laboratory monitoring for hepatocellular and biliary function.

6.5 Study 2215-CL-0101: Summary

In a population of adult patients with R/R AML, gilteritinib exhibited linear, dose-proportional pharmacokinetics at doses ranging from 20 to 450 mg administered once daily. The observed CRc rate at the end of treatment for FLT3 mutation positive patients in initial dose groups of ≥ 80 mg was 40.8%, with an additional 11.3% of patients achieving PR. Median duration of response for these patients was 112 days, and median OS was 214 days, with survival probabilities of 56.6% at 26 weeks and 21.7% at 1 year. These response and survival data compare favorably to historical data in patients with R/R AML [Section 3]. Gilteritinib was generally tolerable at doses up to 300 mg in this study. The MTD for the study was determined to be 300 mg. Based on exposure, response and safety data, a starting dose of 120 mg gilteritinib is expected to result in adequate drug exposure for clinical efficacy (based on response and PIA data) for phase 3 studies in adult patients with FLT3 mutation positive relapsed/refractory AML.

7 GILTERITINIB: PEDIATRIC DEVELOPMENT PLAN

7.1 Overview

The proposed pediatric development plan has been developed in consultation with a panel consisting of US and European medical experts with knowledge and experience in the management of pediatric AML patients. Astellas' pediatric development plan is currently also in review with EMA as a Pediatric Investigation Plan (PIP). Astellas intends to design and conduct a single pediatric development plan to support all regions globally.

Two pediatric patient populations are planned:

Pediatric patients from 2 years and older with FLT3/ITD positive AML, who are refractory to or have a relapse after initial induction therapy, treated with gilteritinib in combination with chemotherapy (Study 2215-CL-0603).

Pediatric patients from 2 years and older with newly diagnosed FLT3/ITD positive AML, treated with gilteritinib in combination with chemotherapy (Study 2215-CL-0604).

7.2 Nonclinical Studies

Nonclinical data suggests that gilteritinib could affect development of the heart in newborns and infants in humans via inhibitory effects of gilteritinib on the serotonin $5HT_{2B}$ receptor. This effect cannot be investigated in animals, because the heart is already mature at the age when administration of gilteritinib can be started experimentally in animals. Consequently, Astellas proposes that gilteritinib will not be used clinically in children under the age of 6 months.

A juvenile toxicology study will be conducted in rats to support the clinical pediatric development of gilteritinib. If supported by the results of this toxicology study, patients between the ages of 6 months and 2 years will be added to the planned pediatric clinical studies.

7.3 Pediatric Formulation

The adult phase 3 trials currently utilize 40 mg tablets, which contain 40 mg of active ingredient as free base. For pediatric clinical studies, Astellas proposes to use the currently available 40 mg tablet used in adult clinical studies, and to develop an additional mini-tablet formulation for use in the pediatric population. The existing 40 mg tablet does not allow appropriate dosing for all children; for instance, smaller children may require a dose of less than 40 mg, or some other fractional dose of the current tablet size (e.g., 50 mg, 60 mg, etc). Therefore, Astellas will develop a 10 mg mini-tablet, which can be administered either as a tablet or as an oral suspension. This information is summarized in [Table 13].

Table 13 Proposed Gilteritinib Administration

Patients	Proposed Gilteritinib Administration
Children who can swallow tablets	40 mg tablet, 10 mg mini-tablet
Children who require liquid dosing	Oral suspension from 10 mg mini-tablet

For the 10 mg mini-tablets, Astellas intends to use the same ingredients contained in the 40 mg tablets, however, the final qualitative composition is not yet available. The intent is to produce round mini-tablet with an anticipated maximum diameter of 3 to 4 mm and a film-coat. The mini-tablets will be formulated to allow their administration as an oral suspension in water.

Palatability of the Planned Pediatric Dosage Forms

Astellas recognizes that acceptable palatability of the drug product is one of the main factors in dosing compliance in the pediatric population. Therefore, the palatability of the oral suspension is being evaluated during development, and a palatable oral suspension will be developed before administration to patients. The development work for the palatability of the oral suspension is being evaluated as part of Study 2215-CL-0601 [Section 7.5].

7.4 Pediatric Clinical Studies

7.4.1 Pediatric Patients with R/R FLT3/ITD AML

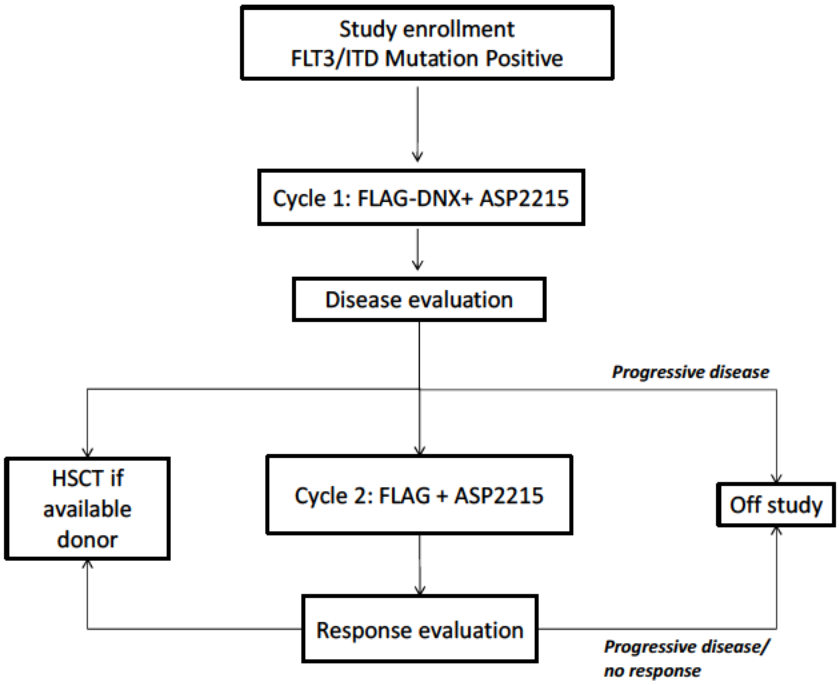
Study 2215-CL-0603: Phase 1/2 Study of Gilteritinib Combined with Chemotherapy in Children with FLT3/ITD Positive AML in First Relapse

Study 2215-CL-0603 is an open-label, single arm, phase 1/2 study. The primary objective of the phase 1 portion of this study is to establish a safe and biologically active dose (the recommended phase 2 dose [RP2D]) for gilteritinib in combination with fludarabine, cytarabine, GCS-F and liposomal daunorubicin (FLAG-DNX). The phase 1 portion will enroll at least 9 and up to 21 patients, ages 2 years to ≤ 21 years old, with a diagnosis of FLT3/ITD AML, in relapse or refractory to induction therapy. Patients between the ages of 6 months to 2 years of age will be enrolled if supported by the results of the juvenile toxicology study.

The starting dose of gilteritinib used for children will be 40 mg/m^2, approximately equivalent to an 80 mg daily dose in adults when converted to per m^2 dosing. This starting dose is 1 dose level lower than the starting dose currently being used in the adult phase 3 studies (120 mg daily, approximately equivalent to 60 mg/m^2). One dose de-escalation to 20 mg/m^2, and 2 dose escalations to 60 mg/m^2 and 90 mg/m^2 will be allowed. Cohorts of 3 patients will be treated at 1 of a series of doses of gilteritinib according to a standard 3+3 patient cohort dose escalation. At study initiation, only patients that can swallow tablets will be enrolled in the study, patients that cannot swallow tablets will enrolled only after the availability of the gilteritinib oral suspension. The RP2D will be based on 2 factors, an acceptable dose limiting toxicity profile and a high degree of gilteritinib biologic activity (as measured by PIA).

The primary objective of the phase 2 portion of the study is to evaluate the CRc rate, defined as a CR, CRp or complete response with incomplete hematological recovery (CRi) after 2 courses of gilteritinib in combination with chemotherapy. Forty patients with a diagnosis of FLT3/ITD AML, in relapse or refractory to initial induction therapy are proposed to be enrolled in phase 2. Additional objectives will include a determination of the mechanisms of innate and acquired resistance to gilteritinib under the conditions of the study, serial measurements of minimal residual disease (MRD), and PK. The primary endpoint will compare the effectiveness of gilteritinib + induction chemotherapy against a null hypothesis CRc rate of 35%.

Treatment Plan



Statistical Design: Phase 1

Cohorts of 3 patients will be treated at 1 of a series of doses of gilteritinib according to a standard 3+3 patient cohort dose escalation. Blood from the patients treated at the MTD will then be assayed for gilteritinib activity, using PIA. Additional patients will be accrued at the MTD as needed to ensure that gilteritinib activity is assessable in at least 9 such patients. For the MTD to be considered biologically active, we will require that 7 of 9 patients achieve PIA of > 90% at 3 of 4 trough time points. If the study dose of 90 mg/m^2/day is well tolerated but does not show sufficient gilteritinib activity, the study may proceed to greater dose levels. If toxicity at the 90 mg/m^2/day dose would allow further escalation, but demonstrates sufficient gilteritinib activity, no further dose escalation will be required. The RP2D will be a safe dose of gilteritinib that demonstrates sufficient activity.

Statistical Design: Phase 2

The phase 2 portion of this trial will be a single arm, 2 stage open label design with a total of 40 response-evaluable patients enrolled. Patients are response evaluable if (1) they are confirmed FLT3/ITD, (2) they receive at least 1 dose of gilteritinib, and (3) they are progression/recurrence free during the first 2 cycles of chemotherapy + gilteritinib and have the required bone marrow evaluations, or have overtly progressed or died of disease or toxicity during the first 2 cycles. The primary endpoint will be CRc rate after 2 cycles of therapy. Patients who die during treatment will be counted as non-responders for purposes of

analysis. In our available dataset (COG AAML 06P1, I-BFM AML 2001-01, Costa dataset) there are a total of 26 CR's out of 73 patients (≈ 35%). With Type I error rate of 5% at the null hypothesis, there will be 80% power to detect a 56% response rate (i.e., a 21% increase in response rate from the null hypothesis value of 35%), and 90% power to detect 60% response rate (i.e. a 25% increase). Operationally, 21 patients will be enrolled during the first stage, with 10 responses required to continue accrual to 40 patients. Ultimately 29 of 40 patients will be required to meet the efficacy threshold of chemotherapy + gilteritinib. The probability of halting the study after the first stage is 84% under the null hypothesis.

Study 2215-CL-0603 is planned to initiate enrollment following the confirmation of the safety and efficacy of gilteritinib in adult FLT3 mutation positive R/R AML patients [Table 4]. Astellas is currently in discussions to conduct this trial in partnership with a pediatric oncology cooperative group.

7.4.2 Pediatric Patients with newly diagnosed FLT3/ITD AML

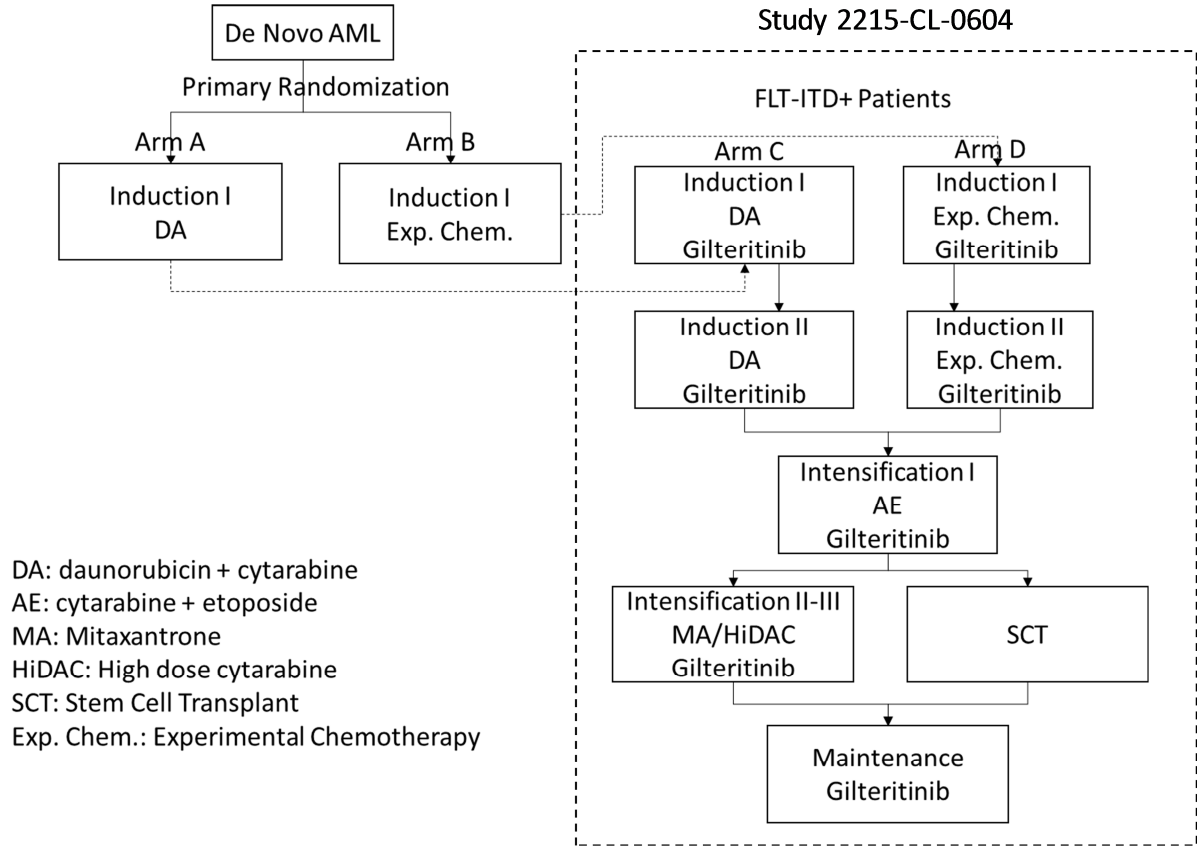
Study 2215-CL-0604: Phase 2 study of gilteritinib in combination with chemotherapy in pediatric patients with newly diagnosed AML with FLT3/ITD mutation

The study described below is proposed to be run as part of a larger cooperative group investigation that will evaluate multiple agents under development, and the overall study design is still under discussion. The information presented here is preliminary and intended to elicit discussion and feedback.

Study 2215-CL-0604 is an open label, phase 2 study investigating the addition of gilteritinib to standard induction chemotherapy and maintenance for patients with newly diagnosed FLT3/ITD positive AML. The patients for Study 2215-CL-0604 will be pulled from a larger phase 3 newly diagnosed AML study being conducted by a cooperative group that compares a standard chemotherapy regimen to an experimental arm (Arms A and B). Newly diagnosed patients participating in the phase 3 trial will be tested for presence of FLT3/ITD mutation. They will then be randomized to either the standard chemotherapy or the experimental therapy arm. Children with FLT3/ITD will be offered participation on separate arms (Arm C/Arm D) of the trial; these arms will provide gilteritinib in combination with their assigned chemotherapy backbone (conventional chemotherapy or experimental chemotherapy). Given that gilteritinib has not yet been combined with daunorubicin and cytarabine (DA) in children or with the experimental chemotherapy, a safety phase (Safety Phase 2) that will address the feasibility of administering gilteritinib in combination with either approach will be incorporated. The starting gilteritinib dose will be the RP2D established in Study 2215-CL-0603. For FLT3/ITD patients who sign a second consent for Arm C or D, gilteritinib will begin on day 11 of Induction I (Arm C) and be administered for 14 days each cycle. For patients enrolled on Arm C or D, maintenance gilteritinib therapy will begin between day 40-100 post stem cell transplant once the maintenance eligibility have been met. Maintenance treatment will continue for 1 year from the time of treatment start.

The primary objective of the study for patients with FLT3/ITD positive AML is to demonstrate the efficacy of gilteritinib in combination with standard treatment in pediatric patients (2 years to 21 years old) with newly diagnosed FLT3/ITD AML, as measured by event-free survival (EFS) at 2 years after initiation of treatment. Patients between the ages of 6 months to 2 years of age will be enrolled if supported by the results of the juvenile toxicology study. Secondary objectives will be to evaluate the efficacy and safety of gilteritinib in combination with conventional chemotherapy in terms of CR, OS, AEs, clinical laboratory, vital signs and electrocardiograms (ECGs). The study will also explore the pharmacokinetics of gilteritinib (and metabolite, if applicable) in the study population using a population pharmacokinetics approach.

Treatment Plan



Statistical Design

The patients in Arm C will be compared to historical data from FLT3/ITD patients treated with standard therapy in prior cooperative group trials, such as Children's Oncology Group Trial AAML0531.

The primary objective of the FLT3/ITD arms is to compare the EFS of FLT3/ITD patients receiving DA + gilteritinib to FLT3/ITD patients treated with standard therapy without a FLT3 inhibitor in previous cooperative group trials (for instance, Trial AAML0531 Arm A).

EFS will be estimated using the Kaplan Meier approach. It is estimated that there will be 56 patients in Arm C included in the EFS analysis. There will be 80% power using a 2-sided test with 0.05 type I error to detect a 17% increase in 2-year EFS (41% versus 58%) compared to the null EFS of 41% (the observed 2-year EFS for Trial AAML0531 Arm A patients with FLT3/ITD positive AML).

DA or Experimental Chemotherapy with Gilteritinib Dose Determination Phase (Safety Phase 2)

Gilteritinib dose determination will occur for patients participating in Arm C and D. The dose finding phase will assess DLTs and determine if 60 mg/m^2/dose PO daily for 14 days is tolerable in combination with DA and with other experimental chemotherapy utilized in Induction I. DLT determination will be based on tolerability in Induction I only.

DLT analysis will be conducted independently for Arm C and Arm D. On a given arm, at least 4 and no more than 10 evaluable patients may be accrued to a dose level in the dose determination portion of the protocol. Accrual to a dose level will stop as soon as more than 3 of the enrolled patients meet dose-limiting toxicity criteria. The recommended phase 2 dose for gilteritinib for that treatment arm will be the highest of the 2 dose levels to be studied at which no more than 3 of 10 patients develop DLT during the first course (Cohort 1). If dose level 1 (60 mg/m^2/dose PO daily) is not tolerated, then patients will be accrued to dose level 0 (40 mg/m^2/dose PO daily). If dose level 0 is not tolerated then that arm of the study will close.

Study 2215-CL-0604 is planned to initiate enrollment following the confirmation of the RP2D from Study 2215-CL-0603.

7.5 Supportive Clinical Studies

Two additional studies will be conducted in adults to support this pediatric investigation plan: a palatability study for the mini-tablet/oral suspension (Study 2215-CL-0601) and a study to assess the relative bioavailability of the gilteritinib 40 mg tablet, mini-tablet, and oral suspension (Study 2215-CL-0602).

8 SUMMARY

AML is a rare but life-threatening disease in adults and children, and patients with FLT3 mutation positive AML are predisposed to particularly poor outcomes. Gilteritinib is an orally available FLT3 inhibitor that has demonstrated anti-leukemic activity in FLT3 mutation positive R/R AML, with a tolerable safety profile.

In consultation with experts in the field of pediatric hematology and oncology, Astellas is considering a pediatric investigation plan that includes both newly diagnosed FLT3/ITD patients and patients with FLT3/ITD AML that have relapsed or were refractory to initial induction chemotherapy, which together represent areas of serious unmet medical need for pediatric AML. Astellas believes that this pediatric plan is robust and will provide sufficient data to support an appropriate label in this patient population.

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10 APPENDIX 1: NONCLINICAL SAFETY PHARMACOLOGY AND TOXICOLOGY SUMMARY

Safety Pharmacology

Gilteritinib showed a concentration-dependent suppression effect on the human ether-a-go-go related gene (hERG) current in hERG-transfected HEK293 cells. The IC_{50} was 1.6×10^{-5} mol/L.

Gilteritinib increased the currents via CaV1.2 calcium channel in Chinese hamster ovary cells and KV7.1/minK potassium channel in HEK293 cells at 1×10^{-6} mol/L and higher concentrations. Gilteritinib did not affect hERG trafficking in hERG-transfected HEK293 cells up to 1×10^{-5} μmol/L.

In rats treated with gilteritinib, decreased urination at 30 mg/kg and higher and decreased defecation at 100 mg/kg were observed. In dogs treated with gilteritinib, retching at 3 mg/kg, vomiting and positive fecal occult blood at 10 mg/kg and higher, a decrease in the blood calcium ion (Ca^{2+}) concentration at 30 mg/kg, and salivation and an increase followed by a decrease in the blood Ca^{2+} concentration at 100 mg/kg were observed.

Toxicology

In the single oral dose toxicity study in rats, the approximate lethal dose level was 300 mg/kg. The major change was a gastrointestinal hemorrhagic disorder at 100 and 300 mg/kg. Reversibility of the changes noted in the surviving animals was seen. No definitive single oral dose toxicity study in dogs was conducted. However, in the 4-week toxicity study in dogs, a dose of 1000 mg/kg per day caused deaths and moribund sacrifices on day 2. The cause of death and moribundity was considered to be deterioration of general condition caused by gastrointestinal hemorrhage.

In the 1-week oral repeated dose toxicity study in rats, interstitial pneumonia in the lung and vacuolar change in the rod-cone layer of the retina were observed at 30 mg/kg per day. In the 13-week oral repeated dose toxicity study in rats, deaths occurred at 20 mg/kg per day. Target organ toxicity was identified in the gastrointestinal tract, immune system, hematopoietic system, eye, lung, kidney and liver. The no observed adverse effect level (NOAEL) was lower than 2.5 mg/kg per day. The changes noted during the dosing period recovered or tended to recover during the 4-week recovery period. In the 4-week oral repeated dose study in dogs, mortality occurred at 10 mg/kg per day or more. Target organ toxicity was identified in the gastrointestinal tract, immune system, hematopoietic system, eye, kidney and liver. The NOAEL was 1 mg/kg per day. Reversibility of most of the test article-related changes was indicated by the end of the 4-week recovery period. In the 13-week oral repeated dose study in dogs, mortality occurred at 5 mg/kg per day. Target organ toxicity was identified in the lung, lacrimal gland, urinary bladder, epithelial tissue, gastrointestinal tract, immune system, hematopoietic system, eye, kidney and liver. The

NOAEL was 1 mg/kg per day. Reversibility of most of the test article-related changes was indicated by the end of the 4-week recovery period.

Gilteritinib did not induce gene mutation in the definitive in vitro reversion test in bacteria. Similarly, gilteritinib did not induce chromosomal aberrations in the definitive in vitro chromosomal aberration test in mammalian cells. The definitive in vivo micronucleus test showed that gilteritinib has a potential to induce micronuclei in mice.

Gilteritinib showed teratogenicity and embryo-fetal deaths in the embryo-fetal development study in rats. The NOAEL for dams and embryo-fetal development was 10 mg/kg per day.

Gilteritinib showed no potential to induce phototoxicity to cultured mammalian cells.

11 APPENDIX 2: ADDITIONAL SAFETY INFORMATION

Table 14 Study 2215-CL-0101: Drug-related Adverse Events Leading to Death

Dose Level (mg)	MedDRA (V16.0) Preferred Term	Day of Death	Last Dose Day	Relationship to Study Drug	Sponsor Comment
20	**Haemorrhage intracranial**	11	11	Possible	The Sponsor assessed the event of intracranial hemorrhage as possibly related to the study drug, based on the available information and in alignment with the investigator; however, the underlying AML was considered a confounder. Concurrent conditions included decreased platelets which may have predisposed the patient to bleeding.
80	**Septic Shock** Renal failure acute Hyponatraemia	14	12	Possible Not related Not related	The Sponsor assessed the event of septic shock as possibly related to study drug considering a plausible temporal relation and known drug profile, however, reduced immunity due to underlying malignancy may have provided a more plausible alternative etiology for the event. The Sponsor assessed the event of acute kidney injury as not related to study drug as current conditions of hypertension, mild chronic kidney disease, disease under study, and anti-hypertensive medications provided more plausible explanations. The Sponsor assessed the event of hyponatremia as not related to study drug as it was probably due to poor oral intake by the patient, additionally multiple concomitant medications may have played a contributory role.
80	**Hemoptysis**	61	57	Possible	The Sponsor assessed the event of hemoptysis as possibly related to study drug per the implied time line. A confounder was underlying AML. Autopsy summary showed that lung involvement of AML and/or concurrent fungal pneumonia likely contributed to the erosion of a pulmonary vessel leading to massive hemoptysis in the setting of chronic pancytopenia and coagulopathy.
120	**Ventricular fibrillation***	12	10	Possible	The Sponsor assessed the event of ventricular fibrillation as possibly related to study drug. Considering the plausible temporal relationship, a causal role of the study drug in the reported event could not be excluded. However, electrolyte abnormalities preceding the reported event, supraventricular tachycardia prior to initiation of study drug, history of smoking, cardiac disorders, concomitant use of levofloxacin, baclofen, amphotericin-B, meropenem, and caspofungin with the potential risk of cardiac adverse reactions were confounders for the reported event.
120	**Respiratory failure** Subdural haematoma Sepsis	15	8	Probable Not related Not related	The Sponsor assessed the event of respiratory failure as probably related to study drug based on the temporal association present and a potential risk of differentiation syndrome and capillary leak with the study drug treatment. The Sponsor assessed, in agreement with reporting Investigator, the event of subdural hematoma as not related to study drug. Of note, the underlying AML and bleeding associated with it may have provided an alternative explanation for the event. The Sponsor assessed the event of sepsis as not related to study drug. The underlying AML with concurrent pleural and pericardial effusions was considered a strong confounding factor.
120	**Neutropenia** Diarrhoea	94	72	Possible Not related	The Sponsor assessed the event of neutropenia as possibly related to study drug based on the plausible temporal relationship present. However, the underlying AML was deemed a strong confounding factor for the fatal event. The patient died due to severe neutropenia with anemia and thrombocytopenia. The Sponsor assessed the event of diarrhea as not related to study drug; the event was attributed to an unspecified concurrent illness.
300	**Pulmonary embolism**	8	8	Possible	The Sponsor assessed the event of pulmonary embolism as possibly related to study drug based on temporal relationship; confounded by underlying disease. Patient was on do-not-resuscitate orders. An autopsy was performed and the cause of death was pulmonary embolism.

Bolded MedDRA Preferred Term indicates the AE that resulted in death

* Same patient described in the table below in Table 15

Table 15 Study 2215-CL-0101: Selected Cardiac Serious Adverse Events

Dose Level (mg)	MedDRA (V16.0) Preferred Term	Day of Death	Last Dose Day	Relationship to Study Drug	Sponsor Comment
120	**Ventricular fibrillation***	12	10	Possible	The Sponsor assessed the event of ventricular fibrillation as possibly related to study drug. Considering the plausible temporal relationship, a causal role of the study drug in the reported event could not be excluded. However, electrolyte abnormalities preceding the reported event, supraventricular tachycardia prior to initiation of study drug, history of smoking, cardiac disorders, concomitant use of levofloxacin, baclofen, amphotericin-B, meropenem, and caspofungin with the potential risk of cardiac adverse reactions were confounders for the reported event. The patient had no QTcF reading that exceeded 400 msec and the patient's rhythm was consistently sinus tachycardia.
200	**Sudden death** Anorectal cellulitis	13	12	Not related Not related	The Sponsor assessed that an association of the event of sudden death with study drug could not be excluded based on a plausible temporal relationship. The patient received concomitant medications labeled for QT prolongation (levofloxacin, fluconazole) and had single QTcF readings that exceeded 450 msec on day 1 (2 hours post-dose, 458 msec; triplicate mean of 415 msec) and day 8 (predose 452 msec; triplicate mean of 437 msec) with the last ECG recorded 6 days prior to the event. The patient had several medical conditions in addition to AML, independent of study drug treatment, which may have contributed to this fatal event including an upper extremity deep vein thrombosis that was not treated with anticoagulation, morbid obesity, sleep apnea, hypomagnesemia, hypokalemia, hypertension, and hypercholesterolemia.
200	**Ventricular tachycardia** Cellulitis Tooth infection Pneumonia fungal Septic shock Hypocalcaemia Respiratory distress Enterococcal bacteraemia Presyncope Febrile neutropenia Diarrhoea Bacteraemia	140	139	Not related Not related Not related Not related Not related Not related Not related Not related Not related Not related Not related Not related	The Sponsor assessed the event of ventricular tachycardia as not related to study drug with septic shock as the alternative etiology. The patient was hospitalized due to bacteremia on the day prior to death. There were blood cultures growing Gram negative rods and Gram positive cocci. The patient received vancoymycin and meropenem (with levaquin prophylaxis at home) on admission. The patient experienced multiple sustained episodes of ventricular tachycardia and became pulseless. The family was at bedside and confirmed the do not resuscitate/do not intubate code status.

Bolded MedDRA Preferred Term indicates the serious AE of interest

* Same patient described above in Table 14

Table 16 Study 2215-CL-0101: Patients with Liver Chemistries that Met Hy's Law Criteria

Dose Level (mg)	MedDRA (V16.0) Preferred Term	Day of Meeting Hy's Law Laboratory Criteria	Last Dose Day	Relationship to Study Drug	Sponsor Comment
120	Hypocalcaemia Febrile neutropenia Febrile neutropenia	90	127	Not related Not related Not related	The liver chemistries met Hy's Law laboratory criteria on Day 90. Study drug was continued and bilirubin level decreased suggesting an etiology other than study drug. Study drug was discontinued on Day 127 due to disease progression.
200	Febrile neutropenia Febrile neutropenia Blood bilirubin increased Pancreatitis Acute febrile neutrophilic dermatosis Arthralgia Alanine aminotransferase increased Blood bilirubin increased Diarrhoea	28 113	250	Not related Not related Not related Not related Not related Not related Possible Possible Not related	The liver chemistries fluctuated during the study and met Hy's Law laboratory criteria on day 28 and day 113. On day 37, the patient underwent transjugular liver biopsy for abnormal liver function tests (LFT). Liver biopsy results confirmed ongoing graft versus host disease. Patient stopped study drug treatment on Day 250 due to disease progression. The Sponsor assessed the liver chemistry elevations as not related to study drug with ongoing graft versus host disease as an alternative etiology.
200	Hypotension Febrile neutropenia Syncope Clostridium difficile colitis Mental status changes Febrile neutropenia Staphylococcal sepsis Respiratory failure Encephalopathy Staphlococcal sepsis	43	42	Not related Not related Not related Not related Not related Not related Not related Not related Not related Not related	The liver chemistries met Hy's Law laboratory criteria on Day 43 during the reported event of Staphlococcal sepsis. The liver chemistry abnormalities are not related to study drug as the ongoing sepsis provides an alternative etiology.