NANT 2015-02: PHASE 1 STUDY OF LORLATINIB (PF-06463922), AN ORAL SMALL MOLECULE INHIBITOR OF ALK/ROS1, FOR PATIENTS WITH ALK-DRIVEN RELAPSED OR REFRACTORY NEUROBLASTOMA

NCT03107988

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NEW APPROACHES TO NEUROBLASTOMA THERAPY (NANT) CONSORTIUM

NANT 2015-02: PHASE 1 STUDY OF LORLATINIB (PF-06463922), AN ORAL SMALL MOLECULE INHIBITOR OF ALK/ROS1, FOR PATIENTS WITH ALK-DRIVEN RELAPSED OR REFRACTORY NEUROBLASTOMA

IND# __133273_____

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ABSTRACT

Advances in treatments for children with high-risk neuroblastoma (NB) have, until recently, involved addition of cytotoxic therapy to dose-intensive regimens. In this era of targeted therapies, substantial efforts have been made to identify optimal targets for different types of cancer. The discovery of hereditary and somatic activating mutations in the oncogene *ALK* has now placed neuroblastoma among other cancers[1-4], such as melanoma and non-small-cell lung cancer (NSCLC), which benefit from therapies with oncogene-specific small-molecule tyrosine kinase inhibitors. Crizotinib, the ATP-competitive ALK/Met/ROS1 inhibitor, has transformed the landscape for the treatment of NSCLC harboring *ALK* translocations and has demonstrated activity in preclinical models of ALK-driven neuroblastomas [5]. These findings motivated a Phase 1 trial of crizotinib (PF-02341066) in children with refractory neuroblastoma or other malignancies driven by *ALK* rearrangements such as anaplastic large cell lymphoma (ALCL) and inflammatory myofibroblastic tumors (IMTs) [6]. Results from this trial underscored the importance of *ALK* across histologically diverse tumors, but recorded less frequent responses in neuroblastoma than in *ALK* rearranged tumors – highlighting likely differences between therapeutic targeting of full-length ALK in neuroblastoma and of cytoplasmic ALK fusion proteins in ALCL, IMTs, and lung cancer. Parallel preclinical work has further revealed differential sensitivity to crizotinib for the most common ALK variants observed in neuroblastoma [5,7,8], with F1174L and F1245C-mutated cells being resistant when compared with those expressing R1275Q-mutated ALK. Therefore, our goal has been to identify a next-generation *ALK* inhibitor with improved selectivity and potency to target these resistant mutants effectively.

To overcome this clinical obstacle, our goal was to identify inhibitors with improved potency that can target intractable ALK variants such as F1174L. We find that lorlatinib (PF-06463922) has high potency across ALK variants, and inhibits ALK more effectively than crizotinib *in vitro*. Most importantly, lorlatinib induces complete tumor regression in both crizotinib-resistant and sensitive xenograft mouse models of NB, as well as in patient-derived xenografts (PDXs) harboring the crizotinib-resistant F1174L or F1245C mutations. These studies demonstrate that lorlatinib has the potential to overcome crizotinib resistance, and exerts unprecedented activity as a single agent against F1174L and F1245C *ALK*-mutated tumors, while also inducing durable responses in R1275Q xenografts. Taken together, these results provide the rationale to move lorlatinib into clinical trials for treatment of patients with *ALK*-mutated NB.

SIGNATURE PAGE

NANT 2015-02: Phase 1 Study of Lorlatinib (PF-06463922), an Oral Small Molecule Inhibitor of ALK/ROS1, for Patients with ALK-Driven, Relapsed or Refractory Neuroblastoma Study Protocol Version 06/MAY/2022, Amendment 11A.

This protocol has been approved by:

Name: Araz Marachelian, M.D., M.S. Study Role: NANT Medical Director

Signature: _____ Date: _____

Name: Yael Mossé, M.D. Study Role: Study Chair

Signature: _____ Date: _____

This protocol describes the NANT 2015-02 ALK Study and provides information about procedures for patients taking part in the ALK Study.

This protocol has been reviewed and acknowledged by:

Name: _____ Study Role: Site Principal Investigator

Signature: _____ Date: _____

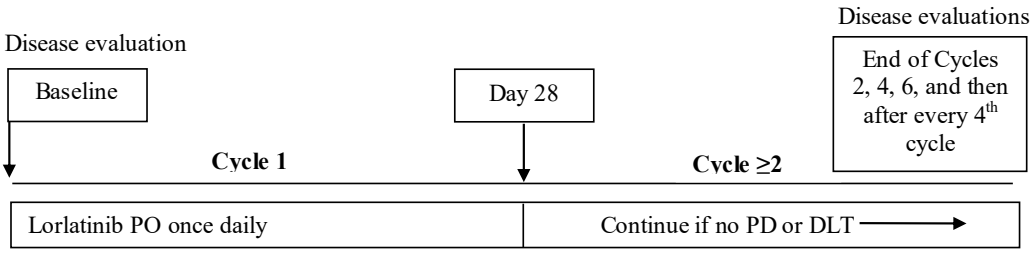
EXPERIMENTAL DESIGN SCHEMA - with Amendment # 7, date 10-31-2019
Lorlatinib will be given orally once daily continuously in 28-day courses. Lorlatinib will be provided as 5mg or 25mg tablets. PK studies will be performed during course 1 only and will be mandatory.

Only patients with confirmed ALK fusion protein, ALK mutation or ALK amplification will enroll on this study. Cohort A1 and A2 will be initiated simultaneously and cohort assignment will be based on age and body surface area (BSA).

Following activation of Amendment 7, cohort B2 will be initiated for patients ≤ 18 YOA at 95 mg/m^2/dose which will be labeled "Dose Level 4B" in combination with chemotherapy. Once cohorts A1 and A2 are complete and the maximum tolerated dose (MTD) is identified and a recommended Phase II dose (RP2D) is selected, cohort B1 will be initiated for patients < 18 YOA, and cohort A2 will be expanded for adults ≥ 18 YOA at the RP2D, to provide single agent lorlatinib therapy for patients ineligible for cohort B2. Patients with prior exposure to ALK inhibitor therapy (except lorlatinib) are eligible to enroll on any cohort. See Section 4.0 for further cohort assignment details.

Cohort Assignment Will Be As Follows:

Schema for Dose Finding and Expansion Cohorts A1, A2 and B1 Lorlatinib (PF06463922)



Cohort A1 (Dose escalation for patients < 18 YOA)
Lorlatinib will be given orally once daily continuously for 28 days. The dose level of lorlatinib will be assigned at the time of study registration. The starting dose for cohort A1 is 45 mg/m^2/dose (see Section 4.2 for dose escalation schedule) with dose escalation based on a 3+3 design with dose levels defined in Table 15a-d.

Cohort A2 (Adult dose escalation & expansion)
Adults ≥ 18 years of age enrolled will follow a 3+3 dose escalation design with dose levels defined in Table 15b. Lorlatinib will be given orally once daily continuously for 28 days. Following the determination of the recommended phase 2 dose (RP2D), A2 will be expanded for patients ≥ 18 YOA who are ineligible for cohort B2.

Cohort B1 (Limited Expansion)
This limited expansion monotherapy cohort is open to patients ≥ 12 months of age and < 18 YOA who cannot enroll on Cohort B2 because (i) they are unable to tolerate topotecan and/or cyclophosphamide or (ii) if a B2 treatment slot is not available. B1 cohort will not begin enrollment until the recommended phase 2 dose (RP2D) is established from the dose escalation cohort A1. Lorlatinib will be given orally once daily continuously for 28 days.

Cohort B2: Combination with conventional chemotherapy (Dose escalation & expansion for patients < 18 YOA; expansion for patients ≥ 18 YOA)
Cohort B2 will initially open to patients ≥ 12 months of age and < 18 YOA. Lorlatinib will be given orally once daily continuously for 28 days starting at "dose level 4B" which is 95 mg/m^2 (with maximum dose of 150 mg) with Topotecan and Cyclophosphamide being given IV once daily on Days 1-5. For patients < 18 YOA, lorlatinib will follow a 3+3 dose escalation design with dose levels defined in Table 15c. Once the RP2D in A2 is established, cohort B2 will open to patients ≥ 18 YOA up to ≤ 30 YOA at the A2 RP2D in combination with Topotecan and Cyclophosphamide with no dose escalation.

Schema for Cohort B2 Lorlatinib (PF06463922) In Combination with Conventional Chemotherapy

Cycle Day							
1	2	3	4	5	6	7	28
Lorlatinib →							
CPM	CPM	CPM	CPM	CPM			
TOPO	TOPO	TOPO	TOPO	TOPO	MGF		

Lorlatinib: PF-06463922 (QD) starting at 95 mg/m^2 (see Table 15c).
CPM: Cyclophosphamide
TOPO: Topotecan
MGF: Myeloid growth factor

A. COHORT ASSIGNMENT OVERVIEW PRIOR TO AMENDMENT 4

<table>
<tr><th>Cohort</th><th>Cohort definition</th><th colspan="2">Age Range (in years)</th><th>BSA for Cohort entry</th><th>Prior ALK Inhibitor (ALKi) Status at Enrollment</th><th>Enrollment Timing</th></tr>
<tr><td rowspan="2">A1</td><td rowspan="2">Dose Escalation</td><td colspan="2" rowspan="2">≥ 12months & ≤ 18 years</td><td><u>Dose Level 1, & 2</u>
≤ 1.72m^2</td><td rowspan="2">N/A</td><td rowspan="2">Study Initiation through dose escalation completion</td></tr>
<tr><td><u>Dose Level 3</u>
≤ 1.42m^2</td></tr>
<tr><td rowspan="3">A2</td><td rowspan="3">Adult & Large BSA</td><td>Adult</td><td>> 18 years</td><td>N/A</td><td rowspan="3">N/A</td><td>Adult: study initiation through study closure</td></tr>
<tr><td rowspan="2">Large BSA</td><td rowspan="2">≥12 months & ≤ 18 years</td><td>≥ 1.73m^2 while Dose Level 1, & 2 are open</td><td rowspan="2">Large BSA: ≥ 1.43m^2 only when A1 enrolling on DL 3</td></tr>
<tr><td>≥ 1.43m^2 while Dose Level 3 is open</td></tr>
<tr><td>B1</td><td>Expansion</td><td colspan="2" rowspan="2">≥ 12 months & ≤ 18 years</td><td rowspan="2">N/A</td><td>ALKi Naïve priority enrollment*</td><td rowspan="2">Open when cohort A1 closes & RP2D has been determined</td></tr>
<tr><td>B2</td><td>Combination with chemotherapy</td><td>Prior ALKi exposure**</td></tr>
</table>

*Prior ALKi exposure may enroll with SMC approval if patient cannot tolerate chemotherapy in B2 or if B2 is complete
**ALKi naïve enrollment when B1 completed

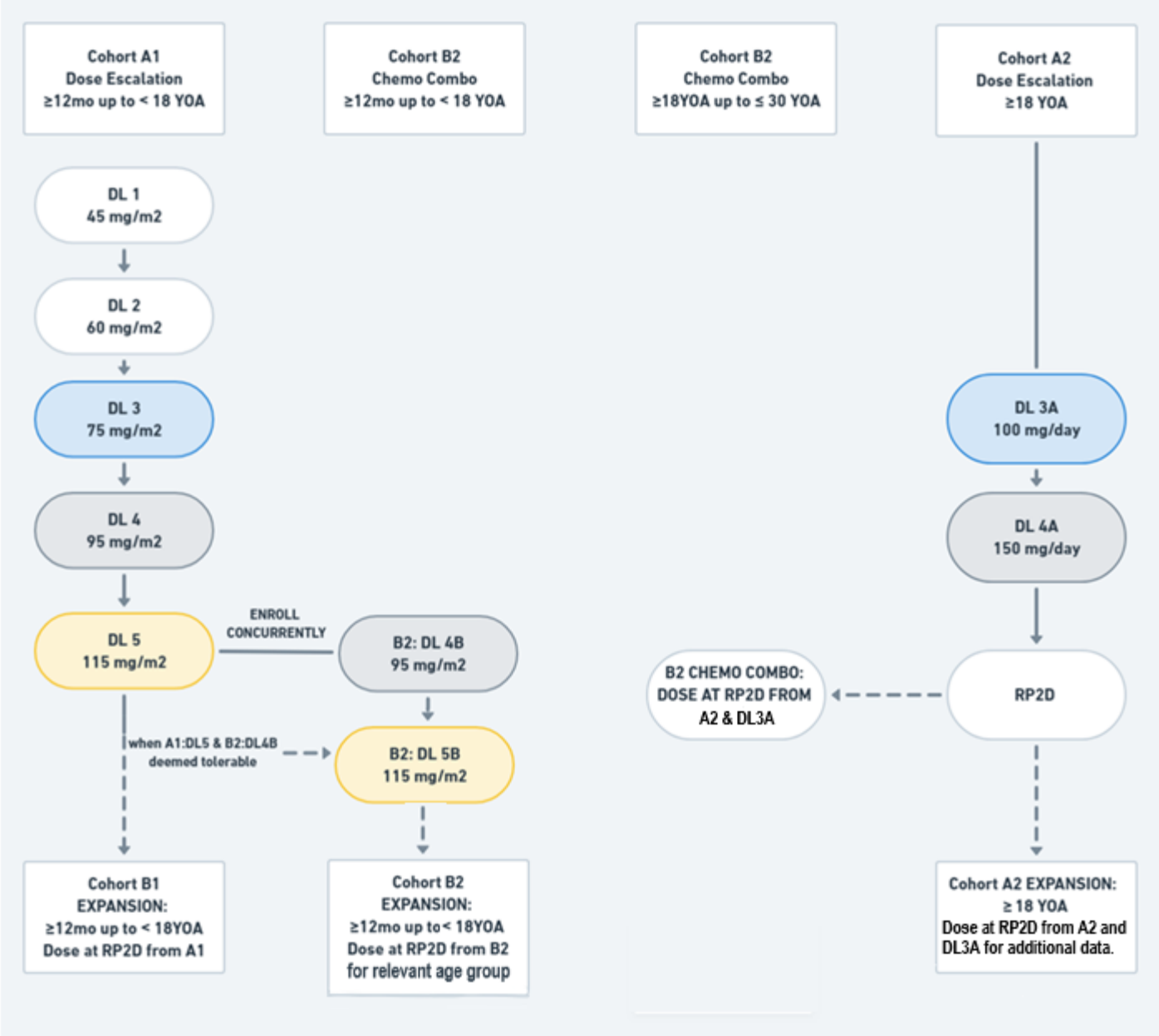
B. COHORT ASSIGNMENT OVERVIEW AFTER ACTIVATION OF AMENDMENT 4 before Amendment 7

<table>
<tr><th>Cohort</th><th>Cohort Definition</th><th colspan="2">Age Range (in years)</th><th>BSA for Cohort entry</th><th>Prior ALK inhibitor (ALKi) Status at enrollment</th><th>Enrollment Timing</th></tr>
<tr><td>A1</td><td>Dose Escalation</td><td colspan="2">≥ 12months & ≤ 18 years</td><td>Dose level 4 & 5
≤ 1.72m^2</td><td>N/A</td><td>AMD 4 through dose escalation completion</td></tr>
<tr><td rowspan="2">A2</td><td rowspan="2">Adult & Large BSA</td><td>Adult</td><td>> 18 years</td><td>N/A</td><td rowspan="2">N/A</td><td rowspan="2">AMD 4 through study closure</td></tr>
<tr><td>Large BSA</td><td>≥12 months & ≤ 18 years</td><td>≥ 1.73m^2 While Dose level 4 & 5 are open</td></tr>
<tr><td>B1</td><td>Expansion</td><td colspan="2" rowspan="2">≥ 12 months & ≤ 18 years</td><td rowspan="2">N/A</td><td>ALKi Naïve priority enrollment*</td><td rowspan="2">Open when cohort A1 closes & RP2D has been determined</td></tr>
<tr><td>B2</td><td>Combination with chemotherapy</td><td>Prior ALKi exposure**</td></tr>
</table>

*Prior ALKi exposure may enroll with SMC approval if patient cannot tolerate chemotherapy in B2 or if B2 is complete
**ALKi naïve enrollment when B1 completed

C. COHORT ASSIGNMENT OVERVIEW AFTER ACTIVATION OF AMENDMENT 7

Cohort	Cohort Definition	Age Range (in years)	Enrollment Timing
A1	Dose Escalation	≥ 12months & < 18 years	Through dose escalation completion
A2	Adult & Large BSA Dose Escalation	≥ 18 years	Through dose escalation completion
A2	Adult Expansion	≥ 18 years	Open when A2 dose escalation cohort closes & RP2D determined for patients ≥ 18 YOA not eligible for B2
B1	< 18 YO Expansion	≥ 12 months & < 18 years	Open when cohort A1 dose escalation closes & RP2D has been determined
B2	Combination with chemotherapy	≥ 12months & < 18 years	Dose level 4B enrolls concurrently with A1 and A2 dose escalation Dose level 5B enrolls if A1:DL5 and B2:DL4B are deemed tolerable
		≥ 18 years & ≤ 30 years	Open after A2 dose escalation completion. Lorlatinib given at RP2D with no dose escalation
B2	Expansion	≥ 12 months & ≤ 30 years	Open after RP2D for Cohort B2 for relevant age group is established


Cohort A1
Dose Escalation
≥12mo up to < 18 YOA
Cohort B2
Chemo Combo
≥12mo up to < 18 YOA
Cohort B2
Chemo Combo
≥18YOA up to ≤ 30 YOA
Cohort A2
Dose Escalation
≥18 YOA
DL 1
45 mg/m2
DL 2
60 mg/m2
DL 3
75 mg/m2
DL 4
95 mg/m2
DL 5
115 mg/m2
ENROLL
CONCURRENTLY
B2: DL 4B
95 mg/m2
when A1:DL5 & B2:DL4B
deemed tolerable
B2: DL 5B
115 mg/m2
DL 3A
100 mg/day
DL 4A
150 mg/day
RP2D
B2 CHEMO COMBO:
DOSE AT RP2D FROM
A2 & DL3A
Cohort B1
EXPANSION:
≥12mo up to < 18YOA
Dose at RP2D from A1
Cohort B2
EXPANSION:
≥12mo up to< 18YOA
Dose at RP2D from B2
for relevant age group
Cohort A2 EXPANSION:
≥ 18 YOA
Dose at RP2D from A2 and
DL3A for additional data.

1.0 GOALS AND OBJECTIVES

PRIMARY AIMS

a. To determine a recommended phase 2 dose (RP2D) of lorlatinib administered orally to children, adolescents and adults with relapsed or refractory neuroblastoma who have tumor containing a confirmed pathogenic *ALK* fusion protein, *ALK* mutation or *ALK* amplification.

b. To describe the toxicities of lorlatinib when administered to this population.

c. To characterize the pharmacokinetics of single agent lorlatinib in children and adolescents with relapsed/refractory neuroblastoma.

d. To define and describe the toxicities of lorlatinib in combination with topotecan and cyclophosphamide in children, adolescents and adults with relapsed or refractory neuroblastoma who have tumor containing a confirmed pathogenic *ALK* fusion protein, *ALK* mutation or *ALK* amplification administered on this schedule.

e. To characterize the pharmacokinetics of lorlatinib when combined with topotecan and cyclophosphamide in children and adolescents with relapsed/refractory neuroblastoma

SECONDARY AIMS

a. To preliminarily evaluate the anti-tumor activity of lorlatinib within the confines of a Phase 1 biomarker-driven study in children and adolescents with relapsed/refractory neuroblastoma harboring confirmed pathogenic *ALK* alterations.

EXPLORATORY AIMS

a. To describe the toxicities, pharmacokinetics, and anti-tumor activity of lorlatinib in the larger adolescent and adult population with relapsed or refractory neuroblastoma who have tumor harboring a confirmed pathogenic ALK fusion protein, ALK mutation or ALK amplification.

b. To prospectively determine the overall frequency of circulating tumor cell-free DNA (ctDNA) detection and the profile of acquired somatic mutations in plasma from peripheral blood at study entry and at each anti-tumor evaluation time point.

c. To describe the clonal heterogeneity and evolution of ALK and other genetic aberrations in relapsed neuroblastoma genomes by comparing matched tumor samples (diagnosis and recurrence) for detection of mutations, copy number alterations and translocations.

d. To assess tumor burden with the NB5 assay [a 5-gene Taqman Low Density Array (TLDA)] prior and during treatment with lorlatinib.

e. To describe the response of anti-tumor activity of lorlatinib in relation to prior exposure to ALK inhibition therapy.

f. To evaluate cognitive and behavioral outcomes (refer to variables in Table 24) compared to baseline functioning in patients with relapsed/refractory neuroblastoma treated with lorlatinib.

g. To characterize additional patterns of cognitive and behavioral functioning in child, adolescent, and adult populations with relapsed or refractory neuroblastoma to examine the association of relevant demographic and medical variables with change in performance overtime.

2.0 BACKGROUND

2.1 Neuroblastoma

Neuroblastomas are embryonal tumors that arise from the sympathetic nervous system and represent the most frequently diagnosed malignancy in the first year of life.[9] Approximately 50% of patients present with metastatic disease. Many of these patients are either refractory to initial therapy or develop recurrent disease after receiving multimodal therapy. The outcome for patients with recurrent or refractory disease remains poor. Novel approaches to treating these patients are required to improve their outcome. *MYCN* amplification is present in approximately 25% of high-risk neuroblastoma and portends a poor prognosis.[10] More recently, Myc protein expression has been observed in neuroblastoma, appears to be independent of *MYCN* amplification, and also portends a poor prognosis.[11] Current treatments rely on dose-intensive chemotherapy, radiation therapy, and immunotherapeutic targeting of the disialoganglioside GD2.[12] The most recent clinical studies of high-risk neuroblastoma have focused on escalating dose intensity in both induction and consolidation therapies, with evidence that this improves outcome. The potential long-term adverse effects of increasing treatment intensity on survival of this childhood cancer are a major concern[13], making it imperative that more effective and rational treatment strategies are developed. Future treatment strategies must rationally exploit known tumor-specific alterations. Kinases are critical components of cellular signal transduction cascades, and are key effectors of cell proliferation and differentiation. Our recent work provides the first evidence for oncogenic activation of *ALK* via mutation of the kinase domain, and these data provide the genetic basis for the observation of sensitization to *ALK* kinase inhibition.

Current disease surveillance strategies for neuroblastoma patients rely on cross sectional imaging and MIBG scans along with urinary catecholamines as sensitive and specific signs of relapse, disease progression, or lack of treatment response. However, these methods are clearly insufficient to detect relapses or disease progression early enough to make a difference in clinical outcome for a significant subset of patients. Detecting circulating tumor DNA (ctDNA) in high-risk neuroblastoma patients may provide an additional sensitive method for disease surveillance. In prior pilot studies using older genomic techniques, children with neuroblastoma have been found to have high levels of ctDNA, especially at the time of diagnosis and relapse, and neuroblastoma specific genomic alterations have reliably been detected in the serum of these children including *MYCN* amplification and gain of chromosome 17q. We recently reported that 78% of relapsed high-risk neuroblastoma harbored lesions in the canonical RAS-MAPK growth promoting pathway, which is a major focus of recent targeted therapeutic development in many human cancers. Thus, prospective analysis of serial peripheral blood samples for ctDNA mutations at defined treatment time points has major diagnostic, monitoring and therapeutic decision-making implications for high-risk neuroblastoma patients.

2.2 ALK as a tractable therapeutic target in Neuroblastoma

Several recent findings have positioned the Anaplastic Lymphoma Kinase (ALK) receptor tyrosine kinase as the only tractable oncogene product for targeted therapy in neuroblastoma. Germline and somatic aberrations in the gene encoding ALK are implicated in approximately 8% of all neuroblastomas[3,4,14,15]. Within the high-risk subset of neuroblastoma patients, the overall frequency of *ALK* aberration at diagnosis is 14% (10% point mutations, 4% amplification) and correlates with inferior outcome [16]. We recently showed that relapsed NBs harbor an increased somatic mutational burden compared to primary tumors with enrichment of ALK-RAS-MAPK activating mutations nearly always present within subclonal populations at diagnosis[17], and validated this in a recent retrospective review of the largest series of relapse samples studied to date[18]. Additional *ALK* mutations at relapse have also been reported[19,20]. We posit that these mutations provide a selective advantage leading to chemoradiotherapy resistance. The activating mutations are found at several sites in the tyrosine kinase domain of full-length ALK [16], including three hot spots (R1275, F1174, and F1245). These findings motivated a Phase 1 trial of the ATP-competitive ALK/Met/ROS1 inhibitor crizotinib (PF-02341066) in children with refractory neuroblastoma or other malignancies driven by *ALK* rearrangements such as anaplastic large cell lymphoma (ALCL) and inflammatory myofibroblastic tumors (IMTs) [6]. Results from this trial

underscored the importance of *ALK* across histologically diverse tumors,but recorded less frequent responses in neuroblastoma than in *ALK* rearranged tumors – highlighting likely differences between therapeutic targeting of full-length ALK in neuroblastoma and of cytoplasmic ALK fusion proteins in ALCL, IMTs, and lung cancer. Parallel preclinical work has further revealed differential sensitivity to crizotinib for the most common ALK variants observed in neuroblastoma[5,7,21], with F1174L-mutated cells being resistant when compared with those expressing R1275Q-mutated ALK. Despite real-time integration of these findings in the clinic, and a recommended phase 2 dose of crizotinib in pediatric patients that is nearly twice the adult maximum tolerated dose [6], these studies emphasize the need to identify an optimal inhibitor for direct ALK kinase inhibition in neuroblastoma in order to maximize clinical benefit.

2.3 Next generation TKI, lorlatinib (PF-06463922) in crizotinib-resistant ALK/ROS1+ preclinical models.

PF-06463922 (Pfizer) is an orally available potent and selective next generation Tyrosine-Kinase Inhibitor (TKI) of ALK and ROS1. In preclinical studies, lorlatinib demonstrated dose dependent inhibition of mutations conferring resistance to treatment with both first and second generation TKIs, including crizotinib[22-24]. Lorlatinib was discovered using structure-guided efforts to maintain potency across a range of resistance mutations and to optimize physicochemical properties[25]. It is a potent macrocyclic ALK inhibitor with good absorption, distribution, metabolism, and excretion, as well as a low propensity for P-glycoprotein-mediated efflux and considerably improved central nervous system penetration. Lorlatinib was also designed and optimized to penetrate the blood-brain barrier and has shown strong distribution in the central nervous system in preclinical studies[25]. This is also likely to be a highly favorable attribute for use of lorlatinib in a disease like neuroblastoma that has a predilection for recurrence in this sanctuary site [26].

In neuroblastoma cell line assays, lorlatinib inhibited ALK kinase activity (measured by inhibition of its autophosphorylation) with cell IC50's of 1.5 nM and 21 nM for EML4-ALK and EML4-ALK (L1196M), the most common mutation that occurs within the gatekeeper residue of the ALK kinase, which compares favorably to crizotinib IC50's of 80 nM and 841 nM, respectively) [27]. Data from *in vivo* efficacy models bearing the EML4-ALK (L1169M] mutation predicted the efficacious concentration (Ceff) to be 51 nM (unbound), which corresponds to achieving tumor stasis (100% tumor growth inhibition) in this preclinical model. We have demonstrated that lorlatinib overcomes crizotinib resistance of *ALK* variants in NB, and exerts unprecedented activity as a single agent against F1174L and F1245C *ALK*-mutated tumors in preclinical models (**Figure 1**). Lorlatinib showed at least 3-4 fold higher potency than crizotinib in peptide phosphorylation assays, and its superior inhibition was consistently observed in cellular analysis of transforming ability. *In vivo*, lorlatinib induced superior and complete tumor regression in cell-line and patient-derived xenograft mouse models harboring both crizotinib-sensitive and crizotinib-resistance [27] (**Figure 1**).

At a tenfold lower dose (10mg/kg) than typically used for crizotinib (100mg/kg), lorlatinib induces complete tumor regression in both cell-line derived (**Figure 1A and D**) and patient-derived (**Figure 1B and C**) xenograft mouse models harboring the most common ALK mutations. Whereas crizotinib-treated mice in models harboring crizotinib-resistant ALK mutations (F1174L and F1245C) experienced rapid tumor growth on therapy, lorlatinib treated mice showed sustained complete responses for several weeks even after treatment was discontinued. Additionally, in xenografts harboring the most common and relatively crizotinib-sensitive R1275Q ALK mutation, mice treated with lorlatinib have superior and sustained

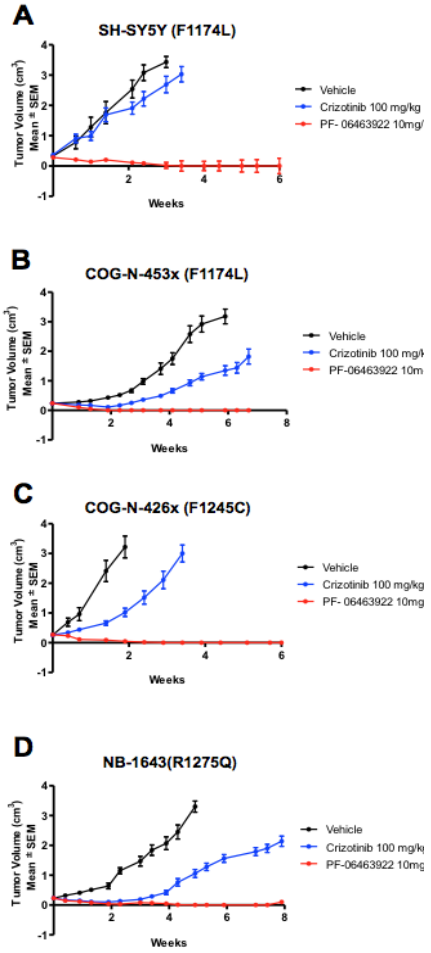


Figure 1. In vivo single-agent efficacy of PF-06463922 (red) compared with crizotinib (blue) in (A) SH-SY5Y neuroblastoma xenograft harboring an F1174L ALK mutation; **(B)** COG-N-453x Patient Derived Xenograft harboring an F1174L ALK mutation; **(C)** COG-N-426x Patient Derived Xenograft harboring an F1245C ALK mutation; and **(D)** NB-1643 neuroblastoma xenograft harboring an R1275Q ALK mutation.

growth inhibition. We are now poised to rapidly develop this agent for integration with conventional chemotherapeutic agents in the treatment of patients with newly diagnosed ALK-driven neuroblastoma.

2.3.1 *In Vitro* Metabolism

Lorlatinib undergoes oxidation and glucuronidation as the primary metabolic pathways. Oxidative metabolism of lorlatinib is primarily mediated by cytochrome CYP3A4 with minor contributions from CYP2C19, CYP2C8, and CYP3A5. Glucuronidation of lorlatinib is mediated primarily by UGT1A4, with minor contribution from UGT1A3.

2.4 Lorlatinib (PF-06463922) Adult Clinical Studies

2.4.1 Adult Phase 1 Studies

The phase 1 portion of a Phase 1/2 trial (NCT01970865) to assess the safety, pharmacokinetics and pharmacodynamics of single agent lorlatinib in adult patients with advanced ALK or ROS1 translocated non-small cell lung cancer (NSCLC) was completed in July of 2015 and presented at the 2016 ASCO meeting. Forty one patients with ALK+ NSCLC11 patients with ROS1+ NSCLC were enrolled across 7 QD dose levels and 3 BID dose levels. Forty four patients were evaluable for safety, 34 for overall tumor response, and 25 for intracranial response. One DLT occurred in the 200-mg QD cohort due to grade 1–2 cognitive effects. The objective response rate (95% confidence interval [CI]) was 44% (27–62), comprising 1 complete response, 10 confirmed partial responses, and 4 unconfirmed partial responses. In 25 patients evaluable for intracranial responses, of which 14 had CNS lesions as target lesions, the objective intracranial response rate (95% CI) was 36% (18–58), comprising 3 confirmed complete intracranial responses, 2 confirmed partial intracranial responses, 1 unconfirmed complete response and 2 unconfirmed partial intracranial responses. 50 (93%) experienced any treatment-related AE. Most treatment related AE's were grade 1 or 2. Hypercholesterolemia/hypertriglycemia were controlled with statins and lipid lowering agents, if indicated. While preclinical data showed pancreatic acinar atrophy in 14-day ETS and 1-month regulatory toxicology studies in both rodent and non-rodent species, there was no clinical pancreatitis during phase 1, only grade 1-2 elevated lipase/amylase. Peripheral neuropathy was usually mild and reversible upon dose hold. Mild to moderate CNS effects with a variety of presentations, including changes in speech, memory and mood, were observed in some patients receiving lorlatinib and were generally intermittent and managed with dose hold or reduction. There were 20 deaths, as of 5 May 2016; all were disease-related. 33.3% of patients had a treatment-related dose delay, 24.1% of patients had a treatment-related dose reduction and 2 patients discontinued treatment due to treatment-emergent adverse events. None of the adverse events that resulted in treatment discontinuation were considered study drug related. The only DLT that occurred was at the 200 mg QD dose level, grade 2 CNS toxicity prevented the patient from getting recommended number of doses in the first course. Therefore, the RP2D was chosen to be 100 mg QD, two dose levels below the DLT. Table 1 below captures the treatment related Adverse Events observed in the adult phase 1/2 trial.

Table 1. Summary of Treatment Related, Treatment–Emergent Adverse Events by MedDRA Preferred Term Occurring in at Least 10% of Patients who Received 100 mg QD (Phase 1/2)		
Preferred Term	Total (n=295)	
	N	(%)
Any AEs	281	(95.3)
**Hypercholesterolemia	249	84.4
**Hypertriglyceridemia	199	67.5
**Edema	135	45.8
**Peripheral Neuropathy	101	34.2
**Cognitive Effects	70	23.7
Weight increased	71	24.1
**Mood Effects	46	16.20
**Fatigue	50	16.9
Diarrhea	37	12.5
Aspartate aminotransferase increased	40	13.6
Alanine aminotransferase increased	37	12.5
Arthralgia	38	12.9
Lipase increased	32	10.8
Constipation	31	10.5

** refer to AE cluster terms OF COGNITIVE EFFECTS, EDEMA, FATIGUE, HYPERCHOLESTEROLEMIA, HYPERTRIGLYCERIDEMIA, MOOD EFFECTS, PERIPHERAL NEUROPATHY. List of Terms that comprise each cluster term as per MedDRA Version 24.0 can be found in Table 28 of the Investigator's Brochure version dated OCT2021.

2.4.2 Adult Phase 2 Studies

The phase 2 portion of the phase 1/2 trial of lorlatinib (NCT01970865) in patients with recurrent/refractory NSCLC was opened to accrual in September of 2015 and has completed enrollment (n = 295). The interim Clinical Study Report has been finalized. The RP2D of 100 mg was being studied for response rate in an estimated cohort of 240 patients. Cognitive and mood assessments were added to the patient evaluations to better characterize CNS events due to lorlatinib in this adult population.

2.5 Adult Pharmacology / Pharmacokinetics / Correlative and Biological Studies

2.5.1 Safety and Pharmacokinetics

There are two ongoing clinical studies in patients with ALK-positive or ROS1-positive NSCLC. B7461001 is a single-agent study currently in phase 2 and described in detail below. B7461006 is a phase 3 randomized controlled study evaluating lorlatinib versus crizotinib in treatment-naïve patients.

The eight healthy volunteer studies that have been completed include two mass balance studies (B7461004 and B7461017), a relative biolavailability study (B7461005), an absolute bioavailability study (B7461007), a PPI study (B7461008), a DDI study with rifampin (B7461011), a DDI study with itraconazole (B7461012), and a bioequivalence study (B7461016).

The studies with relevant safety and PK results are described in detail below.

2.5.1.1 Safety and Pharmacokinetics from Study B7461001

Study B7461001 is a phase 1/2, open-label, multicenter, multiple-dose, dose-escalation, safety, PK, pharmacodynamic (PD) and anticancer efficacy exploration study of lorlatinib as a single-agent in patients with advanced ALK+ and advanced ROS1+ NSCLC.

B7461001 is being conducted in 2 parts: Phase 1 (lorlatinib as acetic acid solvate) and Phase 2 (lorlatinib as free base). The phase 1 portion of the study was aimed at estimating the MTD for single-agent lorlatinib in dose-escalation cohorts in patients with advanced ALK+ or advanced

ROS1+ NSCLC with or without asymptomatic CNS metastases, and enrolled 54 patients. The phase 2 portion of the study has completed enrollment (n = 295) and is being conducted with single-agent lorlatinib at the identified MTD/RP2D in patients with advanced ALK+ NSCLC and patients with advanced ROS1+ NSCLC, with or without asymptomatic CNS metastases.

The phase 1 portion of this study employed a modified continual reassessment method (CRM) to estimate the MTD. The CRM was initiated at 25 mg QD and recommended escalation to 75, 100, 150, and 200 mg QD based on no DLTs observed at the previous dose levels tested. At 200 mg QD, one (1) DLT occurred in a patient who failed to receive 16 of the planned 21 lorlatinib doses in Course 1 due to Grade 1 vision change, abnormal dreams and photosensitivity reaction, and Grade 2 aphasia and cognitive disorder. Although the CRM model recommended continuation to the next higher dose above 200 mg QD, a decision was made among the treating investigators and the sponsor to re-test lower doses (ie, outside of the CRM model) to better understand and evaluate the CNS effects observed at the higher dose levels. These CNS effects observed consisted of mostly Grade 1 and Grade 2 transient effects including changes in speech, cognition, memory and mood.

Overall, 100 mg QD was a well-tolerated dose. None of the patients at this dose required dose reduction and dose delays were not attributed to CNS effects, but rather to hypercholesterolemia or hypertriglyceridemia or disease related events. Based on the PK data observed, simulated patient exposure showed the 100 mg QD dose to be the lowest dose exceeding the lorlatinib Ceff of 150 ng/mL during the majority of the dosing course once steady-state was reached. The Ceff of 150 ng/mL was a concentration predicted to result in >80% tumor growth inhibition of the ALK^{G1202R} resistance mutation.

The 100 mg QD dose was chosen as the recommended phase 2 dose (RP2D) based on the entirety of the safety, efficacy, and clinical pharmacology data. The RP2D was not based on formal DLT and MTD determinations due to the nature of the cognitive effects.

As of June 2020, lorlatinib has been administered to a total of 295 patients at the 100 mg QD dose. HYPERCHOLESTEROLEMIA was reported in 84.4% of patients, HYPERTRIGLYCERIDEMIA was reported in 67.5% of patients, EDEMA was reported in 45.8% of patients, PERIPHERAL NEUROPATHY was reported in 34.2% of patients, weight increased was reported in 24.1% of patient, and COGNITIVE EFFECTS were reported in 23.7% of patients. The most frequent $\geq$ Grade 3 treatment emergent adverse events in the 100 mg QD group were HYPERTRIGLYCERIDEMIA (19.4%), and HYPERCHOLESTEROLEMIA (18.0%).

The phase 2 portion of the study has completed enrollment (n = 295). Overall the safety profile has been consistent with that observed in the phase 1. A notable finding about PR prolongation is described at the end of the clinical summary.

In the Phase 1 portion of this study, patients received lorlatinib doses ranging from 10-200 mg QD and 35-100 mg BID. Single- and multiple-dose PK data were available in a total of 43 patients respectively. Of these patients, 39 and 37 patients had adequate single- and multiple-dose PK for AUC estimation respectively. Pharmacokinetic parameters are summarized in Table 6.1-1 and 6.1-2 of the IB, after single and multiple QD dose administration.

After single oral administration of lorlatinib tablets (as acetic acid solvate) under fasted conditions, median time to peak plasma concentrations (T_{max}) were between 1 and 2 hours across the evaluated dose levels. Following attainment of peak plasma concentration (C_{max}), lorlatinib plasma concentrations showed a bi-exponential decline with a terminal elimination half-life of 19.0-28.8 hours, apparent oral clearance (CL/F) of 6.7-11.5 L/hr and volume of distribution (Vz/F) of 233-382 liters across the evaluated dose levels. Variability in PK was observed with a coefficient of variation (CV %) of 28-77% for AUC_{inf} and 19-45% for C_{max} following single oral administration.

After repeated QD oral administration, steady state should have been achieved before Day 15 based on the lorlatinib single dose terminal elimination half-life. The accumulation indices defined as the ratios of the lorlatinib AUC over the dosing interval (τ) of 24 hours at steady state (AUC_{τ}) to the AUC over a post-dose period of 24 hours after single dose administration (AUC_{24}) across the dose range tested, were less than the predicted values based on the calculated lorlatinib elimination rate (k_{el}) and τ (Table 6.1-1 of the IB), suggesting auto-induction may play a role in lorlatinib disposition.

PK data (January 2016) after 100 mg single and multiple dosing in Phase 1 with lorlatinib tablets (as acetic acid solvate) are summarized in Table 2. The AUC over a post-dose period of 24 hours after single dose administration (AUC_{24}) across the dose range tested was less than the predicted values.

PR interval prolongation has been observed in both healthy volunteer studies (Study B7461008) and clinical trials (Study B7461001). In the healthy volunteer Study B7461008, the PR interval prolongation was associated with 1 episode of transient second- degree atrioventricular (AV) block (Mobitz type 1; Wenckebach). In the clinical Study B7461001, the PR interval prolongation may have been associated with the progression of pre-existing AV block to complete heart block. When the complete heart block was identified, the patient was immediately evaluated and subsequently treated by placement of an implanted pacemaker. In response to the observation of PR interval prolongation, data from all available human studies (approximately 100 patients in clinical studies and 45 in single dose healthy volunteer studies) were reviewed. Additional instances were identified of asymptomatic increases in the PR interval, usually most notable during Cmax (1-2 hours post-dose). Of note, the patients with a PR interval > 200 msec were generally those with a baseline value at the upper end of the normal range. The ECG changes appear limited to the PR interval, with no impact on QRS or QT intervals. This impact on the PR interval is supported by preclinical animal studies, as described in the current IB.

Weight increase with lorlatinib has been reported preclinically in rats treated with lorlatinib, with females being more affected than males. Weight gain has been reported in the adult Phase 1/2 trial, Study B7461001. Of 295 patients treated at 100 mg QD, Grade 1-2 weight gain was observed in 56 (19.0%) patients and Grade 3 weight gain was observed in 15 (5.1%) patients[28]. In the adult studies, B7461001 and B7461006, weight gain was not a reason for permanent treatment discontinuation, and temporary treatment discontinuation and dose reduction rates were low (0.8% and 1.1%, respectively). Based on these findings, weight gain is not a dose-limiting toxicity.

Table 2. B7461001 Summary of Lorlatinib Single and Multiple Doses PK Parameters Following 100 mg QD Administration

Dose	N, n[a]	AUC[b] (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)	CL/F (L/hr)	V_z/F (L)
Phase 1							
Single Dose	16, 16	8672 (28)	577 (44)	2.0 (1.0-4.0)	22.2 (26)	11.5 (28)	357 (38)
Multiple	16, 14	5065 (32)	569 (32)	1.0 (1.0-4.0)	NA	20.0 (32)	NA
Phase 2							
Single Dose	19, 17	9529 (40)	696 (40)	1.0 (0.5-4.0)	23.2 (40)	10.5 (40)	329 (43)
Multiple	26, 15	5078 (32)	581 (31)	1.0 (0.5-3.0)	NA	19.7 (32)	NA

Source data: artifact ID 11523892, 11523893, 11515888 and 11515887
Geometric mean (geometric %CV) for AUC, Cmax, CL/F, and Vz/F; arithmetic mean (%CV) for t1/2; median (range) for Tmax
The Japanese patients were also included in this analysis
[a]N=number of patients whose PK data were available, n=number of patients with adequate data for PK parameter estimation
[b]AUCinf reported for single-dose and AUCτ for multiple dosing

In vitro data indicated that lorlatinib is associated with time-dependent inhibition of CYP3A. The CYP3A substrate drug midazolam was given alone and 14 days after administration of 25 mg QD and 150 mg QD of lorlatinib to a total of 6 patients. Preliminarily, both AUC_{inf} and C_{max} geometric mean (CV%) of midazolam were reduced by about 48 and 63% and 24 and 18% in the presence of daily lorlatinib at 25 mg and 150 mg QD doses respectively, presumably due to lorlatinib induction of CYP3A. Concomitant use of lorlatinib with medications which are CYP3A substrates has potential to reduce the concentration of sensitive CYP3A substrates.

2.5.1.2 Safety and Pharmacokinetics from Study B7461004

Study B7461004 is a completed Phase 1 study which evaluated the mass-balance and pharmacokinetics of lorlatinib in 6 healthy male subjects after a single oral 100 mg dose of radiolabeled lorlatinib containing approximately 100 µCi of [^{14}C] PF-06463922.

Preliminary results indicate a mean of 47.73% of the radioactivity was recovered in urine and 40.91% was recovered in feces through the last collection interval. Most of the administered radioactivity was recovered in the first 144 hours post dose (85.11%). The overall mean recovery of radioactivity in urine and feces samples was 88.64% over the 288-hour study, with recovery in individual subjects ranging from 83.6 to 90.8%.

Preliminary information indicates the presence of metabolites in circulating plasma, urine and feces. In the current B7461012 study, samples will be collected to describe the PK of the identified metabolite(s).

2.5.1.3 Safety and Pharmacokinetics from B7461005

Study B7461005 is a completed Phase 1/2, randomized open-label study in 19 healthy volunteers to estimate the relative bioavailability of two new lorlatinib formulations (free base and maleate salt) (Test) compared to the formulation of the lorlatinib acetic acid (Reference). The results supported the switch to a tablet formulation of lorlatinib as the free base in all future clinical trials.

2.5.1.4 Safety and Pharmacokinetics from Study B7461008

Study B7461008 is a completed Phase 1 study in 24 healthy volunteers, designed to evaluate the effect of rabeprazole and food on the pharmacokinetics of lorlatinib and to assess the relative bioavailability of an oral solution of lorlatinib to the tablet formulation of lorlatinib. The results of this study indicated that a high fat meal had no effect on the systemic exposure of lorlatinib. Furthermore, the proton pump inhibitor rabeprazole had only a marginal effect on the systemic exposure of lorlatinib. Hence, the current recommendation is that lorlatinib can be given orally regardless of food, proton pump inhibitors, H2-receptor antagonists, and locally acting antacids.

Preliminary safety data from this study recently identified asymptomatic PR prolongation. In one healthy volunteer, the PR interval prolongation was associated with one episode of transient second degree atrioventricular (AV) block (Mobitz type 1; Wenkebach). Subsequently, retrospective review of patients in the clinical study B7461001, found one patient with the PR interval prolongation that may have been associated with the progression of pre-existing AV block to complete heart block. When the complete heart block was identified, the patient was immediately evaluated and subsequently treated by placement of an implanted pacemaker.

In response to the observation of PR interval prolongation, data from all available human studies (approximately 100 patients in clinical study B7461001 and 45 in single dose healthy volunteer studies) were reviewed. Additional instances were identified of asymptomatic increases in the PR interval (> 200 msec), usually most notable at the time of C_{max} (1-2 hours post-dose) in healthy volunteers. Of note, the subjects with a PR interval > 200 msec were generally those with a baseline values at the upper end of the normal range.

The ECG changes appear limited to the PR interval, with no impact on QRS or QT intervals. This impact on the PR interval is supported by preclinical animal studies, as described in the current Investigator Brochure. Although isolated PR interval prolongation (first or second degree AV block) may not pose an immediate risk to patient safety, the potential for development of complete heart block warrants that future studies exclude patients with a baseline PR interval ≥ 220 msec, or 2nd or 3rd degree AV block (unless an implanted pacemaker is in place). Further, for healthy volunteers in this study the upper limit of normal for PR interval will be defined as PR interval of 180 msec.

Additional information for this compound may be found in the single reference safety document (SRSD), which for this study is the Investigator's Brochure.

2.5.1.5 Safety and Pharmacokinetics from Study B7461011

Study B7461011 was a phase 1 open-label, two-period, two-treatment, fixed-sequence crossover study to estimate the effect of multiple dose rifampin on a single dose of lorlatinib in 12 healthy volunteers.

Co-administration of multiple doses of rifampin (600 mg QD) decreased lorlatinib (100-mg single dose) total exposure (AUCinf) by 85% and decreased the peak exposure (Cmax) by 76% relative to a single lorlatinib 100 mg dose given alone. Co-administration with multiple doses of rifampin in this study also led to reversible, severe increase of LFT values (AST and ALT) in healthy volunteers; there were no concurrent increases in total bilirubin.

Overall, the use of strong inducers of CYP3A4/5 with lorlatinib is contraindicated.

2.5.1.6. Safety and Pharmacokinetics from B7461012

Study B7461012 was a Phase 1, open-label, 2-period, fixed-sequence, crossover study to investigate the effect of the strong CYP3A inhibitor, itraconazole, on lorlatinib PK in healthy subjects. A total of 16 subjects were screened, assigned to treatment, and completed the study.

Each enrolled subject received lorlatinib 50 mg, 75 mg or 100 mg alone in Period 1 and then lorlatinib 50 mg, 75 mg, or 100 mg in combination with multiple dose itraconazole in Period 2 after a washout period of at least 10 days between lorlatinib doses in Periods 1 and 2. Following administration of lorlatinib in each period, subjects underwent serial PK sampling.

Following the coadministration of lorlatinib and itraconazole, lorlatinib AUCinf and Cmax values for all subjects were higher compared to when lorlatinib was administered alone. For the lorlatinib 100 mg cohort, the geometric mean lorlatinib AUCinf and Cmax values following co-administration of itraconazole increased by 42% and 24%, respectively, compared to when lorlatinib was administered alone.

Lorlatinib was well tolerated in this study. No deaths, SAEs, severe AEs, permanent discontinuations, or temporary discontinuations due to AEs were reported.

2.6 Lorlatinib Pediatric Clinical Studies

There have been no other pediatric studies to date of lorlatinib.

2.7 Overview of Proposed Pediatric Study

This will be a phase 1 dose-finding study of lorlatinib to determine the maximum dose that is safe and tolerable in children with relapsed/refractory neuroblastoma. This will also be a biomarker driven protocol, whereby only patients whose tumor harbor a known activating ALK alteration (mutation, amplification, fusion) will be eligible for treatment with single agent next-generation ALK inhibitor, lorlatinib, and with lorlatinib in combination with conventional chemotherapy. The anti-tumor activity of this drug both alone and in combination with chemotherapy will be assessed in a preliminary fashion within the confines of this phase 1 trial, both during the dose escalation and during the expansion phase and combination phase, with lorlatinib given at the recommended phase 2 dose. Dose escalation will use the standard 3+3 rules, with 3 doses planned prior to Amendment 4. Two more dose levels were added post Amendment 4. Please see Table 15a-d for dose escalation schema for Cohort A1, Cohort A2 and Cohort B2. All treatment cohorts including the dose expansion cohort *will* allow for enrollment of ALK+ patients previously treated with other ALK inhibitors (crizotinib and ceritinib have both been studied in pediatric patients). Additionally, patients with evidence of disease in the CNS will be eligible for this study so long as eligibility criteria are met. Approximately 60-75 patients are expected to be enrolled in the study overall.

Rationale for combining Lorlatinib with Topotecan and Cyclophosphamide. We have shown that crizotinib, when combined with conventional chemotherapy agents, restores sensitivity in preclinical models harboring both sensitive and *de novo* resistant *ALK* mutations [27], and this has served as the rationale for integration of crizotinib with standard of care chemotherapy in the recently activated Children's Oncology Group Phase 3 trial (ANBL1531) with tumor ALK mutations/fusions/amplification. However, we are cognizant that there is limited rationale for this approach, especially in the maintenance phase of therapy when children with resistant ALK mutations will be exposed to single agent crizotinib [5,7,8]. The objective of this trial is to define the recommended phase 2 dose and anti-tumor activity of lorlatinib as a single agent across the range of NB-specific ALK mutations, and to define the toxicity profile and optimal dose of lorlatinib in combination with chemotherapy. This will provide data of this combination for future consideration of lorlatinib in upfront neuroblastoma trials.

Based on the review of the agents and their toxicities, there are no predicted overlapping toxicities of the combination.

Pfizer Pharmacologists have reviewed the published literature from the UW Drug Interaction Database (DIDB) (Copyright University of Washington, accessed on 9/25/2019) on topotecan and cyclophosphamide (topo/cy) metabolism and drug interaction potential. There are no predicted drug-drug interactions (DDIs) with topo/cy that could alter lorlatinib exposure. Based on lorlatinib clinical DDI studies, at steady state, lorlatinib induces CYP3A and P-gp to moderate extent and CYP2B6 and CYP2C9 and UGT to a weak extent via PXR activation. Thus, it is reasonable to assume that lorlatinib may have similar effects on other PXR related enzymes and transporters such as CYP2C19 and BCRP. Topotecan is a substrate of BCRP and P-gp. Cyclophosphamide is a substrate of CYP2B6, CYP2C19, and CYP2C9. Thus, lorlatinib will likely mildly/moderately reduce the exposure of topotecan while mildly increasing the exposure of the active metabolite of cyclopphosphamide. Given there will be a mild difference in exposure, there is no reason to expect increase risk of toxicity with concomitant use of lorlatinib, and topotecan or cyclophosphomide due to PK interaction.

To assess biological correlates of efficacy, we will access banked tumor DNA and/or tissue blocks from diagnosis and relapse (when available), as well as bone marrow prior to and while on treatment from participating patients. We will also obtain peripheral blood at study entry and at each

disease surveillance time point to determine the overall frequency of ctDNA detection of ALK alterations as a potential marker of minimal residual disease, and the profile of acquired somatic mutations during therapy. It has been known for decades that human solid tumors, as well as their nucleic acids, are present in the circulation of patients, but only recently has technological advances made it possible to consider clinical application of methodologies to detect circulating tumor DNA (ctDNA) in patients.[29,30] For children with high-risk neuroblastoma, we envision these so-called "liquid biopsies" as providing not only an improved method for more precise disease surveillance, but by coupling detection with Next Generation Sequencing (NGS) technology, we also can noninvasively and comprehensively quantify clonally acquired oncogenic mutations that may be leveraged with targeted molecular therapies. Although somatic mutations in newly diagnosed neuroblastomas are present in only 10-15% of high-risk patients,[31-35] recent data suggests that neuroblastomas frequently acquire new alterations in known oncogenic pathways under the selective pressures of cytotoxic chemotherapy.[19,20,36] The study will include mandatory pharmacokinetic studies.

2.7.1 Preliminary Toxicity Update of NANT 2015-02 Study (as of October 2019)

Hematological toxicities have been mild on this study thus far, the most frequently seen are the following: Anemia was seen in 11/29 (37%) patients, 3 of which were grade 3+.

The following are the most common non-hematological toxicities observed which were at least possibly related to lorlatinib. Metabolic category: Weight gain was noted in 25/29 (86%) patients, 8 of which were grade 3. Increased appetite (grade 1) was noted in 13/29 (44%) patients. Hypertriglyceridemia was noted in 25/29 (86%) patients, 3 of which were grade 3+. Hyperglycemia was noted in 7/29 (24%) patients, 2 of which were grade 3+. Glucose intolerance was noted in 2/29 patients (7%) patients (Grade 2 = 1, Grade 3 = 1). Cholesterol high was noted in 24/29 (83%) patients (Grade 2 = 9, Grade 3 = 2).

Neuropsychological Category: Cognitive disturbance (grade 1) was noted in 4/29 (13%) patients. Concentration impairment (grade 1) was noted in 6/29 (20%) patients. Memory impairment was noted in 7/29 (24%) patients (Grade 1 = 6, Grade 2 = 1). Agitation (grade 1 = 2, grade 4 = 1) was noted in 3/29 patients. Anxiety was noted in 5/29 (17%) patients (Grade 1 = 4, Grade 2 = 1). Depression (grade 1) was noted in 2 /29 patients. Psychosis, suicidal ideation, and suicidal attempt (grade 4) was noted in 1/29 patients. Peripheral sensory neuropathy was noted in 3/29 (10%) patients (Grade 1 = 2, Grade 2 = 1). Fatigue (grade 1) was noted in 6/29 (20%) patients. Nausea (grade 1) was noted in 8/29 (27%).

2.7.2 Preliminary PK Data for NANT 2015-02 Study (as of August 2019)

Twenty-nine patients in total enrolled to date on the NANT Phase 1 trial have had adequate pharmacokinetic sampling completed after the first course of Lorlatinib and the results analyzed.

The preliminary PK data used in this analysis was based on nominal collection times and quality controlled, non-quality assured bio-analytical data. The PK parameters were determined by non-compartmental analysis (Pharsight; Phoenix WinNonlin version 7.0).

Table 4-9 and associated plots (Figure 2-13), the lorlatinib plasma pharmacokinetic (PK) parameters and concentration-time profiles for dose level 1 (45 mg/m^2), dose level 2 (60 mg/m^2), dose level 3 (75 mg/m^2), dose level 4 (95 mg/m2), dose level 3A (100 mg), and dose level 4A (150 mg) are presented, respectively.

Note: Some half-life estimates could not be reliably estimated and hence the PK parameters should be interpreted with caution.

Overall, the plasma PK patterns of lorlatinib in pediatric patients with ALK-positive neuroblastoma are similar to the PK patterns of lorlatinib in adult patients with advanced ALK-positive or advanced ROS1-positive non-small cell lung cancer. As demonstrated by both the concentration-time profiles

and the PK parameter summaries, the lorlatinib plasma exposure after multiple dosing (Cycle 1 Day 15) is reduced as compared to after single dose (Cycle 1 Day 1); the lack of expected accumulation with multiple dosing indicates auto-induction, which is also seen in adult patients.

The lorlatinib steady state plasma exposure observed at dose level 3 in pediatric patients is generally in the range of exposures observed in adults at the 100 mg QD dose level, which is the current approved dose in adult NSCLC patients. At dose level 3 the lorlatinib steady state AUC_{tau} and C_{max} was 4155 ng•hr/mL and 645.5 ng/mL, respectively, as compared to the adult 100 mg QD steady-state AUC_{tau} and C_{max} of 5650 ng•hr/mL and 576.5 ng/mL, respectively (*B7461001 Clinical Study Report, Table 38. Descriptive Summary of Plasma Lorlatinib PK Parameters Following 100 mg QD Dosing of Lorlatinib in Phase 2*).

The lorlatinib steady-state plasma exposure observed at dose level 4 in pediatric patients is generally in the range of exposures observed in adults at the 200 mg QD dose level, which is the maximum tested dose in adult NSCLC patients. At dose level 4 the lorlatinib steady-state AUC_{tau} and C_{max} was 7545 ng•hr/mL and 1003 ng/mL, respectively, as compared to the adult 200 mg QD steady-state AUC_{tau} and C_{max} of 8690 ng•hr/mL and 1095 ng/mL (n=2, arithmetic mean values reported), respectively (*B7461001 Clinical Study Report, Table 23. Summary of Plasma Lorlatinib Pharmacokinetic Parameters Following Multiple Oral Doses*).

The preliminary PK data used in this analysis was based on nominal collection times and quality controlled, non-quality assured bio-analytical data. The PK parameters were determined by non-compartmental analysis (Pharsight; Phoenix WinNonlin version 7.0).

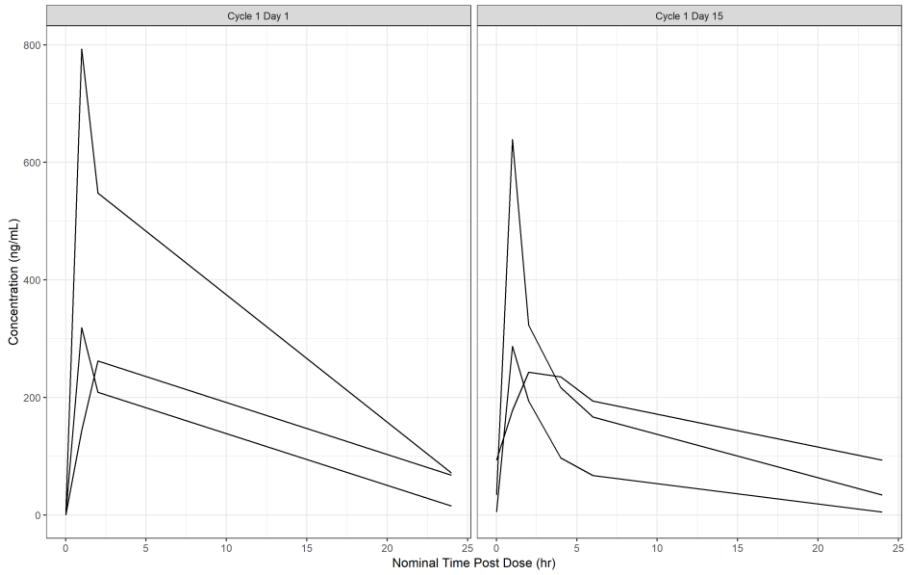
Table 4. Lorlatinib Plasma PK Parameter Summary Statistics by Visit for Dose Level 1 (45 mg/m^2)

Parameters, Units	Parameter Summary Statistics by Visit for Dose Level 1 (45 mg/m^2)	
	Single dose (Cycle 1 Day 1)	Multiple dose (Cycle 1 Day 15)
Number of Subjects	3	3
AUC_{inf} [ng•hr/mL][a]	4093 (64)	NE
AUC_{tau} [ng•hr/mL]	3526 (60)	2473 (64)
CL/F [L/hr][a]	9.298 (49)	15.39 (31)
C_{max} [ng/mL]	404.7 (65)	354.5 (55)
T_{max}[hr]	1.00 (1.00-2.00)	1.00 (1.00-2.00)
Vz/F [L]	101.7 (70)	NE
$t_{½}$ [hr][a]	7.935 ± 2.999	NE

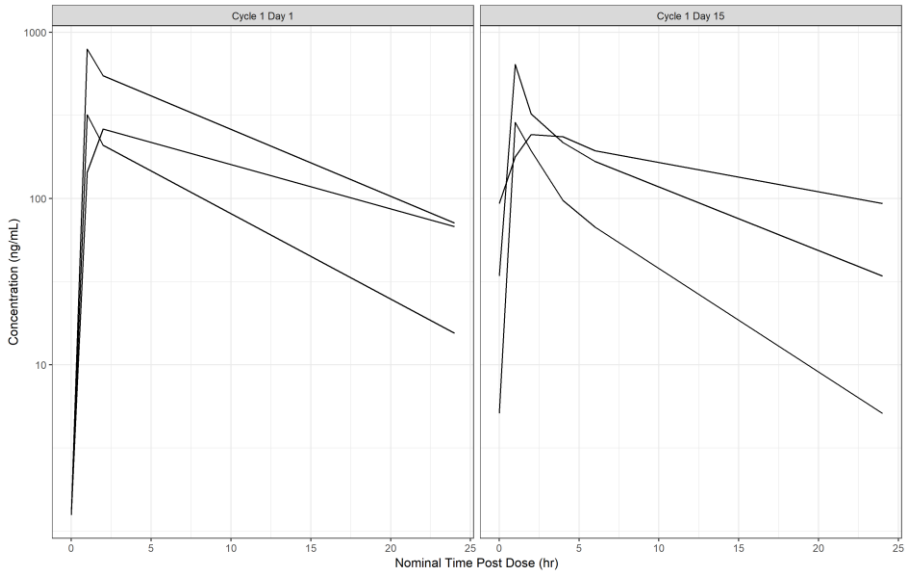
Geometric mean (geometric %CV) for all summarized parameters except: median (range) for T_{max}; arithmetic mean ± Std Dev for $t_{½}$,
AUC_{inf}= Area under the plasma concentration-time profile from time zero extrapolated to infinite time; AUC_{tau}= Area under the concentration-time profile from time zero to time tau (24 hours); CL/F= Apparent oral clearance; C_{max}= Maximum observed plasma concentration; T_{max}= Time for C_{max}; Vz/F= Apparent volume of distribution; NE= not estimable.
[a]Note: some half-life estimates could not be reliably estimated and hence the PK parameters should be interpreted with caution.

Figure 2. Dose Level 1 (45 mg/m^2) Lorlatinib Plasma Concentration-Time Profiles by Patient for Cycle 1 Day 1 and Cycle 1 Day 15 (A: Linear; B: Semi-Log)

A.



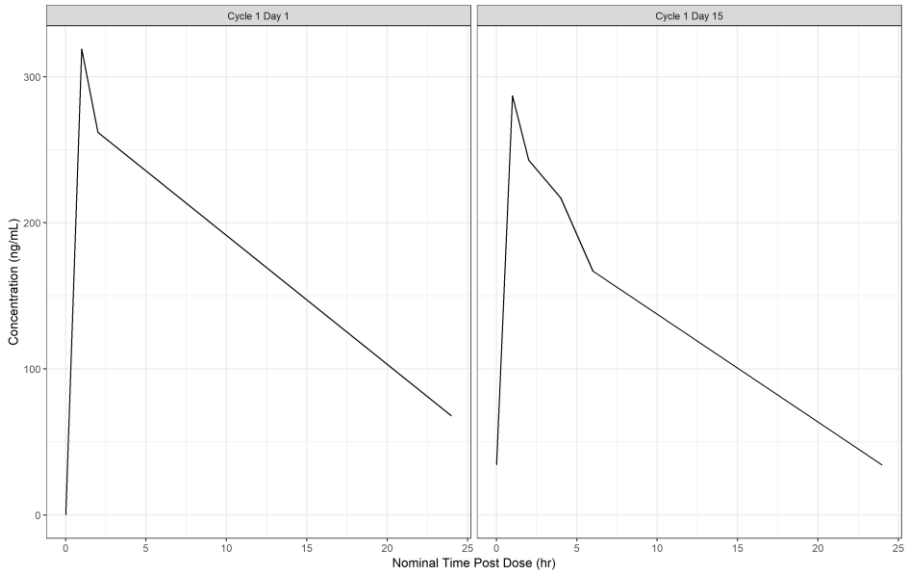
B.



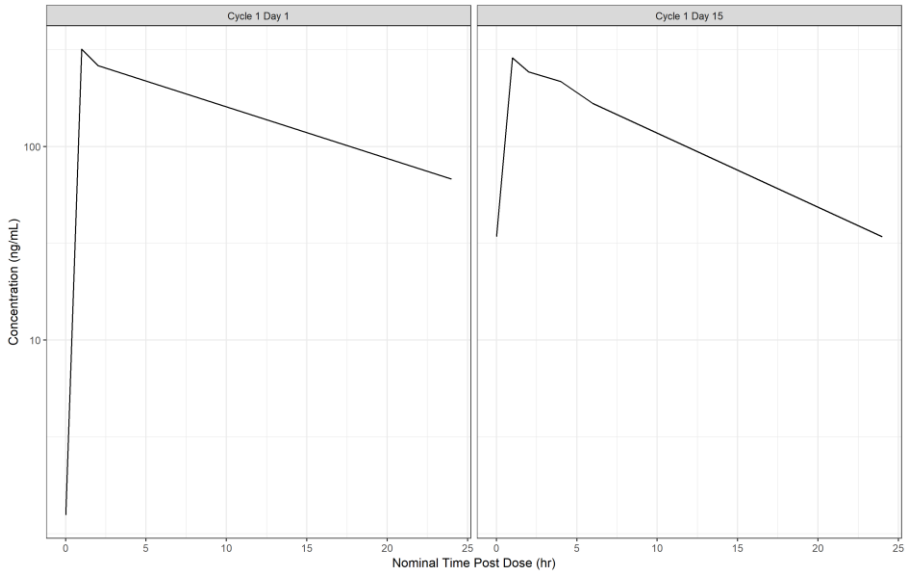
For the semi-log plot, if the concentration was 0, it was substituted as lower limit of quantification (LLOQ(/2 or 1.25 ng/mL

Figure 3. Dose Level 1 (45 mg/m^2) Lorlatinib Median Plasma Concentration-Time Profiles by Visit (Cycle 1 Day 1 and Cycle 1 Day 15) (A: Linear; B: Semi-Log)

A.



B.



For the semi-log plot, if the concentration was 0, it was substituted as LLOQ/2 or 1.25 ng/mL.

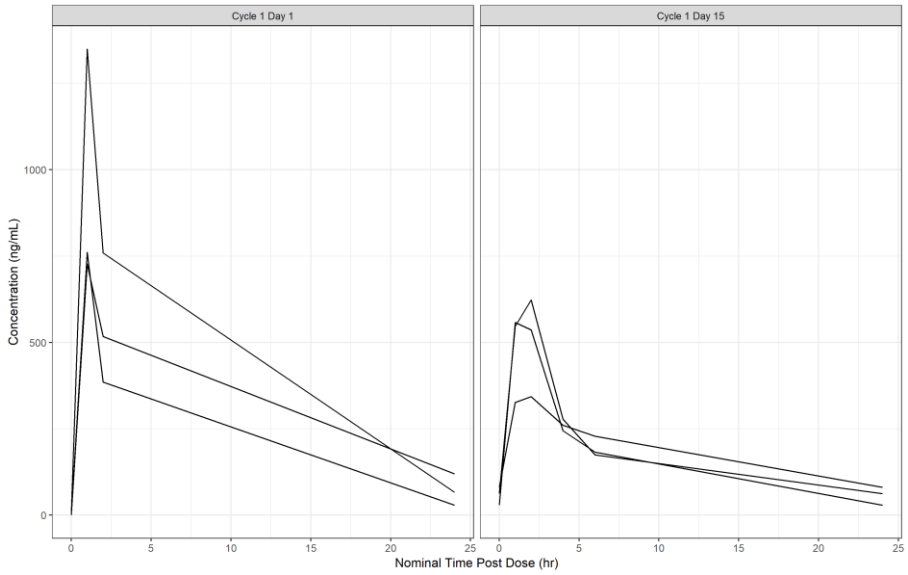
Table 5. Lorlatinib Plasma PK Parameter Summary Statistics by Visit for Dose Level 2 (60 mg/m^2)

Parameters, Units	Parameter Summary Statistics by Visit for Dose Level 2 (60 mg/m^2)	
	Single dose (Cycle 1 Day 1)	Multiple dose (Cycle 1 Day 15)
Number of Subjects	3	3
AUC_{inf} [ng•hr/mL][a]	6720 (43)	NE
AUC_{tau} [ng•hr/mL]	6020 (38)	3927 (10)
CL/F [L/hr][a]	7.544 (26)	12.91 (23)
C_{max} [ng/mL]	907.3 (36)	492.2 (33)
T_{max}[hr]	1.00 (1.00-1.00)	2.00 (1.00-2.00)
Vz/F [L]	71.55 (46)	NE
$t_{½}$ [hr][a]	6.810 ± 2.305	NE

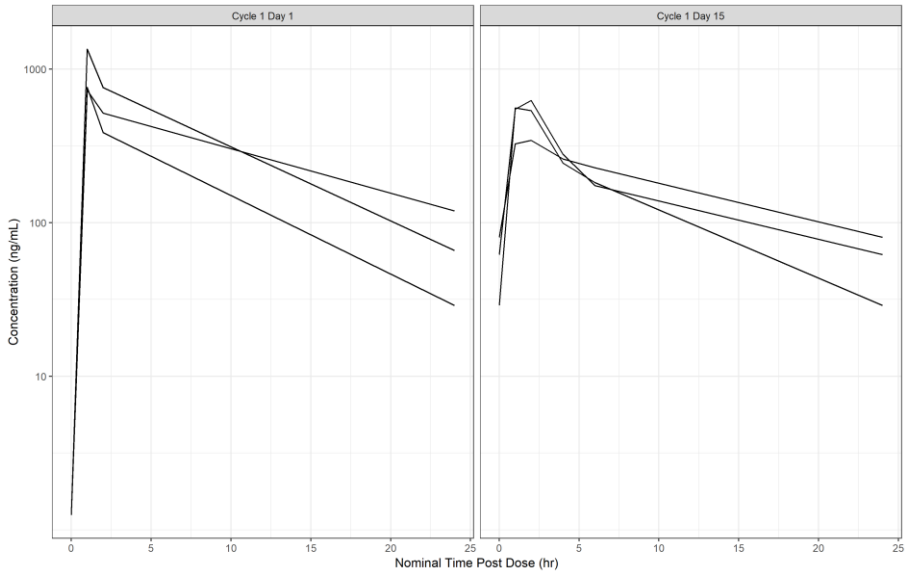
Geometric mean (geometric %CV) for all summarized parameters except: median (range) for T_{max}; arithmetic mean ± Std Dev for $t_{½}$,
AUC_{inf}= Area under the plasma concentration-time profile from time zero extrapolated to infinite time; AUC_{tau}= Area under the concentration-time profile from time zero to time tau (24 hours); CL/F= Apparent oral clearance; C_{max}= Maximum observed plasma concentration; T_{max}= Time for C_{max}; Vz/F= Apparent volume of distribution; NE= not estimable.
[a]Note: some half-life estimates could not be reliably estimated and hence the PK parameters should be interpreted with caution.

Figure 4. Dose Level 2 (60 mg/m^2) Lorlatinib Plasma Concentration-Time Profiles by Patient for Cycle 1 Day 1 and Cycle 1 Day 15 (A: Linear; B: Semi-Log)

A.



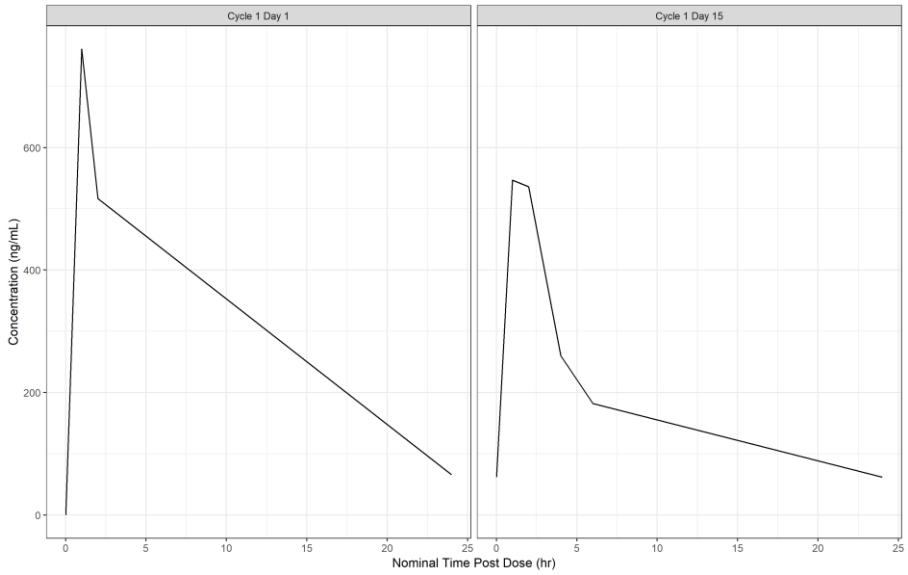
B.



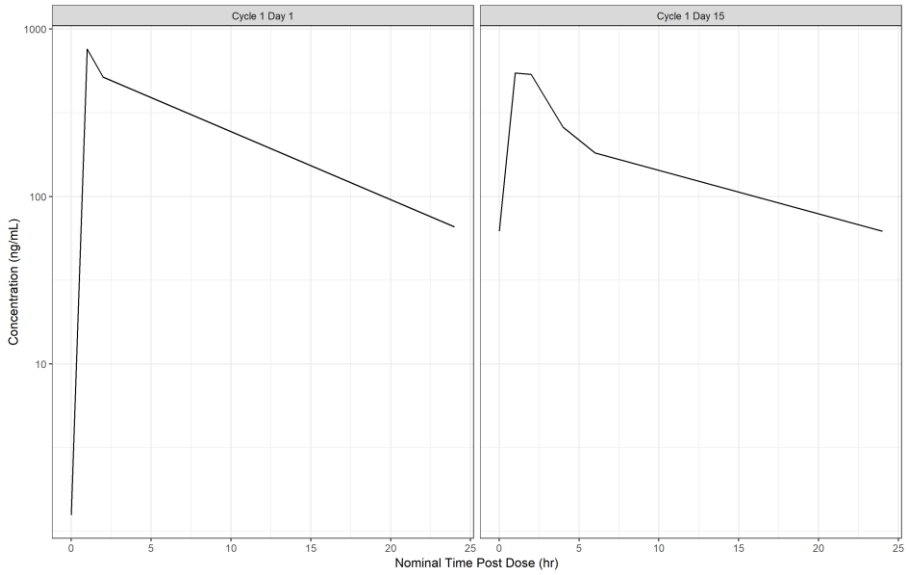
For the semi-log plot, if the concentration was 0, it was substituted as LLOQ/2 or 1.25 ng/mL

Figure 5. Dose Level 2 (60 mg/m^2) Lorlatinib Median Plasma Concentration-Time Profiles by Visit for Cycle 1 Day 1 and Cycle 1 Day 15 (A: Linear; B: Semi-Log)

A.



B.



For the semi-log plot, if the concentration was 0, it was substituted as LLOQ/2 or 1.25 ng/mL.

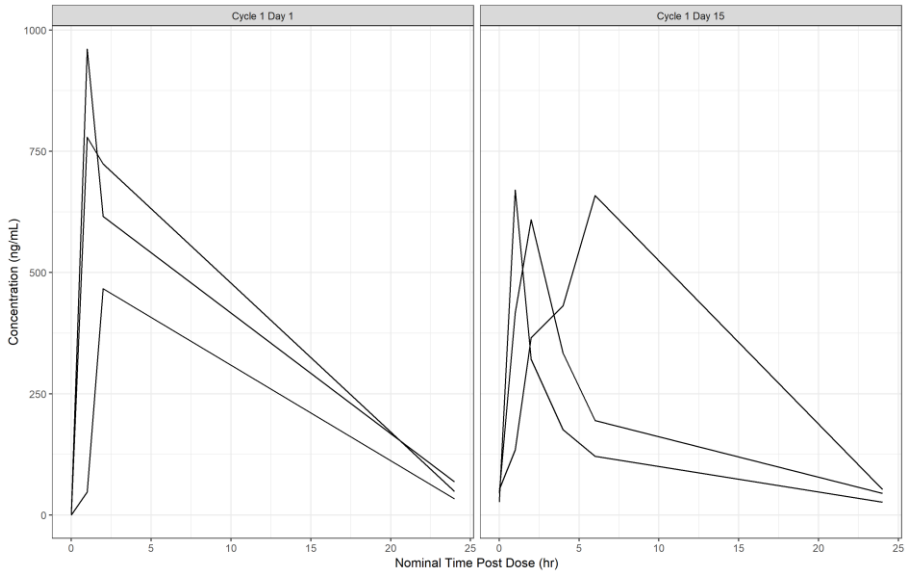
Table 6. Lorlatinib Plasma PK Parameter Summary Statistics by Visit for Dose Level 3 (75 mg/m^2)

Parameters, Units	Parameter Summary Statistics by Visit for Dose Level 3 (75 mg/m^2)	
	Single dose (Cycle 1 Day 1)	Multiple dose (Cycle 1 Day 15)
Number of Subjects	3	3
AUC_{inf} [ng•hr/mL][a]	5997 (33)	NE
AUC_{tau} [ng•hr/mL]	5580 (32)	4155 (46)
CL/F [L/hr][a]	10.77 (12)	15.54 (26)
C_{max} [ng/mL]	704.5 (38)	645.4 (5)
T_{max}[hr]	1.00 (1.00-2.00)	2.00 (1.00-6.00)
Vz/F [L]	92.09 (13)	NE
$t_{½}$ [hr][a]	5.937 ± 0.418	NE

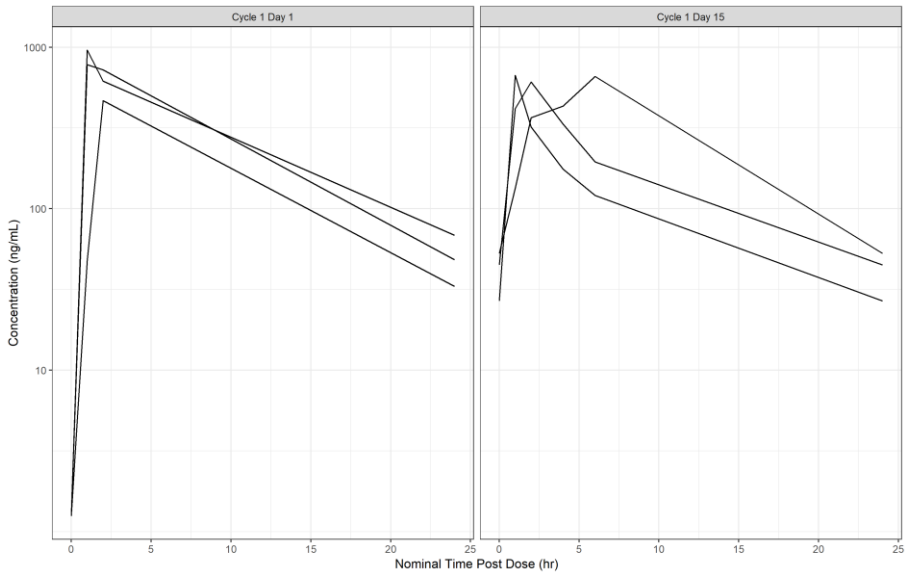
Geometric mean (geometric %CV) for all summarized parameters except: median (range) for T_{max}; arithmetic mean ± Std Dev for $t_{½}$,
AUC_{inf}= Area under the plasma concentration-time profile from time zero extrapolated to infinite time; AUC_{tau}= Area under the concentration-time profile from time zero to time tau (24 hours); CL/F= Apparent oral clearance; C_{max}= Maximum observed plasma concentration; T_{max}= Time for C_{max}; Vz/F= Apparent volume of distribution; NE= not estimable.
[a]Note: some half-life estimates could not be reliably estimated and hence the PK parameters should be interpreted with caution.

Figure 6. Dose Level 3 (75 mg/m^2) Lorlatinib Plasma Concentration-Time Profiles by Patient for Cycle 1 Day 1 and Cycle 1 Day 15 (A: Linear; B: Semi-Log)

A.



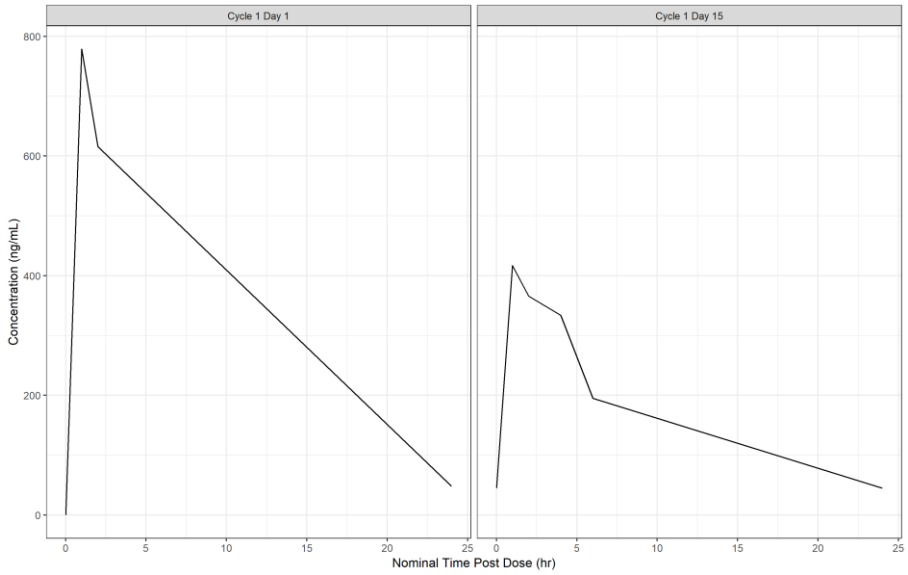
B.



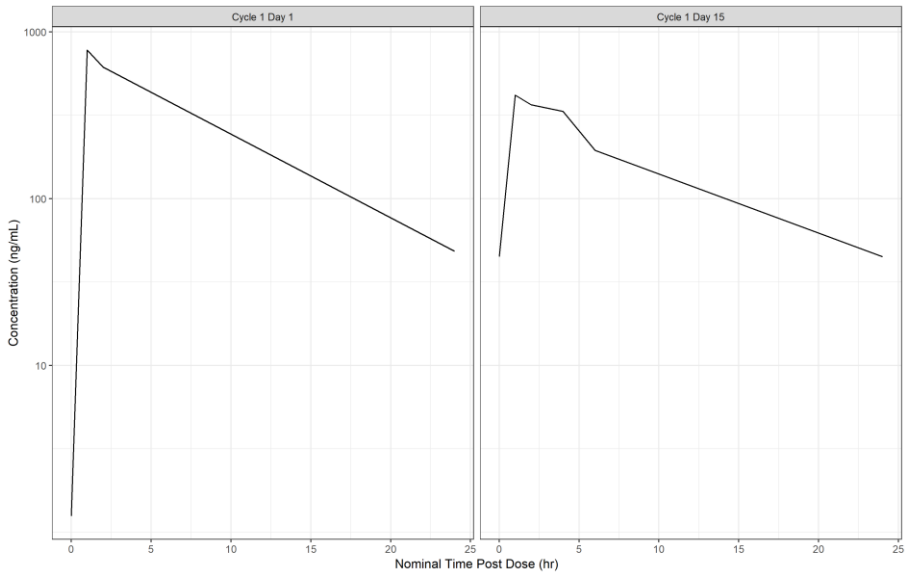
For the semi-log plot, if the concentration was 0, it was substituted as LLOQ/2 or 1.25 ng/mL

Figure 7. Dose Level 3 (75 mg/m^2) Lorlatinib Median Plasma Concentration-Time Profiles by Visit for Cycle 1 Day 1 and Cycle 1 Day 15 (A: Linear; B: Semi-Log)

A.



B.



For the semi-log plot, if the concentration was 0, it was substituted as LLOQ/2 or 1.25 ng/mL.

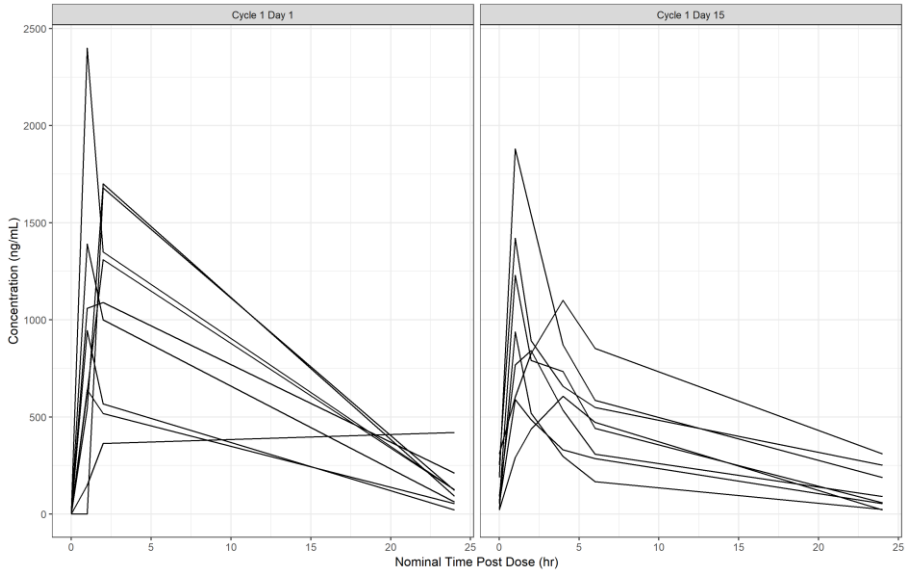
Table 7. Lorlatinib Plasma PK Parameter Summary Statistics by Visit for Dose Level 4 (95 mg/m^2)

Parameters, Units	Parameter Summary Statistics by Visit for Dose Level 4 (95 mg/m^2)	
	Single dose (Cycle 1 Day 1)	**Multiple dose (Cycle 1 Day 15)**
Number of Subjects	9[b]	8
AUC_{inf} [ng•hr/mL][a]	10960 (49)	NE
AUC_{tau} [ng•hr/mL]	9970 (43)	7545 (53)
CL/F [L/hr][a]	6.493 (46)	9.800 (31)
C_{max} [ng/mL]	1148 (58)	1003 (42)
T_{max}[hr]	2.00 (1.00-24.00)	1.00 (1.00-4.00)
Vz/F [L]	57.43 (55)	NE
$t_{½}$ [hr][a]	6.255 ± 1.412	NE

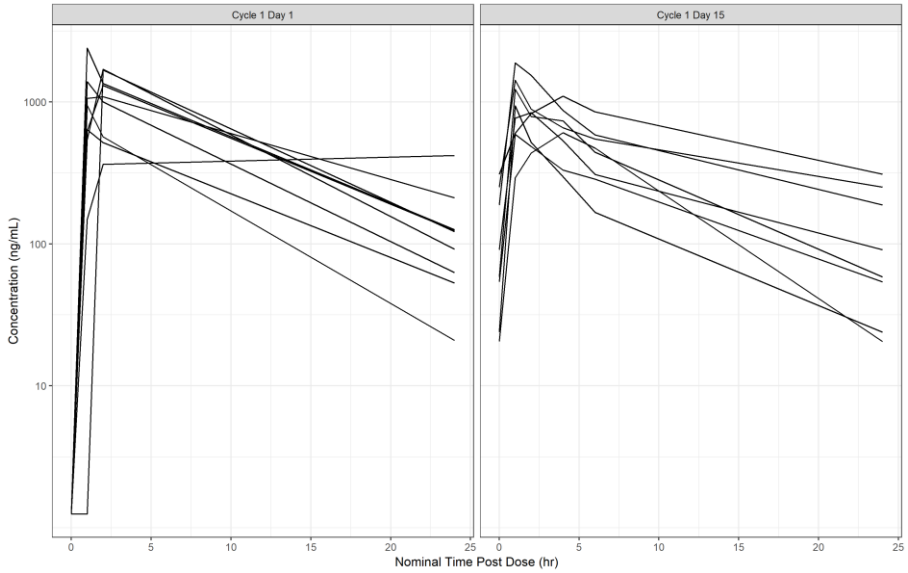
Geometric mean (geometric %CV) for all summarized parameters except: median (range) for T_{max}; arithmetic mean ± Std Dev for $t_{½}$,
AUC_{inf}= Area under the plasma concentration-time profile from time zero extrapolated to infinite time; AUC_{tau}= Area under the concentration-time profile from time zero to time tau (24 hours); CL/F= Apparent oral clearance; C_{max}= Maximum observed plasma concentration; T_{max}= Time for C_{max}; Vz/F= Apparent volume of distribution; NE= not estimable.
[a]Note: some half-life estimates could not be reliably estimated and hence the PK parameters should be interpreted with caution.
[b]The parameters AUC_{inf}, CL/F, Vz/F, and $t_{½}$ have 8 subjects

Figure 8. Dose Level 4 (95 mg/m^2) Lorlatinib Plasma Concentration-Time Profiles by Patient for Cycle 1 Day 1 and Cycle 1 Day 15 (A: Linear; B: Semi-Log)

A.



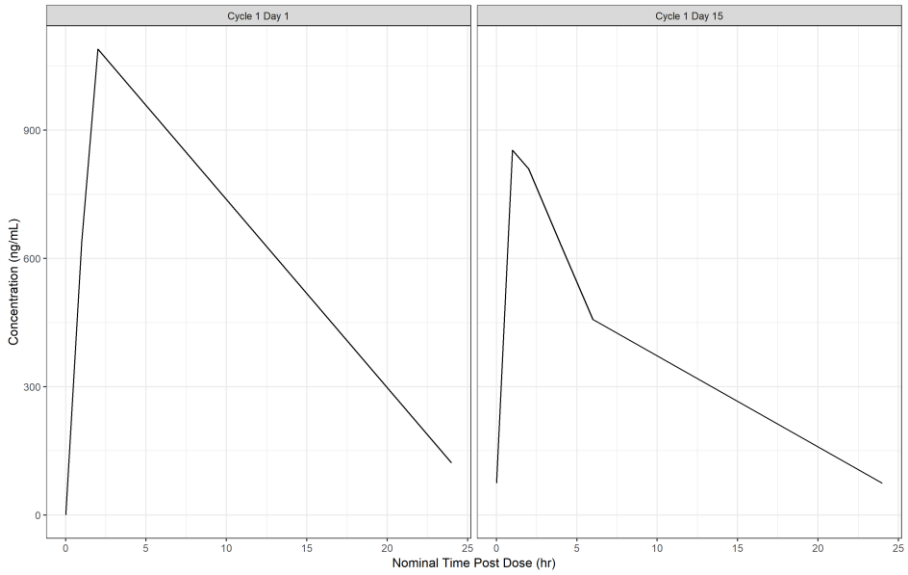
B.



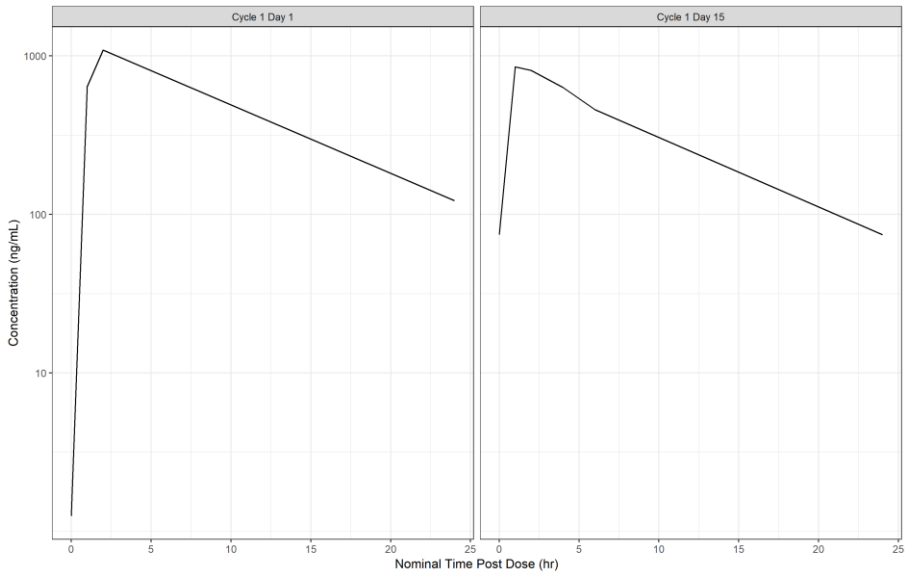
For the semi-log plot, if the concentration was 0, it was substituted as LLOQ/2 or 1.25 ng/mL.

Figure 9. Dose Level 4 (95 mg/m^2) Lorlatinib Median Plasma Concentration-Time Profiles by Visit for Cycle 1 Day 1 and Cycle 1 Day 15 (A: Linear; B: Semi-Log)

A.



B.



For the semi-log plot, if the concentration was 0, it was substituted as LLOQ/2 or 1.25 ng/mL.

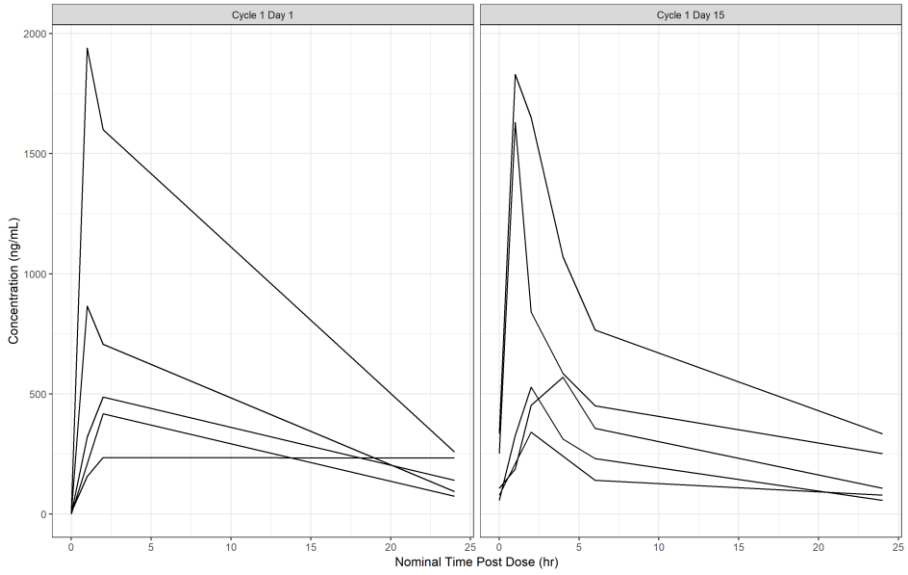
Table 8. Lorlatinib Plasma PK Parameter Summary Statistics by Visit for Dose Level 3A (100 mg)

Parameters, Units	Parameter Summary Statistics by Visit for Dose Level 3A (100 mg)	
	Single dose (Cycle 1 Day 1)	Multiple dose (Cycle 1 Day 15)
Number of Subjects	5[b]	5
AUC_{inf} [ng•hr/mL][a]	10070 (61)	NE
AUC_{tau} [ng•hr/mL]	7636 (58)	6846 (75)
CL/F [L/hr][a]	9.935 (61)	14.61 (75)
C_{max} [ng/mL]	603.7 (95)	788.9 (86)
T_{max}[hr]	1.00 (1.00-2.00)	2.00 (1.00-4.00)
Vz/F [L]	128.4 (72)	NE
$t_{½}$ [hr][a]	9.140 ± 2.197	NE

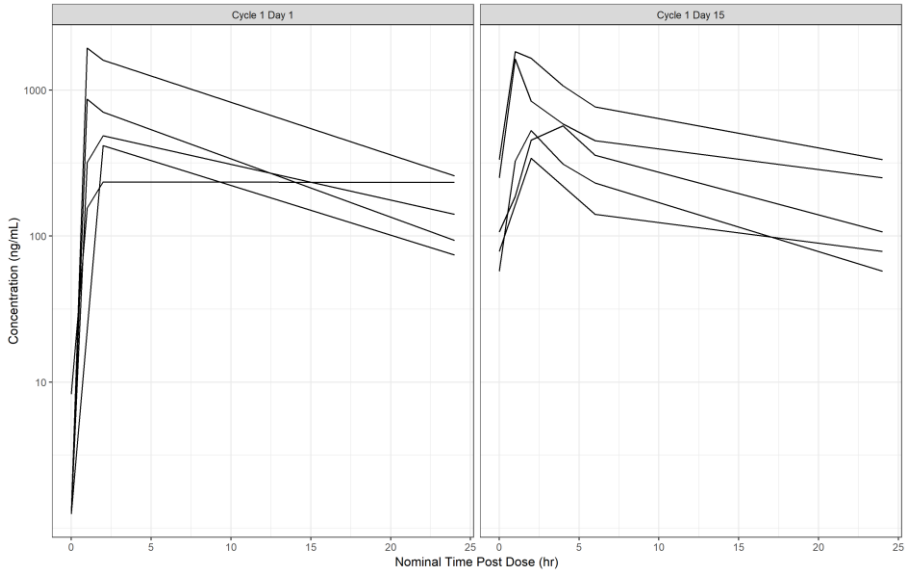
Geometric mean (geometric %CV) for all summarized parameters except: median (range) for T_{max}; arithmetic mean ± Std Dev for $t_{½}$,
AUC_{inf}= Area under the plasma concentration-time profile from time zero extrapolated to infinite time; AUC_{tau}= Area under the concentration-time profile from time zero to time tau (24 hours); CL/F= Apparent oral clearance; C_{max}= Maximum observed plasma concentration; T_{max}= Time for C_{max}; Vz/F= Apparent volume of distribution; NE= not estimable.
[a]Note: some half-life estimates could not be reliably estimated and hence the PK parameters should be interpreted with caution.
[b]The parameters AUC_{inf}, CL/F, Vz/F, and $t_{½}$ have 4 subjects

Figure 10. Dose Level 3A (100 mg) Lorlatinib Plasma Concentration-Time Profiles by Patient for Cycle 1 Day 1 and Cycle 1 Day 15 (A: Linear; B: Semi-Log)

A.



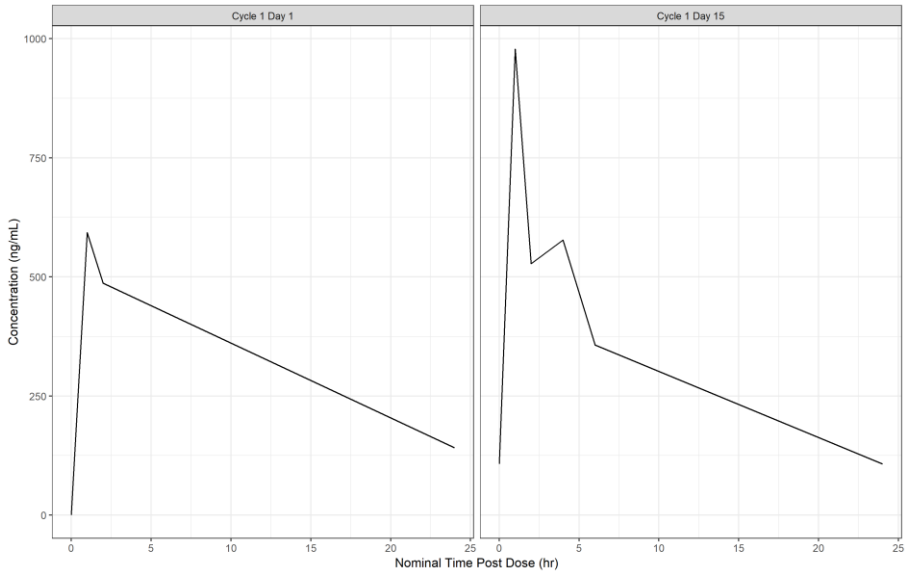
B.



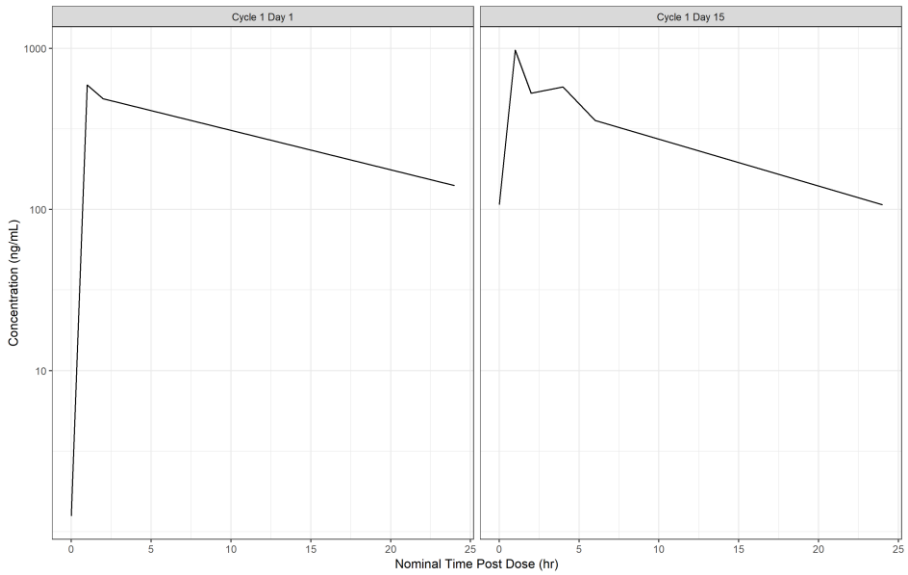
For the semi-log plot, if the concentration was 0, it was substituted as LLOQ/2 or 1.25 ng/mL.

Figure 11. Dose Level 3A (100 mg) Lorlatinib Median Plasma Concentration-Time Profiles by Visit for Cycle 1 Day 1 and Cycle 1 Day 15 (A: Linear; B: Semi-Log)

A.



B.



For the semi-log plot, if the concentration was 0, it was substituted as LLOQ/2 or 1.25 ng/mL.

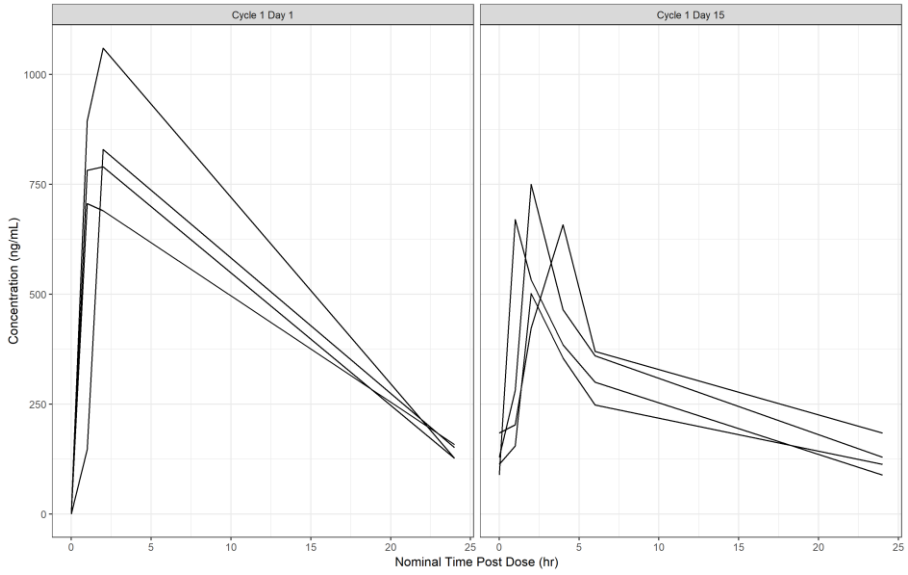
Table 9. Lorlatinib Plasma PK Parameter Summary Statistics by Visit for Dose Level 4A (150 mg)

Parameters, Units	Parameter Summary Statistics by Visit for Dose Level 4A (150 mg)	
	Single dose (Cycle 1 Day 1)	Multiple dose (Cycle 1 Day 15)
Number of Subjects	4	4
AUC_{inf} [ng•hr/mL][a]	11410 (6)	NE
AUC_{tau} [ng•hr/mL]	9606 (10)	6143 (18)
CL/F [L/hr][a]	13.14 (6)	24.42 (18)
C_{max} [ng/mL]	836.7 (17)	638.3 (17)
T_{max}[hr]	2.00 (1.00-2.00)	2.00 (1.00-4.00)
Vz/F [L]	163.7 (19)	NE
$t_{½}$ [hr][a]	8.707 ± 1.315	NE

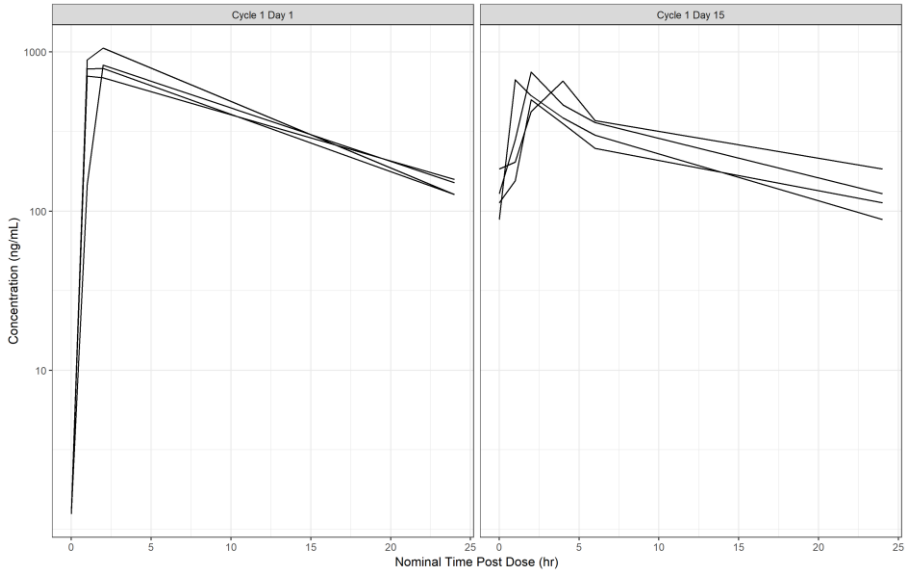
Geometric mean (geometric %CV) for all summarized parameters except: median (range) for T_{max}; arithmetic mean ± Std Dev for $t_{½}$,
AUC_{inf}= Area under the plasma concentration-time profile from time zero extrapolated to infinite time; AUC_{tau}= Area under the concentration-time profile from time zero to time tau (24 hours); CL/F= Apparent oral clearance; C_{max}= Maximum observed plasma concentration; T_{max}= Time for C_{max}; Vz/F= Apparent volume of distribution; NE= not estimable.
[a]Note: some half-life estimates could not be reliably estimated and hence the PK parameters should be interpreted with caution.

Figure 12. Dose Level 4A (150 mg) Lorlatinib Median Plasma Concentration-Time Profiles by Visit for Cycle 1 Day 1 and Cycle 1 Day 15 (A: Linear; B: Semi-Log)

A.



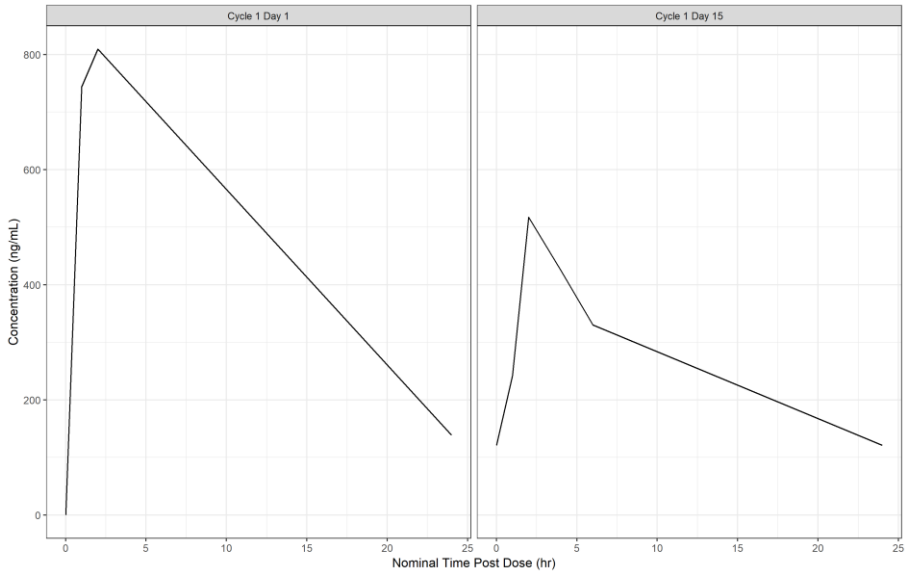
B.



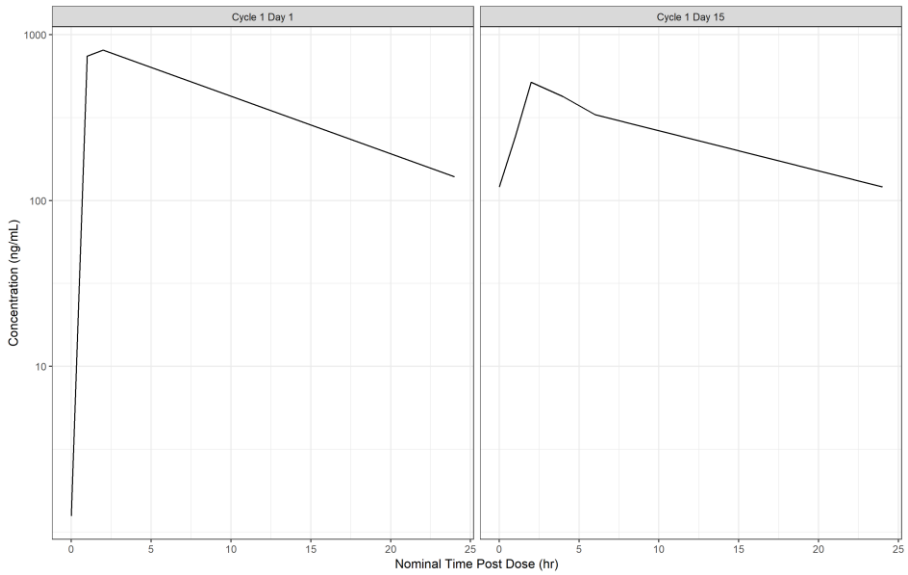
For the semi-log plot, if the concentration was 0, it was substituted as LLOQ/2 or 1.25 ng/mL.

Figure 13. Dose Level 4A (150 mg) Lorlatinib Median Plasma Concentration-Time Profiles by Visit for Cycle 1 Day 1 and Cycle 1 Day 15 (A: Linear; B: Semi-Log)

A.



B.



For the semi-log plot, if the concentration was 0, it was substituted as LLOQ/2 or 1.25 ng/mL.

2.8 Weight gain and increased appetite expected with Lorlatinib

Non-Clinical Data:

Increase of body weight and food consumption was observed following administration of lorlatinib to rats. The magnitude of change was significantly greater in females than males. Inhibition of TrkB is identified as the likely biologic rationale-these kinases are involved in appetite regulation and metabolic balance.

Clinical Data:

Adult studies: Weight increase with lorlatinib has been reported in the adult Phase 1 and Phase 2 study. Of 262 evaluable patients in the phase 2, 80 (30.5%) patients increased by 10–20% of their baseline weight and 33 (12.6%) patients gained >20% of their baseline weight. The adult studies have reported this based on weight as a data point, and not as a reported adverse event. Weight gain appears to be more prominent in females and other phase 1 studies of TrkB inhibitors have reported weight gain, consistent with the underlying biological rationale for this effect. In the adult studies of lorlatinib, weight gain has not been a reason for dose delay or reduction.

As of November 09, 2017 at the time of amendment 2a, 3 patients had enrolled on Cohort A1 Dose level 1 (45mg/m^2). All 3 patients experienced weight gain with therapy. Two patients experienced grade 2 weight gain, and 1 experienced grade 3 weight gain. There were no associated toxicities with the weight gain, specifically no patients experienced dose limiting toxicities of increased glucose, cholesterol or triglycerides. These patients had increased appetite that resulted in weight gain. The study committee reviewed the known preclinical and adult data and based on that analysis, grade 3 weight gain was excluded as a dose limiting toxicity.

As of November 7, 2018, at the time of interim Dose Level 4 evaluation, eighteen patients were evaluable for weight gain. Weight gain was observed in 16/18 patients. Of which 4/18 had grade 3 weight gain, 9/18 had grade 2 weight gain, and 3/18 had grade 1 weight gain. In addition, associated with the weight gain, the BMI of enrolled patients was also increased with two patients reaching the ≥95% BMI according to age and sex. However, hyperglycemia has not been a common finding in this pediatric study with only one adult patient with a baseline severe obesity developing type 2 difficult to control diabetes. The study management committee agreed there is a potential for metabolic syndrome with this agent. The committee recommended the addition of hemoglobin A1c (HbA1c) measurement at time of fasting lipid panels and glucose measurements.

As of January 21, 2020, after enrollment of the third patient on DL 5 and the sixth patient on DL 4A, 32 patients were evaluable for weight gain. Weight gain was observed in 28/32 patients of which 8/32 had grade 3 weight gain, 14/32 had grade 2 weight gain, and 6/32 had grade 1 weight gain.

2.9 Five Gene NB5 assay by TLDA for Neuroblastoma Tumor Cell Detection

Dr. Robert Seeger's laboratory developed the NB5 assay, a five gene TLDA array for sensitive detection of neuroblastoma tumor cells in peripheral blood and bone marrow. Five genes [chromogranin A (CHGA), doublecortin (DCX), dopadecarboxylase (DDC), paired-like homeobox 2B (PHOX2B), and tyrosine hydroxylase (TH)] are highly expressed by neuroblastoma cell lines and tumors. These same genes are rarely expressed by normal blood cells, peripheral blood stem cells (PBSC), and bone marrow. Four housekeeping genes are used for quality control and data analysis. Heterogeneity in expression of the detection genes among neuroblastoma cell lines (n=22) and primary untreated stage 4 neuroblastoma tumors (n=23) is minimal. However, the use of five genes assures that heterogeneity will not impact tumor cell detection.

Spiking experiments demonstrate the sensitivity of neuroblastoma cell detection using this 5-gene signature. Detection sensitivity with five genes (including TH) is superior to that of a single gene (TH). The five-gene detector has nearly 100% sensitivity to detect neuroblastoma RNA at a dose of 10-5, whereas the TH-only detector has sensitivity of <60%. In terms of neuroblastoma cell detection, the 5-gene signature can detect a 10-6 neuroblastoma cell frequency in PBMC with 81% probability compared to <30% for a TH-alone detector.

TLDA Detection Gene Score (DG score) is highly correlated with Immunocytology Score (number of tumor cells/106 total cells) when Immunocytology is positive in bone marrow. Forty-four unselected fresh bone marrow specimens were tested by both assays. The rank correlation between the TLDA DG Score and Immunocytology Score was r = -.93 ($p < 0.001$), which demonstrates a clear relationship between the two assays. The TLDA assay also can detect tumor cells in bone marrow that are not detected by Immunocytology. Thirty-six of the 44 bone marrows were negative by Immunocytology, but 20 of these were positive by TLDA. These data further confirm that the TLDA assay is more sensitive than Immunocytology for detecting tumor cells. Moreover, detection of occult bone marrow tumor cells by TLDA appears to have clinical relevance. In patients with newly diagnosed high-risk neuroblastoma, detection of tumor cells by TLDA in a bone marrow sample negative by Immunocytology at the end of therapy was associated with significantly worse event-free survival than bone marrow samples negative for tumor cells by TLDA assay.

The current study includes an exploratory aim to evaluate neuroblastoma cell detection in blood and bone marrow by TLDA. These samples will be obtained as part of the companion NANT biology study (NANT 2004-05).

2.10 Adult Cohort with Lorlatinib Monotherapy (Cohort A2)

Five evaluable patients enrolled on Cohort A2 Dose Level 3A with lorlatinib monotherapy at 100mg/day. This dose level was reviewed by the Collaborative Governance Committee (CGC) and the decision was made to escalate to Dose Level 4A with lorlatinib monotherapy at 150mg/day. An amendment was required to revise the study design to add the Cohort A2 Dose level 4A at 150mg/day. With Amendment 4, the activation of Dose Level 4A was initiated on 18JUN2018. Six patients were enrolled on Dose Level 4A. Patient toxicity and PK data were reviewed by the CGC and determined this to be the RP2D. The decision was made to expand Dose Level 4A to an additional 6 patients for further analysis of toxicity and PK data. Four additional evaluable patients enrolled on the expansion Dose level 4A. The CGC reviewed and compared Dose level 3A (5 total patients) with the Dose level 4A (10 total patients) patient toxicity and PK data on two separate meetings; 15SEP2021 and 30NOV2021. Preliminary PK data showed comparable exposure at the 100mg/day and 150mg/day dose levels. There were additional toxicities seen with the patients enrolled on the 150mg/day dose level. Therefore, the CGC decided to further expand Dose level 3A (100mg/day) to 5 more patients for a total of 10 evaluable patients on this dose level for a better comparison of toxicity/response data as well as PK. This data will then allow for final determination for recommended phase 2 dose (RP2D) of this patient population. Cohort B2 (lorlatinib in combination with chemotherapy) for the adult patient population will also enroll at 100mg/day.

2.11 Rationale for Protocol Amendments

Amendment #1 v 6-7-2017
Pre-activation amendment dealt with updates and clarifications in eligibility, required observations, toxicity monitoring, dose modifications and statistical design, Corresponding informed consent template changes were made, in addition to administrative changes.

Amendment #2A v 12-15-2017
In addition to editorial, administrative changes and updates to participating institutions, this amendment covers important updates to the eligibility section, drug information changes, clarifications to the required observations section and changes to the informed consent template.
Of note: 1) Requirement for a specific biopsy proven MIBG non-avid site to be present at the time enrollment was removed; 2) Time required from last biologic neoplastic agent was decreased from 14 to 7 days; 3) Grade 3 weight gain was added as an exclusion to non-hematological dose limiting toxicities; 4) Restrictions to the administration of CYP3A inhibitors while on protocol therapy was removed due to updated knowledge on lorlatinib metabolism from the updated version of the IB; 5) Frequency of CBC checks were decreased due to lack of hematological toxicities.

Amendment #3 v 3-7-2018
There was one serious, unexpected event in a patient who began treatment on NANT 2015-02 Cohort A2 (100mg QD). The patient is a 27 year old male who experienced grade 3 hyperglycemia, grade 3 hypertriglyceridemia, grade 2 hypertension, grade 1 cholesterol, grade 1 weight gain, and grade 1 peripheral neuropathies on Course 3 Day 26. Patient has no personal history of diabetes, but has a BMI of 40 and a strong family history of diabetes. Grade 3 hyperglycemia persists despite interruption of lorlatinib and initiation of therapy for Type 2 diabetes.

Upon review of prior experience with lorlatinib, of the 295 adult patients who received lorlatinib (100mg QD) on Ph1/2 trials, grade 3 treatment-related AE of hyperglycemia was reported to be 0.7%.

Review of NANT 2015-02 thus far all patients have experienced weight gain, grades 1-3 without associated hyperglycemia.

Although patient was obese (BMI 40) and had a strong family history of diabetes, considering age and weight gain during therapy and acute onset of hyperglycemia (grade 3), the study team considers grade 3 hyperglycemia and hypertriglyceridemia probably related to lorlatinib therapy. However, exact potential risk of this specific toxicity in others is unknown.

The risk of hyperglycemia was therefore added to the consent document as part of Amendment 3 due to the information based on this event.

Amendment #4 v 6-7-2018
Evaluation of neuroblastoma patients on the highest dose level (DL3, 75 mg/m^2) demonstrated no DLTs or cognitive deficits, supporting safety and tolerability of lorlatinib in pediatric population as of April 2018. PK data also demonstrates that acceptable levels of lorlatinib are achieved in children comparable to adults. Further evaluation of compelling preclinical data in neuroblastoma, however, reveal that lorlatinib doses required for antitumor potency in neuroblastoma are actually higher than effective lorlatinib doses in preclinical NSCLC models, with mouse to human equivalent dosing suggesting that Dose level 3 may be insufficient to target ALK driven neuroblastoma. This is likely due to the different patient population being tested and the different biology of ALK driven neuroblastoma compared to NSCLC.

The study committee discussed the available toxicity, response and *PK* data and in order to maximize lorlatinib exposure for an anti-neuroblastoma response proposed to amend the study to include two additional dose escalations at Dose Level 4: 95 mg/m2, Dose Level 5: 115 mg/m2 (27% and 53% increases from Dose level 3), and to add dose levels 150 mg (similar to dose level 4) and 200mg (similar to dose level 5) to the adult cohort A2, and to adopt a 3+3 dose escalation design in Cohort A2 independent of that in Cohort A1.

While neurocognitive effects are a concern at higher doses as previously seen in one adult at the 200 mg flat dosing who experienced a DLT. Overall the adult experience shows that the CNS effects are mild to moderate with a variety of presentations, including changes in speech, memory and mood, and were generally intermittent and managed with dose hold or reduction. These effects are reversible upon cessation of the drug and/or dose reduction and are being closely monitored within this protocol and these symptoms will be captured in real time in subsequent cycles.

For safety purposes, for patients enrolled after activation of Amendment 4, no more than two patients can simultaneously be enrolled on Course 1 of therapy in each of Cohorts A1 and A2. Furthermore, due to concern about possible delayed neurocognitive toxicities, the DLT evaluation period has been extended to include both Course 1 and Course 2, with any DLT during Course 1 but only neurocognitive DLTs during Course 2 counting for dose escalation/de-escalation decisions.

Two additional neuropsychological exploratory aims were added as part of Amendment 4 in order to adequately describe the results of the neuropsychological testing in this trial.

This amendment also includes the change in the NANT 2015-02 Study Statistician from Susan Groshen, PhD to Richard Sposto, PhD.

Footer #6 in required observations table 23 was updated to allow for course extension due to scheduling conflicts.

Amendment #5 v 12-18-2018
This protocol amendment is being implemented in order to add newly identified risks from the Investigator's Brochure (v 10/2018) of pneumonitis, caution with use of machines/driving and decreased effectiveness of hormonal contraception. In addition, due to weight gain observed on NANT 2015-02 trial, closer evaluation of potential metabolic syndrome was instituted with fasting lipid and glucose measurements and hemoglobin A1c measurements.

Amendment #6 v 04-30-2019
This protocol amendment is being implemented in order to update the risks of lorlatinib based on the most recent toxicity data available from the B7461001 adult trial. Other minor revisions made to this amendment are outlined in the cover memo and tracked changes version of the amendment.

Amendment #7 v 10-31-2019
Evaluation of neuroblastoma patients enrolled on Cohort A1 on the highest dose level (DL4, 95 mg/m^2) demonstrated no DLTs in courses 1 and 2 in five evaluable patients, supporting safety and tolerability of DL4 of lorlatinib in patients < 18 YOA. Therefore, Cohort A1 dose escalated to Dose Level 5 (115 mg/m^2/day) on 9/18/2019.

Evaluation of neuroblastoma patients enrolled on Cohort A2 showed that 1/5 adult patients on the highest dose level (DL4A, 150 mg daily) had a DLT of Grade 4 psychosis in course 2 of therapy that improved upon dose hold. Upon retreatment, patient had recurrent grade 4 psychosis. Cohort A2 which was already expanded is pending evaluation of an additional adult patient at DL4A to confirm tolerability and safety. No further dose escalation is planned for patients > 18 YOA on A2. Based on the severity of the neuropsychological toxicity, additional safeguards were added with restrictions of acute and chronic severe neuropsychological disorders in eligibility, and not allowing retreatment for grade 4 CNS effects. Neuropsychological Assessment Schedule and Reporting Section 7.1.2.3 was also updated to include language for monitoring of psychosis. Psychosis was also added as a rare (<5%) risk of lorlatinib in the protocol and consent documents.

Given the safety and tolerability of DL4 as a single agent in patients ≤ 18 YOA, the Study Committee determined DL4 to be the starting dose to use in combination with chemotherapy in Cohort B2 for patients ≤ 18 YOA. As such this amendment is being implemented to open Cohort B2 using 95 mg/m^2 (150 mg maximum) daily of lorlatinib in combination with topotecan and cyclophosphamide (Cohort B2 dose level 4B) in patients ≤ 18 YOA. Cohort B2 will activate and enroll concurrently with ongoing dose escalation cohorts A1 and A2. For patients ≤ 18 YOA: If dose level 5 in cohort A1 and dose level 4B on cohort B2 are tolerated, cohort B2 will escalate to dose level 5B of lorlatinib in combination with chemotherapy. For patients > 18 YOA: Once the RP2D is determined on cohort A2, then B2 will also open to patients > 18 to ≤ 30 YOA at the RP2D with no dose escalation. Patients > 18 will remain on the A2 expansion cohort with single agent lorlatinib at the RP2D.

In addition, a few additional changes to cohort B2 were included.
- Given the target age population to treat with lorlatinib chemotherapy combination are newly diagnosed HR NBL patients, the eligibile age for cohort B2 has been changed to ≤ 30 YOA.
- With amendment 4, the DLT evaluation period for neurocognitive toxicities for cohort A1 was extended to to 2 courses. Since combination with chemotherapy is not likely to increased this specific toxicity and since single agent data is already available for this toxicity, the DLT period for cohort B2 will be limited to course 1.

- After completion of 4 courses of combination therapy, an option to continue with single agent lorlatinib for this patient cohort will also be available.

Following activation of Amendment 7, patients with prior ALK inhibitor exposure may enroll on any open cohort of the study.

Adults >18 YOA who are not eligible for B2 may continue to enroll in single agent lorlatinib cohort A2 that will be expanded at the RP2D once it is determined.

Due to rare grade 3 hyperglycemia in two patients on this current study, the study committee has reviewed how to best manage high glucose in this study. With amendment 7, Grade 3 hyperglycemia will no longer be considered a DLT but Grade 3 glucose intolerance will continue to be a DLT as per CTCAE V4.0. This was instituted because the study committee believes that assessing the level of glucose intolerance by symptoms and need for medical management is a better indication of persistent hyperglycemia adverse events compared to isolated blood sugar levels that could be transient and be medically less meaningful.

In addition, supportive care management guidelines for elevated HbA1C, Grade 2 fasting hyperglycemia, peripheral neuropathy and peripheral edema have also been added since these toxicities have been observed during dose escalation. Lastly, the table for statin drug choice for hypercholesterolemia has been updated.

The optional correlative study for ctDNA has been revised to collect 2 tubes (8.5ml/tube) instead of 1 tube per time point due to better DNA extraction yield.

Additionally, the consents were revised to reflect the changes made in Amendment 7.

Amendment #8 v. 03-23-2020

This protocol amendment clarified language in dose modifications in regards to grade 4 neutropenia and thrombocytopenia for Cohort B2. Grade 4 neutropenia and thrombocytopenia remain exclusions to DLT for this cohort. Chemotherapy dose reduction will only be required if DLT criteria are met (>14 day delay in course initiation). Lorlatinib can be continued beyond day 28 when in cohort B2 if hematological recovery criteria have not been met.

Minor Changes in risk tables for lorlatinib were updated based on Investigator Brochure dated 17OCT2019. Corresponding risk tables in the consents were updated.

In addition, instructions for the timing of lorlatinb dosing in Cohort B2 were clarified.

Amendment #9A v 08-20-2021

This protocol amendment updates the study in accordance with the most recent lorlatinib Investigator's Brochure (V11.0). Additionally, language in the eligibility criteria for MIBG non-avid disease sites was updated. Clarified platelet count requirements, DLT criteria, and dose modifications for patients who continue on cohort B2 without chemotherapy to parallel the respective non chemotherapy cohort. Additionally, the age ranges for each cohort were clarified, and Cohort B2 was clarified as following a 3+3 design with an expansion cohort opening following determination of the RP2D. Details were added on how best overall response will be calculated for patients with CR/PR and minor response. The informed consent templates were revised to include language for Dr. Mossé's / NANT's Disclosure. The neuropsychological testing time points in the template consent for Cohort A2 were revised to be consistent with the protocol. SAE reporting requirements after a patient comes off protocol therapy was added. An allowance was included to continue receiving the remaining lorlatinib investigational product tablets when patient meets off protocol therapy criteria for disease progression if it seems to be in the best interest of the patient according to the treating physician. In section 4.4, the minimum criteria to be off myeloid growth

factor for patients on cohort B2 prior to starting subsequent course was revised to be consistent with section 4.1.4. The restriction on moderate CYP3A inducers was removed from section 4.5

The Study Statistician was changed from Susan Groshen, PhD to Yueh-Yun Chi, PhD. University of North Carolina was removed as a participating site. Minor clarification of soft tissue and bone marrow response criteria were made for version 2.0 of response criteria.

Amendment #10 v 02-18-2022
Background section was edited to include Cohort A2 lorlatinib monotherapy enrollment data. This amendment allows for expansion enrollment on Dose level 3A (100mg/day). The statistical considerations section was revised accordingly as well. In Section 11.0 Response V2.0; minor revisions were made to the non-target soft tissue lesion for clarification purposes. The Bone Marrow (BM) Minimal Disease definition in Section 11.0 was revised which was inconsistent with the BM response table; the Not Involved definition also had a minor clarification. Minor revision was made to footnote numbers 5 and 6 in Required Observations table. Bayley-III testing timelines and windows were clarified in section 7.1.2.3. Minor revisions were made to the ICFs that included inconsistencies or errors in the lorlatinib risk table.

Amendment #11A 05-06-2022
Lorlatinib risk information was revised based on Pfizer's recommendation to include most recent observations noted in patients who participated in Study B7461001 (N=327) or Study B7461006 (N=149) and received lorlatinib 100 mg once daily orally. Section 13.0 was revised to clarify language about imaging scan and bone marrow biopsy slide submission for central review purposes. The ICFs risk tables were revised accordingly. Additional editorial revisions were made.

3.0 PATIENT ELIGIBILITY CRITERIA AND REGISTRATION

3.1 Patient Preparation for Study Entry and Registration

3.1.1 Patient Registration on Study

NANT sites are required to complete electronic CRFs on the web-based application Medidata Rave in a timely manner. In addition, certain study specific data points will be captured on paper CRFs and sent to the NANT Operations Center. This will include all response data that will be entered into our central review system for validation of response.

Treatment slots are obtained through the standard NANT reservation process by sending an email to NANTrsvp@chla.usc.edu.

When assigned a treatment slot by the NANT Operations Center, sites will initiate the enrollment process by completing the Subject Screen form in the web-based application, Medidata Rave. The Subject Screen form alerts the NANT Operations Center to all prospective enrollments. Sites should send patient signed informed consent and all source documentation confirming eligibility to the NANT Operations Center at Children's Hospital Los Angeles by email to nantcrf@chla.usc.edu or if unable to email by FAX at 323-361-1803, Monday through Friday, 8:30am – 5:00pm Pacific Time except holidays.

Once all necessary source documentation is received in the NANT Operations Center, sites can complete the enrollment process by submitting the eligibility form in Medidata Rave. The NANT Operations Center will verify eligibility and assign a unique NANT registration and study subject number in Medidata Rave. The cohort / dose level (if applicable) for treatment will be assigned by the NANT Operations Center at the time of study registration. Once eligibility is verified, the NANT Operations Center will send an email confirming registration and dose level for treatment. This registration email **must** be received prior to starting any protocol therapy or the patient will be declared ineligible. The registration email will be sent to the treating facilities, Study Chair, Study Vice-Chair, and relevant committee members. The registration steps are summarized in Table 10 below.

Table 10: Summary of Registration Steps

Step	Process	Comment
1	Treatment slots are assigned based on reservation requests processed through the NANT Operations Center.	
2	Once notified by NANT Operations Center that a treatment slot has been assigned for a patient, site completes Subject Screen form in Medidata Rave.	
3	Site sends signed informed consent and all source documentation confirming eligibility to NANT Operations Center.	*Email: nantcrf@chla.usc.edu *If unable to email documents, fax is acceptable. FAX: (323) 361-1803
4	Site completes demographics and eligibility form in Medidata Rave in addition to required paper CRFs.	
5	NANT Operations Center verifies eligibility and assigns unique NANT registration and study subject number in Medidata Rave. NANT Operations Center assigns the dose level/cohort for treatment.	
6	NANT Operations Center sends an email confirming registration.	Confirmation sent to the treating facilities, Study Chair, Study Vice-Chair, and relevant committee members.
7	Patient can begin treatment as specified in the protocol	

A registration worksheet is available on the web site (www.NANT.org) in the data forms packet to assist institutions with registration requirements for this protocol. Please contact NANT Operations Center at the contact information below for questions on registration.

Contact Person: **Research Coordinator**
NANT Operations Center
Children's Hospital Los Angeles
4650 Sunset Blvd, MS #54
Los Angeles, CA 90027
Phone: (323) 361-5687
FAX: (323) 361-1803
nantcrf@chla.usc.edu

To allow non-English speaking patients to participate in this study, bilingual health services will be provided in the appropriate language when feasible.

Timing of Registration and Treatment Initiation:
Initiation of protocol therapy is required within 1 week of study enrollment.

3.1.2 Co-Enrollment on NANT 2004-05

Co-enrollment on NANT 2004-05 (NANT Neuroblastoma Biology Study) is required for all patients enrolling on this trial. Patients are strongly encouraged to submit bone marrow as well as blood prior to starting therapy on NANT 2015-02 and continue to submit with each disease evaluation.

IMPORTANT NOTE:
The eligibility criteria listed below are interpreted literally and cannot be waived.

3.2 Inclusion Criteria

3.2.1 Age

Patients must be ≥ 12 months of age at the time of enrollment on the study.

3.2.2 Diagnosis

Patients must have a diagnosis of neuroblastoma either by histologic verification of neuroblastoma and/or demonstration of tumor cells in the bone marrow with increased urinary catecholamines.

3.2.3 ALK Tumor Alterations

ALK testing will not be performed as part of this trial,but must be completed prior to registration. Patients are required to have an activating *ALK* aberration in their tumor detected by certified genetic assay (i.e. CLIA in the US). The report from this test is required to be submitted for eligibility.

Patients with at least one of the following genetic features in their tumor will be considered to have an activating *ALK* aberration:

a. An *ALK* activating mutation;
b. *ALK* amplification (> 10 signals of the ALK gene);
c. Presence of any ALK fusion protein that arises from a chromosomal translocation.

ALK expression by immunohistochemistry is NOT acceptable for eligibility.

3.2.4 Disease Risk Group

Patients must have high risk neuroblastoma according to COG risk classification at the time of study registration. Patients who were initially considered low or intermediate risk, but then reclassified as high risk are also eligible.

3.2.5 Response to Prior Therapy (using INRC definitions)
Patients must have at least ONE of the following:

3.2.5.1 Recurrent/progressive disease after the diagnosis of high risk neuroblastoma at any time prior to enrollment – regardless of response to frontline therapy. (Note that this excludes patients initially considered low or intermediate risk that progressed to high risk disease but have not progressed after the diagnosis of high risk neuroblastoma).

3.2.5.2 If no prior history of recurrent/progressive disease since the diagnosis of high risk neuroblastoma,

3.2.5.2.1 Refractory disease: A best overall response of no response/stable disease since diagnosis of high risk neuroblastoma AND after at least 4 courses of induction therapy.

3.2.5.2.2 Persistent disease: A best overall response of partial response since diagnosis of high risk neuroblastoma AND after at least 4 courses of induction therapy

3.2.6 Sites of Disease
Patients must have at least ONE of the following (lesions may have received prior radiation therapy as long as they meet the other criteria listed below) based on institutional assessment:

3.2.6.1 Bone Sites

1. MIBG avid tumors: patients must meet one of the following criteria:
    a. Patients with recurrent/progressive or refractory disease:
        i. Must have at least one MIBG avid bone site. A biopsy is not required regardless of number of MIBG avid sites.
    b. Patients with persistent disease:
        i. If a patient has 3 or more MIBG avid bone lesions, then no biopsy is required.
        ii. If a patient has only 1 or 2 MIBG avid bone lesion sites then biopsy confirmation of neuroblastoma and/or ganglioneuroblastoma in at least one MIBG avid site present at the time of enrollment is required. Bone lesions may be biopsied at any time point prior to enrollment.
2. For MIBG non-avid tumors, patients must have at least one FDG-PET avid site and meet the following criteria:
    a. Biopsy confirmation of neuroblastoma and/or ganglioneuroblastoma from a lesion at any time prior to enrollment of at least one FDG-PET avid site.

3.2.6.2 Bone Marrow
Any amount of tumor cells in the bone marrow (including neuroblasts, mature and maturing ganglion cells) done at the time of study enrollment based on routine morphology and/or immunohistochemistry in at least one sample from bilateral aspirates and biopsies.

3.2.6.3 Soft Tissue Sites
At least one soft tissue lesion that meets criteria for a TARGET lesion as defined by:

1. SIZE**:** Lesion can be accurately measured in at least one dimension with a longest diameter ≥ 10 mm, or for discrete lymph nodes ≥ 15mm on short axis. Lesions meeting size criteria will be considered measurable.
2. In addition to size, a lesion needs to meet ONE of the following criteria except for patients with parenchymal CNS lesions which will only need to meet size criteria:
    a. For MIBG avid tumors: lesion must be MIBG avid and meet one of the following criteria:
        i. For patients with recurrent/progressive or refractory disease:
            1. no biopsy is required
        ii. For patients with persistent disease:
            1. If a patient has 3 or more MIBG avid soft tissue lesions, then no biopsy is required.

2. If a patient has only 1 or 2 MIBG avid soft tissue lesion sites) then biopsy confirmation of neuroblastoma and/or ganglioneuroblastoma in at least one MIBG avid site present at the time of enrollment is required. Soft tissue lesions may be biopsied at any time point prior to enrollment.

b. For MIBG non-avid tumors patient must have at least one FDG avid site and meet the following criteria:

i. Biopsy confirmation of neuroblastoma and/or ganglioneuroblastoma from a lesion at any time prior to enrollment of at least one FDG-PET avid site.

3.2.6.4 At least one non-target soft tissue lesion that is not measurable, but had a biopsy positive for neuroblastoma and/or ganglioneuroblastoma at any time prior to enrollment or is MIBG avid.

3.2.7 Performance level

Patients must have a Lansky (≤ 16 years) or Karnofsky (> 16 years) score of ≥ 50 (Appendix I).

3.2.8 Prior Therapy

3.2.8.1 Patients must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to study registration.

3.2.8.2 Concomitant Therapy Restrictions

1. Patients must not be receiving any other anti-cancer agents or radiotherapy.
2. Patients must not be receiving chronic systemic corticosteroids at doses greater than physiologic dosing (inhaled corticosteroids acceptable).
3. CYP3A4 Inhibitors. The concurrent use of known strong CYP3A inhibitors (eg, atazanavir, boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, troleandomycin, voriconazole, grapefruit juice or grapefruit/grapefruit-related citrus fruits [e.g., Seville oranges, pomelos]) within 12 days prior to the first dose of lorlatinib is not permitted. The topical use of these medications (if applicable), such as 2% ketoconazole cream, is allowed. Consult the sponsor if in doubt whether a food or a drug falls into any of the above categories.
4. CYP34A Inducers. The concurrent use or anticipated need for drugs that are known strong CYP3A4 inducers (e.g., avasimibe, carbamazepine, phenobarbital, phenytoin, rifatutin, rifampin, St. John's Wort), including their administration within 12 days prior to the first lorlatinib dose is not permitted. Consult the sponsor if in doubt whether a food or a drug falls into any of the above categories.
5. CYP34A Substrates. The concurrent use of CYP3A substrates with narrow therapeutic indices (e.g., alfentanil, astemizole*, cisapride*, cyclosporine, dihydroergotamine, ergotamine, fentanyl including transdermal patch, pimozide, quinidine, sirolimus, tacrolimus, terfenadine* [*withdrawn from US market]) within 12 days prior to the first dose of lorlatinib is not permitted.

   P-gp Substrates. The concurrent use of drugs which are P-gp substrates with narrow therapeutic index, such as digoxin is not permitted at study entry. The use of these drugs during the study is not recommended and alternate medications should be considered.

3.2.8.3 Prior ALK inhibitor treatment

1. Patients must not have been previously treated with lorlatinib
2. Prior therapy with other ALK inhibitors is allowed.
3. Patients must not have received the therapies indicated below within the specified time period **prior to registration** on this study as follows:

Table 11. Prior Therapies List

Type of Therapy	Specified Time Period	Additional Comments
Myelosuppressive Chemotherapy	≤ 14 days	This includes cytotoxic agents given on a low dose metronomic regimen as well as retinoids.
Biologic Antineoplastic	≤ 7 days	
Monoclonal Antibodies	≤ 7 days or 3 half-lives whichever is longer, but no longer than 30 days (with recovery of any associated toxicities).	Please refer to table posted at www.nant.org for definition of half-lives for specific monoclonal antibodies.
Cellular Therapy (e.g. modified T cells, NK cells, dendritic cells, etc.)	≤ 21 days and with recovery of all associated toxicities	
Radiation		
Small port radiation	≤ 7 days	
Large field radiation therapy	≤ 12 weeks	i.e. total body irradiation, craniospinal, whole abdominal, total lung, > 50% marrow space
Other Substantial Bone Marrow Radiation	≤ 6 weeks	
^{131}I-MIBG therapy	≤ 6 weeks	
Hematopoietic Stem Cell Transplant		
Autologous Stem Cell Infusion Following Myeloablative Therapy	≤ 6 weeks	Patients who have received an autologous stem cell infusion to support non-myeloablative therapy (such as ^{131}I-MIBG) are eligible at any time as long as they meet the other criteria for eligibility.
Any other investigational agents (covered under another IND)	≤ 14 days	

3.2.9 Organ Function Requirements

3.2.9.1 Hematologic Function:

Patients must meet the following hematologic criteria for enrollment regardless of bone marrow disease involvement:

1. ANC ≥750/uL (no short-acting hematopoietic growth factors ≤ 7 days of blood draw documenting eligibility and no long-acting hematopoietic growth factors ≤ 14 days of blood draw documenting eligibility); and
2. Platelet count:
    i. Cohorts A1, A2, and B1 (with omission of chemotherapy): ≥ 50,000/µl, transfusion independent (no platelet transfusions or platelet growth factors ≤ 7 days of blood draw documenting eligibility).
    ii. Cohort B2 (with chemotherapy): ≥ 75,000/µl, transfusion independent (no platelet transfusions or platelet growth factors ≤ 7 days of blood draw documenting eligibility).

3.2.9.2 Renal Function

1. Patients must have adequate renal function defined as age-adjusted serum creatinine ≤1.5 ULN for age (see below):

Table 12. Serum Creatinine Criteria

Age	Maximum Allowable Serum Creatinine
≤ 5 years	0.8 mg/dL
> 5 and ≤ 10 years	1.0 mg/dL
>10 and ≤ 15 years	1.2 mg/dL
> 15 years	1.5 mg/dL

3.2.9.3 Liver Function

1. Total bilirubin ≤ 1.5 x ULN for age; and,
2. SGPT (ALT) ≤ 135 U/L (≤ 3x ULN). Note that for ALT, the upper limit of normal for all sites is defined as 45 U/L.

3.2.9.4 Pancreatic Function

1. Serum total amylase ≤ 1.5 xULN

2. Serum Lipase ≤ 1.5 xULN

3.2.9.5 Neuropsychological Function

Patients must exhibit ≤ grade 1 as defined by CTCAE v4 of the following nervous system disorders and psychiatric disorders listed below based on physician assessment:

a. Nervous System Disorders - Amnesia, Cognitive Disturbance, Concentration Impairment, Depressed level of consciousness, Memory impairment

b. Psychiatric Disorders - Agitation, Anxiety, Confusion, Delirium, Depression, Euphoria, Hallucinations, Mania, Personality change, Psychosis, Restlessness

3.2.9.6 Cardiac Function

1. Corrected QTc ≤ 480 msec
1. Patients with an EKG PR interval within the ULN for age (see Table 13 below adapted from *Park MK, Guntheroth WG:* How to Read Pediatric ECGs, ed 2. Chicago, Year Book Medical Publishers, 1987).

Table 13: PR Interval (ULN) Corresponding to Age	
Age (in years)	**PR Interval (in sec)**
1 – 2	≤ 0.15
3 – 7	≤ 0.17
8 – 11	≤ 0.18
12 – 15	≤ 0.19
≥16	≤ 0.20

3.2.9.7 Pulmonary Function

No evidence of dyspnea at rest, no exercise intolerance.

3.2.9.8 Reproductive Function

All post-menarchal females must have a negative serum or urine beta-HCG ≤ 7 days prior to registration. Male and female subjects of reproductive age and childbearing potential must agree to use two acceptable methods of birth control (i.e., intra-uterine device, diaphragm with spermicide, condom with spermicide, or abstinence) or to abstain from heterosexual intercourse for the duration of their participation in the study. If a hormonal method of contraception is unavoidable, then a condom must be used in combination with the hormonal method.

3.3 Exclusion Criteria

3.3.1 Pregnancy, breast feeding, or unwillingness to use effective contraception during the study will not be entered on this study due to risks of fetal and teratogenic adverse events.

3.3.2 Patients who, in the opinion of the investigator, may not be able to comply with the safety monitoring requirements of the study.

3.3.3 Patients with disease of any major organ system that would compromise their ability to withstand therapy.

3.3.4 Patients must not have received prior allogeneic stem cell transplant.

3.3.5 Patients who are on hemodialysis.

3.3.6 Patients with an active or uncontrolled infection. Patients on prolonged antifungal therapy are still eligible if they are culture negative, afebrile, and meet other organ function criteria.

3.3.7 Patients with known history of human immunodeficiency virus (HIV) infection, hepatitis B, or hepatitis C. Testing is not required in the absence of clinical findings or suspicion.

3.3.8 Patients with known history of acute or chronic severe psychiatric disorders.

3.3.9 Patients with current history of suicidal ideation, and history of suicide attempt in their lifetime.

3.3.10 Patient declines participation in NANT 2004-05. In limited situations an institution may be granted a waiver from biology study participation.

3.4 Regulatory

3.4.1 Informed Consent
The patient and/or the patient's legally authorized guardian must acknowledge in writing that consent to become a study subject has been obtained, in accordance with institutional policies approved by the US Department of Health and Human Services.

3.4.2 Protocol Approval
All institutional, FDA, and NCI requirements for human studies must be met.

4.0 TREATMENT PROGRAM

4.1 Treatment Overview

Drug doses should be adjusted based upon height and weight obtained ≤ 7 days prior to the start of each course. One course consists of 4 weeks of therapy (28 day course).

Patients who have not been previously treated with an ALK inhibitor ("ALKi naïve") and patients who have been previously treated with an ALK inhibitor (except for lorlatinib) are eligible for this study and all treatment cohorts. Please refer to the experimental design schema section of the protocol for revisions made to the treatment overview with the activation of Amendment 7.

Disease evaluation should be performed on week 4 of courses 2, 4, 6 and every 4th course subsequent to course 6 in addition to end of therapy. Patients with stable disease or who are having clinical benefit from lorlatinib in cohorts A1, A2 and B1 may continue receiving protocol therapy provided that the patient meets criteria for starting subsequent courses and does not meet any criteria for removal from protocol therapy or off-study criteria. Patients on cohort B2 may continue to receive protocol therapy for up to 24 courses with chemotherapy or may stop combination chemotherapy after 4 cycles and continue on single agent lorlatinib at the same dosing indefinitely provided the patient meets criteria for starting subsequent courses and does not meet criteria for removal from protocol therapy or off-study criteria.

4.1.1 Lorlatinib (PF-06463922)

Table 14a: Cohorts A1, A2, B1 Treatment Course

Week 1	Week 2	Week 3	Week 4*
Days 1 - 7	Days 8 - 14	Days 15 - 21	Days 22 - 28
Lorlatinib →			

*Disease Evaluation performed after Day 22 of Week 4 of Courses 2, 4, and 6 and every 4th course thereafter in addition to end of therapy.

If a patient vomits within 20 minutes of dose administration, the patient should be re-dosed. If the patient vomits after the second dose, the patient should not be re-dosed again. If a patient vomits more than 20 minutes from dose administration, the patient should not be re-dosed. Refer to Section 6.1 for drug administration guidelines. For patients who are unable to swallow the tablets whole, refer to the Investigational Product Manual for dispersed tablet compounding.

For the oral lorlatinib tablets, the dose should be rounded according to the calculation in Appendix III.

Table 14b: Cohort B2 Treatment Course									
Week 1							Week 2	Week 3	Week 4
Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Days 8-14	Days 15 -21	Days 22-28
Lorlatinib →									
CPM	CPM	CPM	CPM	CPM					
TOPO	TOPO	TOPO	TOPO	TOPO	MGF				

CPM: Cyclophosphamide TOPO: Topotecan
MGF: Myeloid growth factor

The following conventional chemotherapy treatments are for patients registered in cohort B2 only.

4.1.2 Cyclophosphamide

Cyclophosphamide 250mg/m^2/day will be administered as a 30 minute IV infusion on days 1-5 of each course.

Pre-hydration and post-hydration are to be provided according to institutional standards. Mesna may be delivered according to institutional standards but is not mandated nor routinely used for this cyclophosphamide dose.

4.1.3 Topotecan

Topotecan 0.75mg/m^2/day will be administered as a 30 minute IV infusion immediately following cyclophosphamide on days 1-5 of each course.

4.1.4 Myeloid Growth Factor

Filgrastim (5 mcg/kg/day) is to be given with each course beginning 24-48 hours following the completion of cyclophosphamide and topotecan and continued through post-nadir count recovery with an ANC > 2000/mm^3. Filgrastim must be discontinued at least 24 hours prior to the start of the next course of therapy.

Pegfilgrastim (100 mcg/kg; 6 mg maximum dose) may be substituted and is given one time at 24-48 hours from completion of cyclophosphamide and topotecan.

4.2 Dose Escalation Schedule

Cohort A1 of this study will identify a recommended phase 2 dose (RP2D) of lorlatinib as a single agent in pediatric patients ≥ 12 months and < 18 years of age. All toxicities observed during the first course of treatment (day 1 through day 28) and only neuropsychological toxicities observed in the second course of treatment will be assessed to define the maximum tolerated dose (MTD) and guide dose escalation. The lorlatinib dose will be escalated using the standard 3 + 3 phase 1 trial design (Section 10) per the following dose escalation schema (Table 15a-d).

NOTE: Patients ≥ 18 YOA or whose BSA is ≥ 1.73m^2 will be assigned to cohort A2 and receive the adult RP2D (100mg) when Cohort A1 is enrolling Dose levels 1-3. At Dose Level 3 (75 mg/m^2/day) of the dose escalation cohort A1 of the trial, patients < 18 YOA and whose BSA is between 1.43m^2 and 1.72m^2, will also be assigned to Cohort A2 and also receive the adult RP2D (100mg) and not be involved in the dose escalation portion of this trial. After activation of Amendment 4, patients on cohort A2 will receive lorlatinib at a starting dose of 150mg daily and will follow a 3+3 dose escalation design with dose levels defined in Table 15b. With activation of Amendment 7, the dose of lorlatinib at Dose Level 5 in Cohort A1 will not be capped for “large” patients who are < 18 years of age.

Following activation of Amendment 7, the B2 chemotherapy combination cohort will open to patients < 18 YOA at dose level 4B and enroll concurrently with cohort A1 dose level 5 and cohort A2 dose level 4A. Patients on B2 will receive lorlatinib at the starting dose of 95 mg/m^2/day with fixed dosing of topotecan and cyclophosphamide (Table 15c-d.). Lorlatinib should be taken at least 1 hour prior to chemotherapy. Once the RP2D is determined for adults on A2, then B2 will also open to patients ≥ 18 to ≤ 30 YOA at the RP2D with no dose escalation. Patients > 30 YOA will enroll on the A2 expansion cohort with single agent lorlatinib at the RP2D.

Table 15a: Lorlatinib Dose Escalation Schema for patients on Cohort A1

Dose Level	**Lorlatinib** mg/m^2/day orally
-1	30
1 (Starting Dose)	45
2	60
3	75
4	95
5	115

The starting dose of lorlatinib represents approximately 75% of the adult RP2D of 100mg once daily. Dose level 2 corresponds approximately to the adult RP2D (for a BSA of approximately 1.67m^2), Dose level 3 is approximately ~125% of the adult RP2D, Dose level 4 is approximately 160% of the adult RP2D, and Dose level 5 is approximately 190% of the adult RP2D.

Table 15b: Lorlatinib Dose Escalation Schema for patients on Cohort A2

Dose Level	**Lorlatinib** mg/day orally
Pre amendment 4 Dose Assignment	
Dose level 3a	100
Post amendment 4 Dose Assignment	
Dose level 4a	150

Table 15c. Lorlatinib Dose Escalation Schema for patients < 18 YOA on Cohort B2

Combination Dose Level	**Lorlatinib** mg/m^2/day orally (max dose)	**Topotecan** mg/m^2/day IV	**Cyclophosphamide** mg/m^2/day IV
3B	75 (100 mg max)	0.75	250
4B (Starting Dose)	95 (150 mg max)	0.75	250
5B	115 (200 mg max)	0.75	250

Table 15d. Lorlatinib Dose Schema for patients ≥ 18 YOA on Cohort B2			
Combination Dose Level	**Lorlatinib** mg/m^2/day orally (max dose)	**Topotecan** mg/m^2/day IV	**Cyclophosphamide** mg/m^2/day IV
-1 RP2D	-1 RP2D	0.75	250
RP2D (Starting Dose)	RP2D	0.75	250

The dose level will be assigned at the time of registration for patients enrolling on cohort A1, and post amendment 4 on cohort A2, and post amendment 7 on cohort B2.

- For patients enrolled after activation of Amendment 4 of dose escalation: No more than two patients can simultaneously be enrolled on Course 1 of therapy in each of Cohorts A1 and A2.
- Following Amendment 4 during dose escalation: due to concern about possible delayed neurocognitive toxicities, the DLT evaluation period has been extended to include both Course 1 and Course 2, with any DLT during Course 1 but only neurocognitive DLTs during Course 2 counting for dose escalation/de-escalation decisions.
- Following Amendment 7: For cohort B2 evaluation of DLTs will occur during Course 1, since single agent toxicity for all DLTs will be available and chemotherapy combination is not likely to exacerbate neurocognitive toxicity. In addition, standard 3+3 rules will be used for toxicity evaluation and a maximum of 3 patients simultaneously can be enrolled on dose level 4B and when escalated to dose level 5B.

4.3 Definition of Dose-Limiting Toxicity (DLT)

Toxicity will be graded using the CTCAE criteria, version 4. The CTCAE provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTCAE can be downloaded from the CTEP home page (**http://ctep.cancer.gov)**. Any dose-limiting toxicity should be reported immediately through the NANT Operations Center to the Study Chair.

4.3.1 Definition of Unevaluable for Dose Escalation

Refer to Section 10.1.1 for the definition of "evaluable for DLT".

4.3.2 Definition of Dose-Limiting Toxicity

DLT is defined as any of the following events that are possibly, probably or definitely attributable to protocol therapy. Refer to Table 16a for dose modifications.

Note: Although all such events will be recorded, only those DLT's occurring in the 1st course of therapy will be counted in the decisions to dose escalate, expand, or de-escalate – with one exception: for Cohorts A1, A2, and B1 (but not B2), neurocogntive DLT's in the 2nd course will be counted in the decisions to dose escalate, expand, or de-escalate. Patients on cohort B2 who no longer receive chemotherapy should follow DLT and dose modifications criteria as specified for lorlatinib monotherapy cohorts.

Non-Hematological DLT:

1. Any Grade 3 or Grade 4 non-hematological toxicity attributable to the lorlatinib will be considered a DLT **except** for the following toxicities:
    a. Grade 3 nausea and vomiting, anorexia or dehydration resolving to ≤ Grade 2 within 72 hours
    b. Grade 3 AST, ALT, or GGT liver enzyme elevations that return to levels that meet initial eligibility criteria ≤ 7 days. If grade 3 liver enzyme elevation occurs, the next dose of drug should be held and liver enzymes rechecked at least twice weekly of initial date of grade 3 abnormalities. **Note:** For the purposes of this study the ULN for ALT is defined as 45 U/L.

c. Grade 3 fever or infection
d. Grade 3 febrile neutropenia cohort B2. Note: For cohorts A1, A2, B1 febrile neutropenia is a DLT if attributable to lorlatinib monotherapy and if lorlatinib is withheld > 7 days due to toxicity
e. Grade 3 hypophosphatemia, hypokalemia, hypocalcemia or hypomagnesemia responsive to oral supplementation
f. Grade 3 high cholesterol or triglycerides if responsive (to ≤ Grade 2) with statin treatment (See Section 5.3 for statin therapy options)
g. Grade 3 weight gain
h. Grade 3 hyperglycemia if responsive (to ≤ Grade 2) with dietary modification*
i. Grade 3 or Grade 4 obesity

2. Any Grade 2 non-hematological toxicity that persists for > 7 days and is considered sufficiently medically significant or sufficiently intolerable by patients that it requires treatment interruption
3. Recurrence of grade 2 neuropsychological effects
4. Grade 2 radiologically confirmed pancreatitis
5. Recurrence of grade 2 first degree symptomatic heart block
6. Grade 1 second degree (Mobitz Type 1 or 2) asymptomatic heart block
7. Any non-hematological toxicity that results in delay in start of subsequent course by > 14 days
8. Any non-hematological toxicity that requires the patient to miss more than 25% of drug in a course will be considered a DLT

* Grade 3 glucose intolerance is still considered a DLT

Hematological DLT:
For A1, A2 and B1, and B2 (without chemotherapy) hematological dose-limiting toxicity is defined as:

1. Grade 4 thrombocytopenia or Grade 4 neutropenia > 7 day duration (see Table 16a for dose modifications)
2. Delay in the start of subsequent course by > 14 days due to ongoing thrombocytopenia or neutropenia, in the absence of bone marrow disease progression seen on clinically-indicated bone marrow biopsy (if performed)

For B2 (with chemotherapy), hematological dose-limiting toxicity is defined as:

1. Delay in the start of subsequent course by > 14 days due to ongoing thrombocytopenia or neutropenia, in the absence of bone marrow disease progression seen on clinically-indicated bone marrow biopsy after the first dose reduction of cyclophosphamide and topotecan (see Table 16a for dose modification).

Patients who experience dose-limiting neutropenia and/or thrombocytopenia will have these events reviewed by the SMC to discuss attribution (bone marrow disease [baseline and subsequent (if performed and clinically indicated] versus study drug). Patients with bone marrow disease progression will not be considered to have dose-limiting hematological toxicities.

4.3.3 Dose Modifications and Supportive Care for Toxicities Attributable to Protocol Treatment

Table 16a. Dose Modifications for Toxicities (possibly, probably, definitely) attributable to Lorlatinib (Cyclophosphamide, Topotecan for Cohort B2)

Event	Action
NEUROPSYCHOLOGICAL EFFECTS - See Section 3.2.9.5 for list of CNS Function requirements	
Grade 1	• Continue lorlatinib at same dose
Grade 2	• Withhold lorlatinib until recovery to Grade ≤ 1 and restart protocol therapy at same dose* • If toxicity reoccurs a second time, withhold drug until recovery to Grade ≤1, and restart protocol therapy at the next lower dose level* • If toxicity reoccurs a third time, discontinue drug permanently
Grade 3	• Withhold drug until recovery to Grade ≤ 1 and restart protocol therapy at the next lower dose level* • If toxicity reoccurs, discontinue drug permanently
Grade 4	• Discontinue drug permanently
*Repeat testing will be performed ≤ 7 days of withholding drug and then weekly to monitor for recovery to Grade ≤ 1 (See Section 7, Table 24 for neuropsychological testing by age). Patients < 3 years of age will only have repeat parental testing. Appropriate radiologic and laboratory monitoring should be pursued at the investigator's discretion to rule out acute non-related events.	
PANCREATITIS	
Grade 1	• NONE
Grade 2	• If elevated enzymes are observed in the absence of radiological findings of pancreatitis: continue at same dose level. Repeat lipase and amylase (pancreatic isoenzymes required) weekly until total serum amylase is within normal institutional limits • If radiologically confirmed pancreatitis: withhold drug. Repeat radiology and lipase, amylase weekly and if returned to baseline then resume treatment at the next lower dose level • If radiologically confirmed pancreatitis reoccurs, remove patient from protocol therapy
Grade 3 - 4	• Discontinue drug permanently
ELEVATED TOTAL CHOLESTEROL OR TRIGLYCERIDES - See table 17 for statin therapeutic recommendations	
Grade 1	• Continue lorlatinib at same dose • Consider introducing use of a statin or other lipid lowering agent as appropriate based on investigator's medical judgment
Grade 2	• Continue lorlatinib at same dose • If persistent, introduce the use of a statin or other lipid lowering agent as appropriate
Grade 3	• Continue lorlatinib at same dose • Introduce use of a statin or other lipid lowering agent as appropriate, or increase dose of ongoing statin/lipid lowering agent, or change to a new agent • Recheck chol/tgl once a week

Grade 4	• Withhold lorlatinib • Introduce use of a statin or other lipid lowering agent as appropriate, or increase dose of ongoing statin/lipid lowering agent, or change to a new agent • Recheck chol/tgl twice a week • When toxicity is Grade ≤ 3, reduce dose by one dose level. • If grade 4 toxicity reoccurs, withhold lorlatinib again and follow same supportive care guidelines above • When toxicity is Grade ≤ 3, reduce dose to the next lower dose level; if patient is already on dose -1 level, discontinue drug permanently
WEIGHT GAIN ASSOCIATED CO-MORBIDITIES	
Increased Hemoglobin A1C OR Grade 2 fasting hyperglycemia	• HbA1C level between 5.8 - 6.5 range is considered prediabetes • For levels > 5.7 refer to endocrinology consult for observation and monitoring of blood sugar levels as clinically indicated • Refer for Nutrition consult with recommendations for dietary modification • Lifestyle modification with increased exercise recommended
High Blood Pressure	• Assess triplicate (3x) blood pressure measurements if blood pressure >95% threshold for age, height and gender • If blood pressure measurements continue to exceed 95% threshold consider anti-hypertensive agents
PROLONGED QTC INTERVAL	
Grade 1	• Assess electrolytes and concomitant medications • Correct any electrolyte abnormalities • Continue lorlatinib at same dose level
Grade 2	• Assess electrolytes and concomitant medications • Correct any electrolyte abnormalities • Continue lorlatinib at same dose level
Grade 3	• Withhold lorlatinib. Repeat ECG daily until it returns to < 481 ms • Reduce dose by one dose level and resume protocol therapy • Repeat ECG 7 and 14 days after dose resumption • If grade 3 toxicity recurs, discontinue lorlatinib permanently
Grade 4	• Discontinue lorlatinib permanently

ELEVATED LIVER ENZYMES (ALT, AST, GGT)	
Grade 1 - 2	• NONE
Grade 3	Cohort A1, A2, B1 and B2 • Withhold lorlatinib until resolution of toxicity to ≤ Grade 1 (or baseline, whichever is higher) then resume at same dose if resolved ≤ 7 days. • Recheck liver enzymes at a minimum within 5 days of initial date of occurrence of Grade 3 abnormality • If not resolved in 7 days post dose hold, once resolved, lorlatinib will then be resumed at one dose level below assigned initial dose level. Continue cyclophosphamide and topotecan at the same dose (if applicable).
Grade 4	Cohort A1, A2, B1 and B2 • Withhold lorlatinib until resolution of toxicity to ≤ Grade 1 (or baseline, whichever is higher) • Recheck liver enzymes at a minimum within 5 days of initial date of occurrence of Grade 3 abnormality • Lorlatinib will then be resumed at one dose level below assigned initial dose level Continue cyclophosphamide and topotecan at the same dose (if applicable).
FEBRILE NEUTROPENIA	
Grade 1 - 2	• NONE
Grade 3 - 4	For Cohorts A1, A2, B1 • Withhold lorlatinib until resolution of toxicity to ≤ Grade 1 (or baseline, whichever is higher) • If lorlatinib is withheld > 7 days, lorlatinib will then be resumed at one dose level below assigned initial dose level. If toxicity resolves < 7 days from withholding lorlatinib, restart lorlatinib at the same dose level. For Cohort B2 (with chemotherapy) - Grade 3 is not a DLT. Continue as prescribed. Grade 4 is considered a DLT. • Withhold lorlatinib until resolution of toxicity to ≤ Grade 1 (or baseline, whichever is higher) • Continue lorlatinib at the same dose level. Reduce topotecan and cyclophosphamide doses by 25%. If toxicity reoccurs despite chemotherapy dose reduction, reduce lorlatinib by one dose level below the RP2D.

THROMBOCYTOPENIA OR NEUTROPENIA	
Grade 1 - 3	• NONE
Grade 4	Cohort A1, A2, B1 • Withhold lorlatinib until resolution of toxicity to ≤ Grade 1 (or baseline, whichever is higher). • Cohort A1/A2: Resume lorlatinib at one dose level below assigned initial dose level • Cohort B1: Resume lorlatinib at one dose level below the RP2D established in cohort A1 Cohort B2 (with chemotherapy): • Continue lorlatinib at the same dose level. If the patient experiences dose limiting neutropenia or thrombocytopenia (delay >14 days) reduce topotecan and cyclophosphamide doses by 25% in the next course. . Lorlatinib should be continued at the same dose past day 28, during the period of hematologic recovery.If toxicity reoccurs despite chemotherapy dose reduction, reduce lorlatinib by one dose level below the RP2D. For ALL COHORTS • Patients with bone marrow disease progression confirmed with clinically indicated bone marrow biopsy (if performed) will not be considered a DLT.
Any Grade	For Cohorts A1, A2, B1 • Delay in the start of subsequent course by > 14 days due to ongoing thrombocytopenia or neutropenia, in the absence of bone marrow disease progression seen on clinically-indicated bone marrow biopsy (if performed) should resume lorlatinib at one dose level below assigned initial dose level for patients on Cohort A1 and A2. For patients in cohort B1, lorlatinib will be resumed at one dose level below the RP2D established in cohort A1. • If a patient experiences a recurrent delay despite the dose reduction of lorlatinib due to ongoing thrombocytopenia and neutropenia, the patient must be removed from protocol therapy. For Cohort B2 (with chemotherapy) • Patients who experience a delay in the start of subsequent course > 14 days due to ongoing thrombocytopenia or neutropenia (as defined in section 4.3.2), in the absence of bone marrow disease progression seen on clinically-indicated bone marrow biopsy (if performed) should resume subsequent courses at the same lorlatinib dose level. Reduce topotecan and cyclophosphamide doses by 25%. Lorlatinib could be continued at the same dose past day 28, during the period of hematologic recovery as long as drug is still available for the course. • Patients with recurrent delay in the start of subsequent course by > 14 days due to ongoing thrombocytopenia or neutropenia despite the topotecan/cyclophosphamide dose reduction should have lorlatinib held until patient is able to meet criteria. At the start of the subsequent course, patient should have the lorlatinib dose reduced by one dose level. • If a patient experiences a recurrent delay despite the dose reduction of the cyclophosphamide/topotecan and lorlatinib due to ongoing thrombocytopenia and neutropenia, the patient must be removed from protocol therapy.

GENERAL DOSE MODIFICATIONS FOR ALL DLTS

For Cohorts A1, A2, B1 and B2

- Withhold lorlatinib until resolution of toxicity to ≤ Grade 1 (or baseline, whichever is higher)
- If the toxicity resolves to meet eligibility requirements or baseline ≤ 21 days of study drug interruption, patient may resume lorlatinib treatment at one dose level below assigned initial dose level. For patients in cohort B1, lorlatinib will be resumed at one dose level below the RP2D established in cohort A1. Patients in cohort B2 may resume lorlatinib at the next lower dose level and continue cyclophosphamide and topotecan at the same dose.
- Patients already receiving therapy at dose level -1 at the time of initial DLT will be removed from protocol therapy.
- Doses reduced for toxicity will not be re-escalated, even if there is minimal or no toxicity with the reduced dose.
- If toxicity does not resolve to meet initial eligibility criteria or baseline ≤ 21 days of drug discontinuation, the patient must be removed from protocol therapy.
- If the same toxicity reoccurs at the reduced dose level, patient must be removed from protocol therapy. For patients in cohort B2, if the attribution to lorlatinib is undetermined, cyclophosphamide and topotecan must be reduced to 75% and lorlatinib must be reduced to the next lower dose level. However, if the DLT reoccurs a third time, patient will be removed from protocol therapy.

Table 16b. Dose Modifications for Prolonged PR Interval

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
1st Degree Heart Block	**Asymptomatic** • **No dose hold or reduction needed**. • Assess concomitant medications. • Monitor closely by obtaining ECG within 72 hours, even if unscheduled. • Instruct patient to call if symptoms develop that may be related to heart block. • assess weekly until resolution	**Symptomatic** • **Withhold dose.** • Assess concomitant medications. • Monitor closely by obtaining ECG within 72 hours and re-assess symptoms and PR-interval. • Restart at same dose when symptoms resolve. • If symptoms reoccur, hold study drug, repeat ECG within 72 hours and when symptoms resolve, restart at reduced dose. • If symptoms reoccur a third time, remove patient from protocol therapy.	N/A	N/A	N/A
2nd Degree Heart Block Mobitz Type 1 or 2	**Asymptomatic** • **Withhold dose.** • Assess concomitant medications. • Monitor closely by obtaining ECG within 72 hours, even if unscheduled. • When subsequent ECG does not show 2nd degree heart block, restart at reduced dose.	**Symptomatic** • **Withhold dose**. • Refer for cardiac observation and monitoring and cardiology consult. • Assess concomitant medications • Monitor closely by obtaining ECG within 72 hours, even if unscheduled. • When symptoms resolve, restart at reduced dose.	**Symptomatic and incompletely controlled** • Remove from protocol therapy	**Life Threatening** • Remove from protocol therapy	**Death** N/A
Complete Heart Block	N/A	**Non-urgent intervention indicated** • Remove from protocol therapy. • Refer for cardiac observation and monitoring.	**Symptomatic and incompletely controlled** • Remove from protocol therapy	**Life Threatening** • Remove from protocol therapy	**Death** N/A

4.3.3.1 Hyperlipidemia Supportive Care - Lipid Lowering Therapy In the lorlatinib Phase 1/2 Study B7461001, hypercholesterolemia was the most common AE reported. Elevations in lipids usually begin in the first few courses and, if statins are not introduced, can rise to Grade 3 levels by the next treatment course. Therefore, the suggested management is to consider a statin for Grade 1 elevations in either cholesterol or triglycerides and to increase the statin dose if adequate control is not obtained, as outlined in the below Table 17.

Members of the statin class of agents are differentially sensitive to CYP3A4, and the following table may be used to facilitate management of elevated lipid levels. Of note, muscle toxicity (from myalgia to rhabdomyolysis) is a documented side effect of certain statin therapy. This risk is increased with concurrent use of medications that inhibit CYP3A4, especially when given with statins that are CYP3A4 substrates. In randomized controlled trials, the incidence of statin myopathy was ~1.5–5.0% (1). One study showed that the most hydrophilic statins were least likely to cause myalgia, whereas the most lipophilic ones were most likely to be associated with muscular adverse effects (2). Therefore, if myalgias occur in a patient being treated for hypercholesterolemia with a statin on

this trial, please review concurrent medications and laboratory testing and consider replacing the statin with a different statin that is less lipophilic and less of a CYP substrate (See Table 17.

Table 17: Statin Usage

STATIN	CYP3A	Lipophilicity	Potential Effect* of Lorlatinib on Statin AUC	Recommendation About Statin Selection and Dose**
Rosuvastatin (Crestor)	Not a substrate	No	No change expected	Recommended No dose change
Pravastatin (Pravachol)	Substrate	No	30-40% decrease in AUC	Consider increasing the pravastin dose
Pitavavastatin (Livalo)	Not a substrate	Yes	No change expected	No dose change
Fluvastatin (Lescol)	Substrate	No	~25 % decrease in AUC	No dose change
Atorvastatin (Lipitor)	Substrate	Yes	4 % decrease in AUC	Consider increasing the atorvastatin dose (e.g., 10 -->20 mg)
Simvastatin (Zocor)	SENSITIVE Substrate	Yes	50-80% decrease in AUC	Selection not recommended
Lovastatin (Mevacor, Altocor)	SENSITIVE Substrate	Yes	50-80% decrease in AUC	Selection not recommended

*Estimated based on the reported effect of strong and moderate CYP3A inducers on statins. AUC: area under the plasma concentration-time curve.
** Dose adjustment to be based on changes in cholesterol levels (e.g., worsening by 1 CTCAE grade level).

4.3.3.2 Peripheral Neuropathy Supportive Care

Treatment with vitamin B1 and vitamin B6 and medications for pain associated with peripheral neuropathy (e.g. gabapentin or pregabalin) may provide symptom relief in some cases of peripheral neuropathy.

4.3.3.3 Peripheral Edema Supportive Care

Compression stockings, leg elevations, and lifestyle modifications, such as increased exercise and limiting dietary salt, should initially be considered in patients with low grade edema before commencing with dose modifications. These conservative measures in combination with diuretics (usually furosemide) have shown to be effective in the management of edema in adult studies**.**

4.4 Treatment Duration and Criteria to Start Next Treatment Course

In the absence of disease progression or toxicity that necessitates drug discontinuation, patients may receive protocol therapy indefinitely unless they are on Cohort B2. Patients who are on Cohort B2 can receive up to 24 courses with chemotherapy or may stop combination chemotherapy after 4 cycles and continue on single agent Lorlatinib at the same dosing (or at the RP2D, when determined) indefinitely provided the patient meets criteria for starting subsequent courses and does not meet criteria for removal from protocol therapy or off-study criteria. Patients experiencing dose-limiting toxicity (DLT) may continue to receive therapy modified as described in Section 4.3.

Criteria to start treatment course 2 and all subsequent courses of therapy - patients must show no clinical or radiographic evidence of disease progression and must meet renal, hepatic, CNS and other organ function requirements listed in section 3.2.9.2 – 3.2.9.8 except for hematological and

QTc criteria listed below. NOTE: Cardiac evaluations should only be repeated per Required Observations, Table 23.

Patients must meet the following hematologic criteria for subsequent courses:

1. ANC: ≥750/uL
    a. For Cohort B2 with chemotherapy: Patients must be off myeloid growth factor for a minimum of 24 hrs.
2. Platelet count:
    a. For Cohorts A1, A2, B1 and B2 (with omission of chemotherapy): ≥ 50,000/µl, transfusion independent as defined by 5 days with no platelet transfusion
    b. For Cohort B2 (with chemotherapy): ≥ 75,000/µl, transfusion independent as defined by 5 days with no platelet transfusion
3. QTc Interval: ≤ 500 ms (Grade 2) (Applicable if an ECG required at end of course)

If criteria to begin subsequent course of therapy are not met for > 28 days, then patient will be removed from protocol therapy.

4.5 Concomitant Therapy

4.5.1 No other cancer chemotherapy or immunomodulating agents will be used.

4.5.2 Palliative radiotherapy is not allowed on study.

4.5.3 Appropriate antibiotics, blood products, anti-emetics, fluids, electrolytes and general supportive care are to be used as necessary (see Section 5.0).

4.5.4 Patients may not receive pharmacologic doses of corticosteroids above that needed for physiologic replacement EXCEPT as needed to manage allergic/infusion reactions or to prevent transfusion reactions. Inhaled corticosteroids are allowed.

4.5.5 The *in vitro* studies have demonstrated that CYP3A, and UGT1A4 are primarily involved in the metabolism of lorlatinib, with additional minor contributions from CYP2C19 and CYP2C8. Inhibition or induction of the above enzymes may result in potential alteration of lorlatinib systemic exposure.

Coadministration of 200 mg daily doses of itraconazole (a strong CYP3A4/5 inhibitor) with a single 100 mg of lorlatinib increased lorlatinib AUCinf by 42% and Cmax by 24%. Coadministration of 600 mg daily doses of rifampin (a strong CYP3A4/5 inducer) with a single 100 mg dose of lorlatinib decreased lorlatinib AUCinf by 85% and Cmax by 76%. Concomitant administration of lorlatinib and rifampin led to elevated AST and ALT levels in all subjects. Thus, use of strong CYP3A4/5 inducers with lorlatinib is contraindicated.

In the lorlatinib clinical DDI studies, at steady state, lorlatinib induced CYP3A and P-gp to moderate extent and CYP2B6 and CYP2C9 and UGT to a weak extent .

Thus, to protect patient safety, the following action should be exercised

1. Lorlatinib metabolism may be inhibited by strong CYP3A inhibitors leading to a potential increase in lorlatinib toxicities. Co-administration of strong CYP3A inhibitors (e.g., atazanavir, boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, troleandomycin, voriconazole, grapefruit juice or grapefruit/grapefruit-related citrus fruits [eg, Seville oranges, pomelos]) is not permitted at study entry and until the last lorlatinib dose. The use of these drugs during the study is not recommended and alternate medications should be

considered. If absolutely needed during the study, strong CYP3A inhibitors should be used with caution and patient closely monitored for safety.

2. Use of strong CYP3A inducers with lorlatinib is contraindicated. Lorlatinib metabolism may be induced when taking strong CYP3A inducers (e.g., carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's Wort) resulting in reduced plasma concentrations. Furthermore, when lorlatinib was coadministered with rifampin (Study B7461011), increases in AST and ALT were noted. Discontinue strong CYP3A inducers for 3 plasma half-lives of the strong CYP3A inducer prior to initiating lorlatinib and until study treatment discontinuation.
3. At steady state, lorlatinib induces CYP2C9 by a weak extent. Concurrent use of drugs that are CYP2C9 substrates with narrow therapeutic indices, such as warfarin, phenytoin or celecoxib, may have decreased effect. Thus, concomitant CYP2C9 substrates should be used with caution.
4. At steady state, lorlatinib induces CYP2B6 by a weak extent. Concurrent use of drugs that are CYP2B6 substrates, such as bupropion and efavirenz, may have less effect. Thus, concomittant CYP2B6 substrates should be used with caution.
5. Lorlatinib induces CYP3A which may lead to a decreased effect of concurrently used CYP3A substrates (eg. hormonal contraceptives etc.). Co-administration of lorlatinib with CYP3A substrates with a narrow therapeuric index (NTI) such as alfentanil, fentanyl (including transdermal patch), astemizole*, cisapride*, cyclosporine, dihydroergotamine, ergotamine, pimozide, quinidine, sirolimus, tacrolimus, terfenadine* (*withdrawn from US market) is not permitted at study entry and until 12 days after the last lorlatinib dose. However if it is absolutely necessary to use, sponsor approval is required and the dose of the CYP3A substrate may need to be increased. The NTI CYP3A substrate should be started only after at least 14 days of continuous lorlatinib dosing. If there is a change in the lorlatinib dosing regimen such as a dosing interruption or dose reduction, the administration of the NTI CYP3A substrate should be stopped and resumed at a readjusted dose only after at least 14 days of resumed lorlatinib dosing.
6. At steady state, lorlatinib induces P-gp by a moderate extent. Concurrent use of drugs which are P-gp substrates with a narrow therapeutic index may have decreased effect. The concurrent use of drugs which are P-gp substrates with narrow therapeutic index, such as digoxin is not permitted at study entry. The use of these drugs during the study is not recommended and alternate medications should be considered. If absolutely necessary to use during the study,it should be initiated following sponsor approval, and be used with caution.
7. The Sponsor can be contacted with questions regarding concomitant use of specific drugs.

4.5.6 Hormonal Contraception

Females of childbearing potential should be advised to avoid becoming pregnant while receiving lorlatinib. A highly effective nonhormonal method of contraception is required for female patients during treatment with lorlatinib because lorlatinib can render hormonal contraceptives ineffective. If a hormonal method of contraception is unavoidable, then a condom must be used in combination with the hormonal method. Effective contraception must be continued for at least 21 days after completing therapy. During treatment with lorlatinib and for at least 97 days after the final dose, male patients with female partners of reproductive potential must agree to use effective contraception, including a condom, and male patients with pregnant partners must agree to use condoms.

5.0 SUPPORTIVE CARE

5.1 Prophylaxis for Pneumocystis Jiroveci Pneumonia (PJP)

All patients should receive PJP prophylaxis according to institutional guidelines. Bactrim (sulfamethoxazole and trimethoprim) Trimethoprim is a substrate for CYP2C8/9 and CYP3A4. It also is a moderate inhibitor of CYP2C8/9. Lorlatinib is metabolized by CYP3A4/5, CYP2C8, CYP2C19 and UGT1A4. It is also an inhibitor and inducer of CYP3A4 with the net effect being induction. It also inhibits CYP2C9. And it induces CYP2B6.

Effect of lorlatinib on Bactrim: Because lorlatinib is an inhibitor of CYP2C9, it could increase trimethoprim concentrations. At the same time, lorlatinib also has a net induction effect on CYP3A4 which could decrease trimethoprim concentrations. The overall effect is hard to predict.

Effect of Bactrim on lorlatinib: since trimethoprim is an inhibitor of CYP2C9 it could increase lorlatinib concentrations.

Hence, overall the use of Bactrim is permitted but the site/investigator should do so with caution, being aware of the possibility of increased lorlatinib concentrations and difficulty to predict change in trimethoprim concentrations. Alternative PJP prophylaxis medications such as pentamidine are acceptable without caution.

5.2 Use of Myeloid Growth Factors

Myeloid growth factors are allowed on cohort B2, concomitant chemotherapy arm when chemotherapy is being administered. In all other cohorts, myeloid growth factors are only to be utilized in the setting of Grade 3 or 4 neutropenia together with documented invasive fungal infection, bacteremia, or fever with sepsis physiology. The study chair should be notified in the event of myeloid growth factor use. Patients who receive myeloid growth factor for Grade 3 neutropenia will not be evaluable for dose-limiting neutropenia in that course.

5.3 Antiemetic

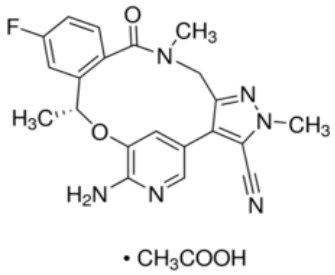
Lorlatinib is not anticipated to be emetogenic. For patients who develop nausea in any cohort, appropriate non-corticosteroid antiemetics should be utilized according to institutional guidelines.

5.4 For Supportive Care of Toxicities Attributable to Protocol Treatment, please see Section 4.3.3

6.0 DRUG INFORMATION

6.1 Lorlatinib (PF-06463922)

Structure and molecular weight:



Name: Lorlatinib (PF-06463922) acetic acid solvate.
PF-0643922 and lorlatinib can be used interchangeably

Molecular weight 466.46 Daltons (acetic acid solvate)

Table 18. Toxicities:
Information is based on observation of 476 patients with advanced ALK-positive or ROS1-positive non-small cell lung cancer who participated in study B7461001 (N=327) or Study B7461006 (N=149) and received lorlatinib 100 mg once daily orally.

The following side effects considered to be related to lorlatinib have been reported:

Very Common (may affect 10 or more in 100 people)	**Common** (may affect from 1 up to less than 10 in 100 people)
• Hypercholesterolemia • Hypertriglyceridemia • Mood effects • Cognitive effects • Peripheral neuropathy • Vision Disorder • Hypertension • Diarrhea • Constipation • Joint pain • Edema (especially peripheral) • Fatigue • Weight gain • Hyperglycemia	• Hallucination and loss of contact with reality • Mental status changes • Speech effects • Pneumonitis

The following events have also been reported in patients while they were taking lorlatinib, although there is not sufficient evidence that lorlatinib is related to them:

Very common (may affect 10 or more in 100 people)
- Liver enzyme elevation
- Pancreative enzyme elevation
- Anemia
- Headache
- Myalgia
- Sleep effects
- Rash

Common (may affect from 1 up to less than 10 in 100 people)
- Ejection fraction decreased
- Syncope
- Electrocardiogram changes (QT prologation)

Uncommon (may affect less than 1 in 100 people)
- Pancreatitis
- Suicidal ideation
- Psychosis

Formulation and Stability: Lorlatinib will be provided in bottles containing 5 mg or 25 mg tablets (as the acetic acid solvate). Each bottle will contain 32 tablets. The 5mg bottle has a blue label and tablets are round with a white to off-white color. The 25mg bottle has a yellow label and tablets are hexagonal in shape with a white to off-white color. The film coated tablets contain lactose.

Guidelines for Administration: See also Treatment and Dose Modification in Section 4.0. Lorlatinib will be provided in bottles containing 5 mg or 25 mg tablets. Each bottle will contain enough medication for 1 treatment course. The bottles will be labeled with different color labels to differentiate between dosage strengths. Site personnel must ensure that patients clearly understand the directions for self-medication. Patients will be provided with patient diaries to record daily lorlatinib administration. Patients must be instructed to record all doses including vomited or missed doses in the patient diaries. If doses are missed or vomited, this must be indicated in the source documents and CRFs. If a patient vomits within 20 minutes of dose administration, the patient should be re-dosed. If the patient vomits after the second dose, the patient should not be re-dosed again. If a patient vomits more than 20 minutes from dose administration, the patient should not be re-dosed and the next dose will occur at the next scheduled time.

Lorlatinib will be dispensed at the beginning of each treatment course once criteria to initiate a treatment course have been met (Section 4.4) and in the absence of evidence of clinical or radiographic disease progression. If a patient meets criteria for an extended course, a bottle may be dispensed prior to day one of the next course. Drug reconciliation needs to be completed after each bottle administered and after each course per protocol in circumstances where the patient may not return to the pharmacy. Patients should be instructed to keep their medication in the bottles provided and not transfer it to any other container. Patients should be instructed to take lorlatinib at approximately the same time each day and not to take more than the prescribed dose at any time. However, a variance of up to 12 hours is allowed for any given dose, rather than miss a day's dose. If a patient misses a daily dose, they must be instructed not to "make it up" the next day. If a patient inadvertently takes 1 extra dose during a day, the patient should not take the next dose of lorlatinib.

Whole Tablet Administration: Lorlatinib tablets should be taken with at least 8 oz. (240 mL) of water or enough water to fully swallow the tablet(s) if not able to take the full 8oz. Patients should be instructed to swallow the Lorlatinib tablets whole and not chew the tablet prior to swallowing. No Lorlatinib tablet should be ingested if it is broken, cracked or otherwise not intact.

Dispersed Tablet Compounding and Administration (see instructions): If the subject is unable to swallow the tablets whole, they may be dispersed in a suitable liquid and administered as an oral dispersion. Instructions are included in the Investigational Product Manual, which describes the procedures for dispersing PF-06463922 5 mg and 25 mg tablets to deliver doses ranging from 10 mg through 100 mg in oral dosing syringes. Changes to bioavailability between the whole and dispersed tablet are not expected. Patients/caregivers who will be administering the oral dispersion will have mandatory, supervised, hands-on training at all NANT sites prior to performing the process at home. Additionally, written instructions for preparation and administration of lorlatinib oral dispersion will be given to patients/caregivers to take home.

6.1.1 Drug Supply and Accountability

Lorlatinib will be supplied by Pfizer, Inc. Lorlatinib will be shipped to treating institutions through the contract pharmacy, Almac. Instructions and forms for ordering lorlatinib from Almac are posted to the NANT website.

Accountability for lorlatinib at the trial site is the responsibility of the investigator. The investigator will ensure that the study drug is used only in accordance with this protocol. Where allowed, the investigator may choose to assign some of the drug accountability responsibilities to a pharmacist or other appropriate individual. Drug accountability records indicating the drug's delivery date to the site, inventory at the site, use by each patient, and drug disposition/destruction will be maintained by the clinical site. These records will adequately document that the patients were provided the doses as specified in the protocol and should reconcile all study drug received from Almac Accountability records will include dates, quantities, batch/serial numbers, expiration dates (if applicable), and patient numbers. Upon confirmation that the last patient enrolled into the study has completed the treatment period, all unused, unopened, or expired lorlatinib should be maintained until notice from NANT Operations Center regarding destruction of drug or instructions regarding shipment to another facility. These events will be performed in accordance with site pharmacy SOPs. The site will maintain detailed records of the drug reconciliation and destruction with the study files. All material containing study drug will be treated as hazardous waste in accordance with governing regulations.

6.2 Topotecan (SKF-104864, Hycamtin®) NSC #609699 (06/03/13)

Source and Pharmacology:

Topotecan hydrochloride is a semi-synthetic derivative of camptothecin (an alkaloid derived from the camptothecin tree which grows widely throughout Asia) and is an anti-tumor drug with topoisomeraseI-inhibitory activity. Topoisomerase I relieves torsional strain in DNA by inducing reversible single strand breaks. Topotecan binds to the topoisomerase I-DNA complex and prevents re-ligation of these single strand breaks. The cytotoxicity of topotecan is thought to be due to double strand DNA damage produced during DNA synthesis, when replication enzymes interact with the ternary complex formed by topotecan, topoisomerase I, and DNA. Mammalian cells cannot efficiently repair these double strand breaks. Topotecan undergoes a reversible pH dependent hydrolysis of its lactone moiety; it is the lactone form that is pharmacologically active. At pH ≤ 4, the lactone is exclusively present, whereas the ring-opened hydroxy-acid form predominates at physiologic pH. In vitro studies in human liver microsomes indicate that metabolism of topotecan to an N-demethylated metabolite represents a minor metabolic pathway. Topotecan exhibits multi-exponential pharmacokinetics with a terminal half-life of 2 to 3 hours. Total exposure (AUC) is approximately dose-proportional. Binding of topotecan to plasma proteins is about 35%.

In humans, about 30% of the dose is excreted in the urine and renal clearance is an important determinant of topotecan elimination. In patients with mild renal impairment (Cl_{cr} of 40 to 60mL/min.), topotecan plasma clearance was decreased to about 67% of the value in patients with normal renal function. In patients with moderate renal impairment (Cl_{cr} of 20 to 39 mL/min.), topotecan plasma clearance was reduced to about 34% of the value in control patients, with an increase in half-life. Dosage adjustment is recommended for these patients. Plasma clearance in patients with hepatic impairment (serum bilirubin levels between 1.7 and 15.0 mg/dL) was decreased to about 67% of the value in patients without hepatic impairment. Topotecan half-life increased slightly, from 2 hours to 2.5 hours, but these hepatically impaired patients tolerated the usual recommended topotecan dosage regimen.

Table 19. Topotecan Toxicity

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, vomiting, diarrhea (L), constipation, fever, pain (abdominal, skeletal, back pain)	Anorexia, headache, asthenia, rash (urticaria, pruritis, bullous eruption) (L), asymptomatic hypotension, dyspnea	Anaphylaxis, angioedema, chest pain, rigors
Prompt: Within 2-3 weeks, prior to next course	Myelosuppression, fatigue, febrile neutropenia	Stomatitis/mucositis, increased SGOT (AST)/SGPT (ALT)/alkaline phosphatase, sepsis	Elevated bilirubin, paresthesias, myalgia, arthralgia, intratumoral bleeding
Delayed: Anytime later during therapy	Alopecia		Microscopic hematuria, increased creatinine, proteinuria
Unknown Frequency and Timing:	Teratogenic effects of topotecan have been noted in animal models at doses ≤ to those used in humans. It is not known if topotecan is excreted into human breast milk.		

Formulation and Stability: Topotecan is available as a lyophilized powder for reconstitution and as a solution concentrate. Each vial of lyophilized powder contains topotecan hydrochloride equivalent to 4 mg of topotecan as free base. Inactive ingredients are mannitol 48 mg, and tartaric acid 20 mg. Hydrochloric acid and sodium hydroxide may be used to adjust the pH. Topotecan concentrate solution for injection is supplied as a sterile, non-pyrogenic, clear, yellow to yellow-green solution at a topotecan free base concentration of 4 mg/4 mL (1 mg/mL) available in single use vials. Each mL of topotecan injection contains topotecan hydrochloride equivalent to 1 mg of topotecan as free base, 5 mg tartaric acid, NF and water for injection, USP. Hydrochloric acid and/or sodium hydroxide may be used for pH adjustment. The pH of the solution is approximately 2.6 to 3.2; both products must be further diluted prior to administration in a minimum of 50 mL of compatible fluid for infusion. Both types of vials should be protected from light in the original cartons and stored at controlled room temperature between 20° and 25°C (68° and 77°F).

Guidelines for Administration: See also Treatment and Dose Modification in Section 4.0. Reconstitute each topotecan 4 mg vial with 4 mL SWFI to concentration of 1 mg/mL. Further dilute in 50-250 mL D5W or NS. Reconstituted vials of topotecan diluted for infusion are stable at approximately 20°-25°C (68°-77°F) and ambient lighting conditions for 24 hours.

Supplier: Commercially available. See package insert for further information.

6.3 Cyclophosphamide (Cytoxan) NSC #26271 (03/13/13)

Source and Pharmacology: Cyclophosphamide is an alkylating agent related to nitrogen mustard. Cyclophosphamide is inactive until it is metabolized by P450 isoenzymes (CYP2B6, CYP2C9, and CYP3A4) in the liver to active compounds. The initial product is 4-hydroxycyclophosphamide (4-HC) which is in equilibrium with aldophosphamide which spontaneously releases acrolein to produce phosphoramide mustard. Phosphoramide mustard, which is an active bifunctional alkylating species, is 10 times more potent in vitro than is 4-HC and has been shown to produce interstrand DNA cross-link analogous to those produced by mechlorethamine. Approximately 70% of a dose of cyclophosphamide is excreted in the urine as the inactive carboxyphosphamide and 5-25% as unchanged drug. The plasma half-life ranges from 4.1 to 16 hours after IV administration.

Table 20. Cyclophosphamide Toxicity

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Anorexia, nausea & vomiting (acute and delayed)	Abdominal discomfort, diarrhea	Transient blurred vision, nasal stuffiness with rapid administration, arrhythmias (rapid infusion), skin rash, anaphylaxis, SIADH
Prompt: Within 2-3 weeks, prior to next course	Leukopenia, alopecia, immune suppression	Thrombocytopenia, anemia, hemorrhagic cystitis (L)	Cardiac toxicity with high dose (acute – CHF hemorrhagic myocarditis, myocardial necrosis) (L), hyperpigmentation, nail changes, impaired wound healing, infection secondary to immune suppression
Delayed: Anytime later during therapy	Gonadal dysfunction: azoospermia or oligospermia (prolonged or permanent)[1] (L)	Amenorrhea[1]	Gonadal dysfunction: ovarian failure[1] (L), interstitial pneumonitis, pulmonary fibrosis[2] (L)
Late: Any time after completion of treatment			Secondary malignancy (ALL, ANLL, AML), bladder carcinoma (long term use > 2 years), bladder fibrosis
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of cyclophosphamide (alone or in combination with other antineoplastic agents) have been noted in humans. Toxicities include: chromosomal abnormalities, multiple anomalies, pancytopenia, and low birth weight. Cyclophosphamide is excreted into breast milk. Cyclophosphamide is contraindicated during breast feeding because of reported cases of neutropenia in breast fed infants and the potential for serious adverse effects.		

[1]Dependent on dose, age, gender, and degree of pubertal development at time of treatment
[2]Risk increased with pulmonary chest irradiation and higher doses. (L) Toxicity may also occur later.

Formulation and Stability: Cyclophosphamide for injection is available as powder for injection or lyophilized powder for injection in 500 mg, 1 g, and 2 g vials. The powder for injection contains 82 mg sodium bicarbonate/100 mg cyclophosphamide and the lyophilized powder for injection contains 75 mg mannitol/100 mg cyclophosphamide. Storage at or below 25°C (77°F) is recommended. The product will withstand brief exposures to temperatures up to 30°C (86°F).

Guidelines for Administration: See Treatment and Dose Modifications sections of the protocol. Cyclophosphamide for Injection: If the drug will be administered as undiluted drug at the 20 mg/mL concentration, then reconstitute to 20 mg/mL with NS ONLY to avoid a hypotonic solution. If the drug will be further diluted prior to administration, then first reconstitute with NS, SWFI, or Bacteriostatic Water for Injection (paraben preserved only) to a concentration of 20 mg/mL. Following reconstitution, cyclophosphamide may be further diluted in dextrose or saline containing solutions for IV use.

Supplier: Commercially available from various manufacturers. See package insert for further information

6.4 Neulasta (PEG-FILGRASTIM)

Source and Pharmacology:
Pegfilgrastim is the pegylated form of recombinant methionyl human G-CSF (filgrastim). Pegfilgrastim is produced by covalently binding a 20-kilodalton (kD) monomethoxypolyethylene glycol molecule to the N-terminal methionyl residue of filgrastim. The molecular weight of peg-filgrastim is 39 kD. G-CSF is a lineage specific colony-stimulating factor which regulates the production of neutrophils within the bone marrow and affects neutrophil progenitor proliferation, differentiation, and selected end-cell functional activation (including enhanced phagocytic ability, priming of the cellular metabolism associated with respiratory burst, antibody dependent killing, and the increased expression of some functions associated with cell surface antigens). After subcutaneous injection the elimination half-life of peg-filgrastim ranges from 15 to 80 hours and the time to peak concentration ranges from 24 to 72 hours. Serum levels are sustained in most patients during the neutropenic period post chemotherapy, and begin to decline after the start of neutrophil recovery, consistent with neutrophil-dependent elimination. After subcutaneous administration at 100 mcg/kg in 37 pediatric patients with sarcoma, the terminal elimination half-life was 30.1 (+/- 38.2) hours in patients 0 to 5 years-old, 20.2 (+/- 11.3) hours in patients 6 to 11 years-old, and 21.2 (+/- 16) hours in children 12 to 21 years-old.

Unknown frequency and timing:
Fetal toxicities and teratogenic effects of peg-filgrastim in humans are unknown. Conflicting data exist in animal studies. It is unknown whether the drug is excreted in breast milk.

Supplier: Commercially available. See package insert for further information.

Formulation and Stability:
Supplied as a preservative-free solution containing 6 mg (0.6 mL) of peg-filgrastim (10 mg/mL) in a
single-dose syringe with 27 g, ½ inch needle with an UltraSafe® Needle Guard. The needle cover of the prefilled syringe contains drug natural rubber (a derivative of latex). Store refrigerated at 2 º-8ºC (36º-46ºF) and in the carton to protect from light. Prior to injection, peg-filgrastim may be allowed to reach room temperature protected from light for a maximum of 48 hours. Avoid freezing.

Guidelines for Administration:
See Treatment and Dose Modifications sections of the protocol. Pegfilgrastim should not be administered in the period between 2 weeks before and 24 hours after chemotherapy. Do not shake. The manufacturer does not recommend use of the 6-milligram (mg) fixed-dose formulation of pegfilgrastim in infants, children, or adolescents under 45 kilograms.

Table 21: PEG-Filgrastim Neulasta Toxicity:

Likely (happens to 21-100 children out every 100 children)	**Less Likely** (happens to 5-20 children out every 100 children)	**Rare** (happens to < 5 children out every 100 children)
• Mild to moderate medullary bone pain	• Local pain or irritation at injection site • Headache • Increased alkaline phosphatase, lactate dehydrogenase and uric acid. • Thrombocytopenia	• Low grade fever, • Allergic reactions (anaphylaxis, angioedema, or urticaria), generalized erythema and flushing • Splenomegaly, splenic rupture, sickle cell crises in patients with sickle cell disease (SCD) • Excessive leukocytosis, Sweet's syndrome (acute febrile neutrophilic dermatosis) • Adult respiratory distress syndrome

6.5 GRANULOCYTE COLONY STIMULATING FACTOR (G-CSF) (Filgrastim, Neupogen)

Source and Pharmacology:
Filgrastim is a human granulocyte colony-stimulating factor (G-CSF), produced by recombinant DNA technology. Filgrastim is a 175 amino acid protein with a molecular weight of 18,800 daltons manufactured by recombinant DNA technology utilizing E.coli bacteria into which has been inserted the human granulocyte colony stimulating factor gene. It differs from the natural specific colony-stimulating factor which regulates the production of neutrophils within the bone marrow and affects neutrophil progenitor proliferation, differentiation, and selected end-cell functional activation (including enhanced phagocytic ability, priming of the cellular metabolism associated with respiratory burst, antibody dependent killing, and the increased expression of some functions associated with cell surface antigens). The elimination half-life is similar for subcutaneous and intravenous administration, approximately 3.5 hours. The time to peak concentration when administered subcutaneously is 2 to 8 hours.

Formulation and Stability:
Supplied as a clear solution in 300 ug/ml (1 ± 0.6 x 108 U/mg) (1 ml or 1.6 ml) vials. Vials are preservative free and are intended to be single-use vials; do not reuse opened vials. Filgrastim must be stored between 2° and 8°C. Stability has been demonstrated for at least 24 months when stored under these conditions. Do not use if discolored or if there is particulate matter. For IV use, dilute in D5W to concentrations > 15 ug/ml; G-CSF is incompatible with normal saline. At dilutions from *5* ug/ml to 14 ug/ml, add human serum albumin to a final albumin concentration of 2 mg/ml to protect against absorption of the GCSF to container walls (glass or plastic). Filgrastim, when diluted as described above, is compatible with a number of plastics commonly used in the manufacture of syringes, IV bags, infusion sets, and IV pump cassettes. These include polyvinyl chloride, polyolefin, and polypropylene. Diluted Filgrastim should be stored at 2° to 8° C and used within 24 hours. **Do not shake or freeze.**

Supplier: Commercially available. See package insert for further information.

Guidelines for Administration: See Treatment, Dose modifications and Supportive Care sections of the protocol. Administer once daily, subcutaneously without dilution or if necessary dilute with 5% dextrose in water, preferably to concentrations of 15 ug/ml or greater for IV administration. Dilutions should be prepared as close to the time of administration as possible (up to 24 hours), since the product is preservative-free. When diluting Filgrastim to *5*-14 ug/ml in D5W, it is necessary at all times to add human serum albumin, to reach a final albumin concentration of 2 mg/ml.

Table 22: Granulocyte colongy Simulating Factor (G-CSF) (Filgrastim, Neupogen) Toxicty

Likely (happens to 21-100 children out every 100	**Less Likely** (happens to 5-20 children out every 100	**Rare** (happens to < 5 children out every 100 children)
• Mild to moderate medullary bone pain	• Local pain or irritation at injection site • Increased alkaline phosphatase, LDH and uric acid • Thrombocytopenia • Fever	• Allergic reactions (more common with IV than subcutaneous administration) • Skin rash, urticaria and/or facial edema • Respiratory wheezing and/or dyspnea • Hypotension and/or tachycardia • Low grade fever • Splenomegaly • Splenic rupture • Worsening of existing skin rashes • Sickle cell crises in patients with Sickle cell disease • Excessive leukocytosis • Cutaneous vasculitis • Adult respiratory distress syndrome • MDS or AML (in patients with severe chronic neutropenia and long term administration

7.0 REQUIRED OBSERVATIONS/MATERIAL AND DATA TO BE ACCESSIONED

7.1 Clinical and Laboratory Assessments

All laboratory tests, physical exam including a neurological exam must be performed ≤ 14 days prior to study registration, except for β-HCG pregnancy test (if applicable) which must be done within 7 days of study registration. Baseline tumor disease evaluation (including appropriate imaging studies, bilateral bone marrow aspirate and biopsy for standard histology and urine catecholamines), EKG are required within 4 weeks prior to study registration and subsequent to any prior therapy. All patients regardless of marrow disease status at study registration are REQUIRED to have repeat bone marrow evaluations at each subsequent disease evaluation. Initiation of protocol therapy is required within 1 week of study registration. Neuropsychological evaluations and testing are part of the required observations; please see section 7.1.2.2 for details. Baseline neuropsychological testing for patients' ≥ 3 years of age is to be performed after study registration and no later than day 1 of protocol treatment. For patients' < 3 years of age, a neuropsychological evaluation performed by a licensed psychologist is to be performed after study registration and no later than the end of the second week of therapy (Course 1 Day 14).

OBTAIN OTHER ASSESSMENTS AS NEEDED FOR GOOD PATIENT CARE.

Table 23. Required Observations

Observation	Baseline	Course 1	Course 2	Courses 3+	End of Therapy
Physical Exam* (Ht, Wt, BSA, VS) + Neurological Exam[1] *Performance status required only at entry	X	Weekly	Start of course	Start of each course	X
CBC, Diff, Platelets[1]	X	A1, A2, B1: Weekly B2: Twice weekly	A1, A2, B1: Start of course B2: Weekly	Start of each course for A1, A2, B1 Weekly for B2	X
AST, ALT, Alk Phos, Total + Direct Bilirubin, Albumin, Electrolytes, Calcium, Magnesium, Phosphorus, BUN, Serum Creatinine[1]	X	Weekly	Start of course and once again in Week 2 or 3	Start of each course	X
Serum Amylase and Lipase[1]	X	Weekly	Start of course	Start of each course	X
HDL, LDL, total cholesterol and triglycerides, glucose (Fasting preferred) [1]	X	Every other week	Start of course	Start of each course	X
Hemoglobin A1C (HbA1c)	X		End of course	With Disease Evaluations in Courses 4 and 6 and after every 4 Courses thereafter	X
Serum or urine β-HCG[1,2]	X		Start of course	Start of each course	
EKG (12-lead)[3]	X	1 hour post day 1 dose	End of course	With Disease Evaluations in Courses 4 and 6 and after every 4 Courses thereafter	X

Observation	Baseline	Course 1	Course 2	Courses 3+	End of Therapy
Plasma pharmacokinetic samples[3] (required for all patients)		X See Section 8.1			
Neuropsychological assessments[5]	X	End of course	End of course	With Disease Evaluations in Courses 4 and 6 and after every 4 Courses thereafter	X
Bayley-III neuropsychological assessment for patients < 3 years of age only[5]	X		End of course	End of course 6, 10 and then every 8 courses thereafter	
Collect, Review and Submit Patient Diaries		X	X	X	X
Tests Obtained During Disease Evaluation Time Points					
Bilateral BM Aspirate + Biopsy for morphology[6]	X		X	With Disease Evaluations in Courses 4 and 6 and after every 4 Courses thereafter	X
Anatomic imaging (CT or MRI scan) of chest/abdomen/pelvis plus any other known sites of measurable disease [4, 6]	X		X		X
MIBG diagnostic scan[4, 6] (Use same isotope with each scan)	X		X		X
Blood and Bone Marrow for N04-05	X		With Disease Evaluation[6]		X
Blood for circulating tumor DNA (ctDNA) profiling[7] (optional)	X		With Disease Evaluation[6]		X
Archival tumor tissue submission (optional)		X See Section 8.3			
Bone Marrow aspiration for Optional Correlative Study	X		With Disease Evaluation[6]	With Disease Evaluations in Courses 4 and 6 and after every 4 Courses thereafter	

1. Physical exams and laboratory assessments timed for the start of a course may be obtained within 96 hours prior to day 1 of each subsequent course of protocol therapy. For cholesterol and triglycerides, 8 hour fasting level preferred; if non-fasting and elevated needs to be repeated in fasted state preferrably within 72 hours.
2. Obtain for females 10 years of age and older or post-pubertal.
3. EKGs should be performed ≤ 4 weeks prior to study enrollment, Day 1 1 hour post-dose, and on day 22 – day 28 of course 2, 4, 6 and every 4th course thereafter and at the end of treatment. When EKG and PK sample collection coincide, the PK will take priority so that it is collected at nominal time point and the EKG can be collected after the PK is collected.
4. Tumor imaging = CT and/or MRI (Chest abdomen pelvis) plus CT/MRI Imaging of any other sites with MIBG uptake for optimum visualization of all areas of bulk tumor (primary & metastasis). If patient has a history of tumor lesions in the skull, orbits or brain, OR if MIBG scan shows uptake in these same areas, then a CT or MRI of the brain/orbits is strongly suggested. For patients with epidural or hepatic tumor lesions, MRI is the recommended imaging technique. ^{123}I-MIBG scans are preferred. Omit for

patients known to be MIBG non-avid and replace with ^{18}FDG-PET (preferred) or bone scan. FDG-PET is required if used at baseline to document evaluable tumor lesion(s) for response. All patients are required have a diagnostic bone marrow sent with each disease evaluation.

5. For patients < 3 years old, a neuropsychological evaluation (Bayley-III testing) will be performed by a licensed psychologist after study registration but no later than the end of the second week of therapy (day 14 of course). Bayley-III will only be done at baseline, end of course 2, 6, 10 and then every 8 courses thereafter for duration of treatment (+/- 5 days). However, parent questionnaires for patients < 3 years of age will be done at the same time points as for patients' ≥ 3 years of age. More frequent neuropsychological monitoring may be needed if results identify risk of cognitive or behavioral decline (see Section 4.3, Table 16a and section 7.1.2.3 for assessment schedule details). Final testing will occur at end of treatment with the exception of Bayley-III.
6. All disease status tests must be performed ≤ 4 weeks prior to study enrollment and on week 4 (day 22-28) of courses 2, 4, and 6, and after every 4 courses thereafter (i.e. day 22-28 of course 10, 14, etc.). Any course can be delayed by up to 4 days due to scheduling conflict or delays only if the prescribed bottles for that given course have sufficient tablets (32 tablets/bottle) to allow for course extension.
7. Blood Specimens for Circulating Nucleic Acid (CNA) Profiling: blood specimen optimized for plasma preparation for nucleic acid analysis (e.g., circulating tumor DNA (ctDNA) or RNA (cfRNA)) will be collected at baseline and at every disease evaluation time point as well as end of therapy.

7.1.2. Neurologic assessments

The information below is provided to augment and help grading of CTCAE criteria.

7.1.2.1 Neurologic Examination

A gross neurological exam will be performed by the oncologist prior to each course.

7.1.2.2 Assessment of Neuropsychological Functioning

Research investigating adult response to lorlatinib revealed dose limiting toxicity secondary to CNS effects. Specifically, mild to moderate cognitive symptoms including changes in speech, memory, and mood were observed. Such treatment related adverse events were noted to be generally intermittent and managed with dose hold or reduction. Therefore, it will be important to closely monitor neuropsychological functioning in children and young adults treated with this agent.

Neuropsychological functioning will be routinely assessed via computerized and questionnaire screening instruments in order to measure potential changes in cognition, behavior, and mood associated with lorlatinib administration. Given the broad age range of patients enrolled on the study, effort was made to select measures that could assess the widest age range possible. As no single measure exists that covers infancy through adult years, separate test batteries were needed for children less than three years of age and those age three years and older. Adjustments were also made as necessary between certain age brackets based upon specifications of the measures. Batteries are comparable in domains assessed such that some analyses will be possible across batteries. Additionally, given the frequency in which neuropsychological monitoring must be conducted, measures were strategically selected so to minimize sensitivity to practice effects that can result from serial evaluation. The patient's country of origin and primary language will be determined at the time of registration. Only measures with established language translations may be administered (See Appendix IV). Institutions will contact central site for specific test battery for non-United States English speaking patients. Any tests that do not have normative data from the patient's country of origin will not be interpreted for clinical purposes. If neuropsychological questionnaires are not available in patient's primary language, neuropsychological toxicity assessment will be based on the treating physician's assessment.

Neuropsychological Monitoring: Computerized measures (using iPads provided to sites by CogState) will be administered to patients at the time-points described in the Required Observations Table (Section 7.1) and Section 7.1.2.3 below. The computerized measure, Cogstate Research Battery, will be administered by qualified site personnel and will take approximately 10-30 minutes to complete depending upon age of the patient. The CogState battery administered prior to course 1 will be performed twice to eliminate practice effects and then administered only once in subsequent courses. This measure is developed and validated by Cogstate. The specific age-based battery of test items (at time of testing) and descriptions are listed below, Table 24 and Section 7.1.2.4. Behavioral ratings questionnaires assessing health-related quality of life and

social, emotional, and behavioral functioning will also be completed by patients 18 years and older or by the parents of patients under 18 years of age.

All neuropsychological monitoring measures will be interpreted by a pediatric neuropsychologist with extensive training in neuropsychological evaluation with medical populations. A baseline report will be provided to families if deficits or concerns are identified within 1 week of evaluation. Subsequent feedback will be provided only if a reportable event occurs and will be communicated to the family by the medical team in the context of their overall discussion of response to treatment and clinical decision making. All study coordinators will have received specialized training in administration of pediatric measures and are familiar with limitations associated with children, adolescents, and young adults presenting with medical complications.

Neuropsychological Evaluation for Children < 3 Years of Age: Given limited availability of performance based measures for young children, a more comprehensive evaluation of global functioning will be conducted periodically for children less than 3 years of age (See Section 7.1.2.3 for schedule). It is likely that medical management and health status of the patient will in part guide feasibility and timing of assessments as it is important that patients are well enough to participate so as to ensure valid neuropsychological data. Neuropsychological function of children less than three years of age will be measured using a single comprehensive battery, the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III; Section 7.1.2.4). Administration time is approximately 60-90 minutes. The Bayley-III must be administered and interpreted by a licensed psychologist. Institutions are encouraged to provide interpretive feedback to the patient and family, particularly if there is an issue of clinical concern.

7.1.2.3 Neuropsychological Assessment Schedule and Reporting

Neuropsychological monitoring for patients ≥ 3 years of age will be conducted at baseline, as defined by after study registration and no later than day 1 of course 1. Serial monitoring will be conducted on day 22-25 of course 1, course 2, 4, 6 and every 4th course thereafter. Final screening will occur at end of treatment. Monitoring will coincide with disease evaluations and be in accordance with this standard required observation schedule unless toxicities observed require more frequent monitoring as detailed below. Cogstate will be administered twice in succession at baseline to allow for familiarization with the tasks and to eliminate practice effects. The second administration at baseline is recorded as true baseline performance data. Cogstate will be administered only once during all subsequent screening time points. Behavioral measures are completed once at all time points.

Central review of testing measures, including Cogstate testing and behavioral questionnaires, will be completed with notification of results within 72 hours (between days 26-28) via a neuropsychological status report (Appendix V). Reliable Change Index (RCI) scores will be generated for individual tests or scales for each visit to determine whether a clinically meaningful change in performance occurred relative to baseline or previous evaluations. The status report will indicate absence, risk, or presence of clinically significant decline. Risk for possible decline and modification of retest interval for neuropsychological monitoring will be determined utilizing a 25% impairment classification model in an effort to reduce the potential for type 1 error. Stated otherwise, increased screening to day 22-25 of every course is warranted when there exists evidence of significant change in performance in 25% of select administered measures. Meaningful change in performance is considered to occur when clinically significant decline is present in 50% of select administered measures. In such occurrences, the status report will note significant decline and corresponding severity grading criteria for consideration by the medical team as per study protocol. Plan for retest interval will be determined based upon decision by the medical team regarding dosing and in accordance with Section 4.3, Table 16a.

Psychosis, as defined by confused thinking and altered sense of reality, has been reported as an adverse response in association with higher doses of lorlatinib administration. Neuropsychological evaluation within the context of this study cannot adequately assess for, screen, or address symptoms of psychosis. Given the necessary constraints of the technician administered, broad-

based brief serial cognitive and behavioral assessment system utilized for the current study, screening of certain nervous system and psychiatric disorders will continue to be deferred to the medical team as part of the in person gross neurological exam. Special attention via qualitative review of behavioral rating measures will be given to item responses within the current neuropsychological screening and monitoring battery that suggest endorsement of potential atypical behaviors and, if present, will be included in the narrative of the neuropsychological status report for review by the medical team to further augment and help grading of CTCAE criteria by medical providers.

Neuropsychological monitoring for patients < 3 years of age will also be conducted at baseline, as defined by after study registration but prior to Day 1 lorlatinib administration. Specifically, parent questionnaires for patients < 3 years of age will be completed according to the same observation schedule as for patients' ≥ 3 years of age (baseline and day 22-25 of course 1, 2, 4, 6, and every 4th course thereafter). Given the more lengthy administration time and required access to personnel with speciality professional licensure, the Bayley-III testing may be completed no later than the end of the second week of therapy (day 14 of course). Repeat Bayley-III evaluation will occur at end of course 2, course 6, 10 and every 8 courses thereafter (±5 days) for the duration of protocol therapy. Institutions will not be required to conduct more comprehensive neuropsychological evaluations for individuals over 3 years of age; however, referral for more in-depth evaluation of cognitive skills is encouraged, particularly if there is an issue of clinical concern.

Table 24. Serial Neuropsychological Monitoring

Serial Neuropsychological Monitoring						
	Child's Age (Years: Months)					
Test	<2:0	2:0-2:11	3:0-5:11	6:0-9:11	10:0-17:11	≥18:0
Cognitive Measures						
Global Cognitive Function and Development						
Bayley-III	X	X				
Detection *(3 min)*			X	X	X	X
Identification *(3 min)*			X	X	X	X
One Card Learning *(6 min)*				X	X	X
One Back *(4 min)*				X	X	X
Groton Maze Learning Test *(7 min)*				X	X	X
International Shopping List *(10 min)*					X	X
Behavioral Measures						
Behavioral/Social/Emotional Function						
ABAS-3 *(15 min)* [c]	X	X	X	X	X	X[a]
BASC-3 *(15 min)*[d]		X	X	X	X	X[a]
BRIEF *(10 min)*[e]		X	X	X	X	X[a]
PedsQL - Generic Version *(5 min)*[f]		X	X	X	X	X[a]
PedsQL - Multidimensional Fatigue *(5 min)*[f]		X	X	X	X	X[a]
PedsQL – Infant Scales *(5 min)*	X					
Beck Depression Inventory-II (5 min)						X
Columbia Suicide Severity Rating Scale				X[b]	X[b]	X[b]

[a] Patients ≥ 18 years of age will complete a self-report form. No parent report will be used for patients ≥18 years.
[b] Patients < 7 years of age do not complete. Patients 7-11 years of age will be provided with the C-SSRS Children's Baseline and Since Last Visit Versions. Patients >12 years of age will be provided with the C-SSRS Baseline and Since Last Visit Versions.
[c] Version depending on age in years: ABAS-3 Parent/Caregiver Form Ages 0-5=0-5:11, Parent Form=6:0-17:11, Adult Self-Report Form= ≥18
[d] Version depending on age in years: BASC PRS-P =2:0-5:11, PRS-C = 6:0-11.11, PRS-A = 12:0-17:11, SRP-College = 18-25.

[e] Version depending on age in years: BRIEF-P=2-5:11, BRIEF=6-17:11, BRIEF-A= ≥18
[f] Version depending on age in years: PedsQL Parent Report for Toddlers=2-4, Parent Report for Young Children=5-7, Parent Report for Children=8-12, Parent Report for Teens=13-18; Young Adult Report=18-25, Adult Report= ≥26

7.1.2.4 Description of Neuropsychological Computerized Screening Measures

Detection (Psychomotor Function)
The Detection task is a measure of psychomotor function and uses a well-validated simple reaction time paradigm with playing card stimuli. In this task, the playing cards all depict the same joker. The patient is asked to press the "Yes" key as soon as the card in the center of the screen turns face up. The software measures the speed and accuracy of each response.

Identification (Attention)
The Identification task is a measure of visual attention and uses a well-validated choice reaction time paradigm with playing card stimuli. In this task, the playing cards are all either red or black jokers. The patient is asked whether the card displayed in the center of the screen is red. The patient responds by pressing the "Yes" key when the joker card is red and "No" when it is black. The software measures the speed and accuracy of each response.

One Card Learning Test
The One Card Learning Test uses a pattern separation paradigm to measure visual memory. In this test, a playing card appears in the center of the screen. The patient must immediately indicate whether or not the same card has been presented before in this task by selecting the "Yes" button or "No" key. If an incorrect response is given an error noise is heard. Only a few of the cards will repeat during the task. Patients must work as quickly and as accurately as they can. The proportion of total correct responses is recorded to assess accuracy of performance.

One Back (Working Memory)
The One Back task is a measure of working memory and uses a well-validated n-back paradigm with playing card stimuli. In this task, the playing cards are identical to those found in a standard deck of 52 playing cards (without the joker cards). The patient is asked whether the card displayed in the center of the screen is the same as the card presented immediately previously. The patient responds by pressing the "Yes" or "No" key. The software measures the speed and accuracy of each response.

The Groton Maze Learning Test (Executive Function)
The Groton Maze Learning Test is a measure of executive function using a maze learning paradigm. The subject is shown a grid of tiles on a computer touch screen. A pathway is hidden among these locations. The patient is instructed to start at the top left blue tile and then move one tile at a time toward the end (bottom right) while adhering to specific task rules. The task utilizes a trial and error feedback approach in which after each move the computer indicates whether this is correct or incorrect move. Once completed, the test is repeated approximately 4 times. The software records total number of errors across five consecutive trials.

The International Shopping List Task (Verbal Learning)
The International Shopping List task is a measure of verbal learning and uses a well-validated list-learning paradigm. A list of high frequency, high imagery, concrete nouns (items from a shopping list) are read to the patient by the qualified site personnel at the rate of one word every 2 seconds. Once all 12 words have been read, the patient is asked to recall as many of the words as he/she can. As the patient recalls each word, the qualified site personnel uses the mouse or stylus to select the appropriate button on the computer screen. When the patient cannot recall any more items, the entire word list is read a second time in the same order. The qualified site personnel records the words recalled by the patient on this trial. This process is then repeated a third time. The software measures the number of correct responses as recorded by the qualified site personnel.

International Shopping List Test – Delayed Recall (Verbal Memory)
The delayed recall condition requires the patient to recall the words from the list 10-30 minutes later without having the list read again. The qualified site personnel records all words recalled by selecting the corresponding button on the screen. The software measures the number of correct responses.

7.1.2.5 Description of Objective Neuropsychological Evaluation Measures (administered by licensed psychologist)

Intelligence/Global Measures of Functioning

Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III)
The Bayley-III assesses a wide range of functioning, including cognition, language, motor, social-emotional, and adaptive development. Cognition, language, and motor function are assessed via child interaction through tasks and activities administered by a qualified examiner. Social-emotional and adaptive behavior are measured via parent questionnaire. The measure is a well-standardized instrument (normative sample size of 1,700 stratified by age) commonly used to assess development and cognitive functioning in infants. Reliability is adequate, as evidenced by the internal consistency of the cognitive (.87), gross motor (.91), and fine motor (.86) scales. The validity of this measure can be found through its correlations with other well validated measures of infant development (e.g., the Bayley-II, the Preschool Language Scale-4), Peabody Development Motor Scales-2, and Adaptive Behavioral Assessment System-II). Additionally, scores on this measure have been shown to reliably differentiate among groups of children with clinical and medical conditions including Down syndrome, cerebral palsy, prematurity, and pervasive developmental disorders.

7.1.2.6 Parent or Self-Report Questionnaires

Adaptive Behavior Assessment System – 3rd Edition (ABAS-3)
The parent-report and self-report forms from the ABAS-3 will be used for the assessment of adaptive skills for individuals across all ages. Separate scaled scores are available for 9-11 areas of functioning dependent upon age. Internal consistency has been reported to be 0.96 or greater for the composite adaptive behavior scale and between 0.86 and 0.99 for the sub-scales. Construct, convergent, and discriminant validity have also been established for this measure.

The Behavior Assessment System for Children, Third Edition (BASC-3)
The BASC-3 is a questionnaire assessing behavioral, emotional, and adaptive functioning across home, school, and community settings. There are several forms based on age and respondent role. For purposes of this study, the Parent Rating Scales (PRS) will be used for ages 2-5 (Preschool form, PRS-P), 6-11 (Child form, PRS-C), 12-17 (Adolescent form, PRS-A). The Self-Report of Personality (SRP) College Form will be used for ages 18-25. The form generally contains 9 clinical scales and 5 adaptive indices. The clinical scale includes the externalizing problems, internalizing problems, and behavioral symptom indices. Adaptive scales include overall adaptive skills, including functional communication, activities of daily living, social and leadership skills, and adaptability. The reliability of the BASC-3 is strong with internal consistency averaging above .80 for all the age-specific versions of this questionnaire (preschool, child, adolescent) and average test-retest reliability is .86. This measure correlates strongly with other well-validated broad band child behavioral checklists such as the Child Behavior Checklist (CBCL). Note: General combined sex norms should be used when scoring the BASC-3.

The Behavior Rating Inventory of Executive Function (BRIEF)
The BRIEF is a questionnaire designed to assess behavioral manifestations of executive functioning and includes multiple versions. Parents of participants ages 2-5 years will complete the 63-item preschool version (BRIEF-P). Parents of participants ages 6-17 years will complete the BRIEF Parent Form, which consists of 86 individual items from which eight clinical scales, two

indices, and one composite score are derived. Patients who are ≥18 years of age will complete a 75-item self-report adult version (BRIEF-A). Scores are standardized by age and gender. High internal consistency (.73-.98) and test-re-test reliability (.76-.90). Construct, content, convergent, and discriminant validity have been established.

Pediatric Quality of Life Inventory Version 4 (PedsQL 4.0) – General Core Scales

The PedsQL 4.0 is a modular approach to measuring health-related quality of life in healthy children and adolescents as well as those with acute and chronic health conditions. The Generic Version consists of 23 items, with separate parent-report forms for ages 2-4, 5-7, 8-12, and 13-18. Patients who are 18-25 and ≥26 years of age will complete the Young Adult Report and Adult Report (self-report) forms, respectively. The questionnaire yields domain scores for Physical, Emotional, Social, and School Functioning as well as summary scores for Total Quality of Life, Physical Health, and Psychosocial Health. Reliability and validity have been established for this measure.

Pediatric Quality of Life Multidimensional Fatigue Scale

The PedsQL Multidimensional Fatigue Scale is an 18-item questionnaire comprised of three subscales: general fatigue, sleep and rest fatigue, and cognitive fatigue. The parent version can be completed for children ages 2-18, with separate parent-report forms for ages 2-4, 5-7, 8-12, and 13-18. Patients who are 18-25 and ≥26 years of age will complete the Young Adult Report and Adult Report (self-report) forms, respectively. Reliability and validity have been established for this measure. Research has demonstrated that scores on the fatigue scale significantly differentiated between patient samples and healthy controls.

Pediatric Quality of Life Infant Scales

The PedsQL Infant Scales were designed as a generic parent report measure of health-related quality of life for healthy and ill infants ages 1-24 months. It is composed of 36 items for infants ages 1-12 months and 45 items for infants ages 13-24 months comprising 5 dimensions: physical functioning, physical symptoms, emotional functioning, social functioning, and cognitive functioning. Research demonstrated excellent internal consistency reliability for the Total Scale Scores (.92), strong construct validity, and distinguished between healthy controls and patient samples.

Beck Depression Inventory - Second Edition (BDI-II)

The BDI-II is a 21-item, self-report rating inventory that measures characteristics of attitudes and symptoms of depression, including scale items capturing mood, suicidal ideation, somatic complaints (appetite, sleep, fatigue), and cognitive symptoms (punitive thoughts, poor concentration, self-criticism). Requires a fifth to sixth grade reading level to adequately understand questions. Internal consistency ranges from .84 to .93. Over short intervals, test-retest correlations are adequate (.74-.75) to strong (.93-.96). Research demonstrates strong construct validity.

Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a simple and short method of assessing both behavior and ideation that tracks all suicidal events and provides a summary of suicidality. It assesses the lethality of attempts and other features of ideation (frequency, duration, controllability, reasons for ideation and deterrents), all of which are significantly predictive of completed suicide. Research demonstrated good convergent and divergent validity and high sensitivity and specificity. It has been validated for use in individuals age 12 years and older. The children's version is an un-validated measure developed for use in pediatric populations ages 7-11 years.

7.2 Recommended Follow-Up Observations

The following are recommendations only, but may be altered at discretion of treating physician. Repeat the following if abnormal on a monthly basis until stable or normalized after the end of therapy. If normal at the end of therapy then repeat only as clinically indicated:

1. History, physical exam (Ht, Wt, VS)
2. CBC/Differential, Platelets, AST, ALT, Bilirubin, BUN, Creatinine HDL, LDL, total cholesterol and triglycerides

Patients will be followed for life for any delayed toxicities related to protocol therapy and for the development of second malignancies.

After completion of protocol therapy, the disease status, sites of relapse, and last alive date will be recorded until first relapse/progression, after which only last alive date will be reported, as well as date of death and cause of death (if applicable).

7.3 Documentation of Tumor Response

Disease evaluation will take place on or after Week 4 of courses 2, 4, and 6, and after every 4 courses thereafter (i.e. after day 1 of week 4 of courses 10, 14 …). It is recommended that all scans and tests previously done to document disease status be performed in subsequent evaluations of disease status (see Section 7.1).

All patients are required to have a bilateral diagnostic bone marrow aspirate and biopsy done with each disease evaluation.

Once a patient receives therapy other than prescribed on this protocol, no further scans or bone marrow evaluations will be required for this protocol since the patient will no longer be evaluable for response to protocol therapy.

8.0 PHARMACOKINETIC AND BIOLOGY STUDIES

Collection of plasma samples for lorlatinib pharmacokinetic studies is required during course 1 for all patients during both the dose escalation and expansion cohort phases of the study. In addition, samples are required for evaluation of minimal residual disease via NB5 assay by TLDA.

Collection of other samples for correlative biology studies is optional and not required for study entry. Although these studies cannot be mandated, all institutions are strongly urged to submit specimens for all consenting patients.

Table 25 summarizes pharmacokinetic samples to be collected during course 1. Please see Appendix II for a detailed summary of blood draws that also includes samples for correlative studies. For patients with a weight below the minimum required to tolerate all blood draws requested for correlative studies, please consult with study chair to determine prioritization of samples.

8.1 Lorlatinib Pharmacokinetics (PK) (Required)

8.1.1 Sample Schedule

All efforts will be made to obtain the pharmacokinetic samples at the exact nominal time relative to dosing. However, samples obtained within 10% of the nominal time (e.g., within 6 minutes of a 60 minute sample) from dosing will not be captured as a protocol deviation, as long as the exact time of the sample collection is noted on the source document and case report form (e.g., Medidata Rave).

Samples will be collected at the following time points for the first treatment course:

Table 25. PK Sample Collection Schedule

Sample #	Course	Day	PK Sample Time Point (hours)	Amount of Blood Needed
1	1	1	Pre-dose	3.0 mL
2	1	1	1 hr	3.0 mL
3	1	1	2 hr	3.0 mL
4	1	2	24 hr (pre-2nd dose)	3.0 mL
5	1	15*	Pre-dose	3.0 mL
6			1 hr	3.0 mL
7			2 hr	3.0 mL
8			4 hr	3.0 mL
9			6 hr	3.0 mL

*Day 15 PK sampling can be performed within a +/- 2 day window. Please contact NANT Operations Center to discuss if you cannot abide by this schedule.

8.1.2 Plasma PK Sample Collection Procedure and Processing Instructions

NOTE: Lorlatinib is light sensitive; all steps must be performed out of direct light! It should be noted that once collected, samples should be processed immediately and kept out of direct light due to the light sensitive nature of lorlatinib. Once frozen, samples must not thaw, including during shipment. If sample(s) are inadvertently thawed, please notify the NANT Operations Center so the results can be appropriately tagged and if shipped, should be included in the transmittal form.

TIME FROM BLOOD COLLECTION TO FREEZING OF PLASMA MUST NOT EXCEED 45 MINUTES

1. Collect 3 mL whole blood into a K_2EDTA (lavender top) tube at specified time points.
2. After collection, gently invert sample 15 times to completely mix whole blood and anticoagulant.

3. Blood sample should then be immediately placed into an ice bath to be kept at 2°C - 8°C during the harvesting of plasma.
4. Whole blood samples should be centrifuged at 4°C for 10 min at 1,700 x g to separate the plasma from the blood cells.
5. Transfer plasma using a clean pipette; split each sample into 2 2mL AMBER cryovial aliquot tubes, each aliquot containing approximate 0.75 mL plasma.
6. Store plasma samples immediately in a -20°C freezer. Excursions +/- 10°C are permitted.
7. Samples must be shipped frozen on dry ice. Sufficient dry ice should be used to ensure that samples remain frozen for at least 72 hours.

The PK samples must be processed and shipped as indicated to maintain sample integrity. Any deviations from the PK processing steps, including any actions taken, must be documented and reported to the NANT Operations Center. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any sample deemed outside of established stability, or of questionable integrity, will be considered a protocol deviation.

8.1.3 Sample Labeling Instructions

PK samples will be labeled with pre-filled labels provided by Covance. It will include NANT ID #, Protocol # N15-02, collection date, time point (including course and day such as, C2D2) as well as the nominal time point of the sample (such as pre-dose, 1hr, 2hr, etc.). Please ensure the samples are de-identified and contain no protected health information (PHI).

8.1.4 Shipment of Pharmacokinetic Samples

All primary PK plasma samples should be batched at the end of Course 1 and shipped to:

For US and Canada site(s)
Covance Central Laboratory Services, Inc.
8211 SciCor Drive
Indianapolis, IN 46214-2985
Phone: 317-271-1200
Fax: 317-273-4030

For EU site(s)
Covance Central Laboratory Services SA
Rue Moise-Marcinhes 7
1217 Meyrin, Geneva Switzerland
Phone: +41-58-989-7000
Fax: +41-58-989-1999

NOTE; Lorlatinib back up PK plasma samples should be stored on site as per protocol and batch shipped at a later time upon request.

8.1.5 Methodology

1. Lorlatinib plasma samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures.
2. Plasma concentrations of lorlatinib and other possible metabolites of lorlatinib may be determined using validated or non-validated methods.

8.2 Correlative Pharmacodynamics Studies from peripheral blood (Optional)

8.2.1 Sampling Strategy for Plasma Collection for cell-free ctDNA Analyses

The purpose of this optional correlative study is to prospectively and serially assay the blood of children treated with lorlatinib on this trial for cell-free circulating tumor DNA (ctDNA). We will perform these studies using Foundation Medicine's cell-free DNA technology. Peripheral blood

samples will be obtained at study entry and at each anti-tumor evaluation time point. The vast majority of peripheral blood draws will be obtained through a central venous line (CVL). Older subjects may elect routine venipuncture, but blood for this study will be drawn at a time when blood is being obtained for standard-of-care evaluations (typically with a CBC, see Table 23 for time points). For logistical purposes, it is preferable to obtain and ship these specimens on a Monday – Thursday schedule. Please complete a specimen transmittal form to be sent to NANT Operations Center at the time of shipment. Whole blood samples will be collected in one Streck Cell-Free DNA BCT tube (8.5 mL).

All samples passing laboratory criteria will be tested. At the time of testing, laboratory personnel at Foundation Medicine will prepare DNA from plasma samples, perform DNA sequencing of the panel of genes, and analyze the results per approved and pre-specified internal laboratory protocols.

The results are for research use only and will not be used for clinical management. No research data will be disclosed to participating subjects, families or clinicians not part of the study team.

8.2.2 Sample Handling Instructions

At time of enrollment, please contact NANT operations to request FoundationACT kits.

1. Step #1: Check special tube provided in FoundationACT kits to confirm liquid is clear and without cloudiness or crystals
2. Step #2: Label tube with instructions specified in section 8.2.3 below.
3. Step #3: Collect two tubes of whole blood (8.5mL/tube)
    - Prevent backflow: tube contains chemical additives and it is important to avoid backflow into patient
    - Fill tube completely (8.5mL/tube)
4. Step #4: Remove the tube from adapter and immediately **mix by gentle inversion 8 to 10 times**. Inadequate or delayed mixing may result in inaccurate test results. One inversion is a complete turn of the wrist, 180°, and back.
5. Step #5: Place specimens, completed requisition form and NANT transmittal form found on the NANT 15-02 protocol page of the NANT website onto the FoundationACT specimen collection kit.
6. Step #6: Preferably, on the same day of collection ship via FedEx overnight delivery at ambient temperature. Do not freeze or refrigerate blood samples. Keep at 43-99° F (6-37°C).

8.2.3 Sample Labeling Instructions

Please ensure that each sample has an appropriate adhesive label printed and affixed to each tube with the following information: Patient Study ID #, Protocol # N15-02, Time point (including course and day such as, C2D28), and the date of the blood draw. No other identifiers should be included on the label.

8.2.4 Sample Shipment

Accessioning, Clinical Laboratory
Foundation Medicine, Inc.
150 Second Street, Cambridge, MA 02141
Phone: 888-988-3639

8.3 Correlative Biology Studies from Tumor Tissue and Bone Marrow (Optional)

The purpose of this optional correlative study is to decipher whether actionable driver mutations in ALK are found in all or a subset of tumor cells, and to compare diagnostic and relapse tissue when available. Additionally, we will define pre-existing and emerging sub-clonal and clonal driver mutations throughout the ALK-RAS-MAPK pathway using a neuroblastoma-specific ultra-deep sequencing platform to assay for sub-clonal mutations of all tumors (preferably pairs) obtained on this study. Samples will be evaluated for exploratory analyses to predominantly define the clonal

evolution of relapsed neuroblastoma genomes by comparing matched tumor samples (diagnosis and/or recurrence) for detection of mutations, copy number alterations and translocations.

Tumor tissue will be requested for all research subjects who consent to this part of the study from all time points. The optimal and most important sample will be tumor at the time of study enrollment, but tumor tissue from diagnosis or at any other time point during therapy prior to treatment with lorlatinib will be accepted. This can be archived tissue (frozen or paraffin) from the primary institution. If a tumor block is not available, then 15 unstained slides (4-6uM in thickness) of tissue cut from the block may be shipped instead.

Bone marrow aspirates: 4mL obtained bilaterally from each iliac crest (right and left) placed in separate green top (heparinized) tubes to be sent at room temperature to Mosse Laboratory. Aspirate specimens are collected at the same time the patient is undergoing baseline and subsequent disease evaluations on treatment and end of therapy. These specimens are to be collected Monday – Thursday ONLY and must be shipped the same day as the procedure is performed using Federal Express overnight priority delivery. These samples must be received within 24 hours of obtaining the sample. No Friday shipments are allowed. Archival samples should be shipped during Course 1 of protocol therapy and no later than Course 2.

Tumor tissue and bone marrow aspirate specimens should be sent to:

Yael P. Mosse, MD
The Children's Hospital of Philadelphia
The Colket Translational Research Building
Room 3300
3501 Civic Center Blvd
CTRB 9006
Philadelphia, PA 19104
Office: 215-590-0965
Fax: 267-426-0685

8.3.1 Sampling Strategy

All specimens must be labeled with the patient's NANT ID number, specimen type (primary or metastatic, bone marrow R and L), collection date and timing: for tumor tissue label with diagnosis, second look surgery, first relapse, subsequent relapse sample, for bone marrow: label with treatment course number. Submit with NANT specimen transmittal form.

8.4 Evaluation of Minimal Residual Disease by NB5 Assay

Patients will be required to co-enroll onto the NANT Biology Study to support assessment of minimal residual disease (MRD) by NB5 assay. We will employ the NB5 assay on blood or bone marrow obtained from patients on study. This assay is a well-developed assay for the quantification of MRD within the NANT consortia. It will be performed at CHLA. It is a 5-gene RT PCR TLDA detection assay, which quantifies expression of 5 NB specific mRNAs in bone and bone marrow (CHGA, DCX, DDC, PHOX2B, and TH). Blood and bone marrow samples will be submitted at baseline and at the time of each disease evaluation following instructions in the NANT Biology Study protocol. Patients can submit only bone marrow for NB5 assay if blood volumes for research do not allow for blood submission.

Patients are required to enroll on N04-05, NANT Biology Study. Refer to N04-05 protocol for specimen requirements. Patients can submit only bone marrow for NB5 assay if blood volumes for PK studies do not allow for blood submission for additional studies, as priority for blood volumes is given to the PK analyses.

9.0 CRITERIA FOR REMOVAL FROM PROTOCOL AND OFF STUDY CRITERIA

9.1 Criteria for Removal from Protocol Therapy

1. Disease Progression Before Active Treatment
2. Disease Progression, Relapse During Active Treatment
3. Patient/Parent Withdrawal/Refusal Before Beginning Protocol Therapy
4. Patient/Parent Withdrawal/Refusal After Beginning Protocol Therapy
5. Unacceptable Adverse Events By Protocol Criteria
6. Other Adverse Event / Side Effects / Complications
7. Patient Off-Treatment For Other Complicating Disease
8. Initiation Onto Another Therapeutic Study and/or Another Anti-Cancer Therapy
9. Treatment Completed Per Protocol Criteria
10. No Treatment
11. Lost To Follow-Up
12. Death While On Protocol Therapy

For patients who have 'disease progression, relapse during active treatment' may continue treatment with lorlatinib beyond the time of imaging-defined disease progression, at the discretion of the investigator, if the patient is perceived to be experiencing clinical benefit or to avoid rapid progression associated with immediate withdrawal of tyrosin kinase inhibitor therapy. These patients may receive up to one additional course of lorlatinib investigational product and may receive radiation treatment during this time, giving the treating physician time to secure commercial lorlatinib supply.

Patients who are off protocol therapy are to be followed until they meet the criteria for off study. Patients who are removed from therapy prior to progression will be followed for progressive disease until they progress, die, or start another therapy (in which case the date of the new therapy and the type of therapy will be recorded). All patients will be followed until death for survival analysis, unless consent is withdrawn or patient is lost to follow-up. Protocol follow-up forms will be completed every 6 months after patient comes off protocol therapy for the first year and then once a year thereafter (see data submissions schedule for further detail).

9.2 Off Study Criteria

1. Death
2. Lost to follow-up
3. Patient/Parent withdrawal of consent

10.0 STATISTICAL CONSIDERATIONS

Note: This section has been modified to reflect changes to the study design implemented in Amendment 7 (dated 10/31/2019).

The main objectives of the study design and statistical analysis are to (1) establish a recommended phase 2 dose (RP2D) of single agent lorlatinib in children and adolescents (Cohort A1), (2) to establish a RP2D of single agent lorlatinib in adults (Cohort A2), (3) to obtain additional toxicity and efficacy information of single agent lorlatinib at the Cohort A1/A2 RP2D in patients ≥ 12 months of age up to ≤ 18 years of age (YOA) (expansion cohort B1) and > 18 YOA (expansion cohort A2), and (4) to identify RP2D and obtain preliminary toxicity and efficacy information of lorlatinib in combination with topotecan/cyclophosphamide in children ≥12 months of age up to ≤ 30 YOA (Cohort B2 dose escalation and expansion).

Cohort A1 will follow a 3+3 dose escalation design with dose levels defined in Table 15a-d. For patients enrolled after activation of Amendment 4, no more than two patients can simultaneously be enrolled on Course 1 of therapy.

After Amendment 4, Cohort A2 followed a 3+3 dose escalation design independent of that in Cohort A1 with dose levels defined in Table 15b. No more than two patients can simultaneously be enrolled on Course 1 of therapy.

Once the RP2D of lorlatinib as a single agent dose has been established in Cohort A1, Cohort A1 will close and expansion Cohort B1 will open to accrual for patients ≥ 12 months of age and up to ≤ 18 years of age who are unable to tolerate chemotherapy or due to lack of treatment slot on B2.

Once the RP2D of lorlatinib as a single agent dose has been established in Cohort A2, this cohort will be expanded at the RP2D to patients > 18 YOA who are ineligible to enroll on cohort B2 due to inability to tolerate chemotherapy, or lack of treatment slot on B2, or age $\geq$ 30 YOA. Cohort A2 expansion will remain open as long as either Cohort B1 or B2 is open. After Amendment 10, cohort A2 expansion will open to enrollment at DL 3A (100mg/day) to collect additional PK, toxicity and response data due to concern of toxicities observed in DL4A.

Cohort B1 will be open to enrollment to 6 or more patients until it is reasonably assured that at least 12 patients who are evaluable for DLT have been enrolled at the Cohort A1 RP2D (Cohorts A1 and B1 combined).

After Amendment 7, Cohort B2 will open to enrollment at DL 4B (95 mg/m2) for patients $\geq$ 12 months to < 18 years of age (YOA) concurrently with Cohort A1 DL 5 (115 mg/m2). Cohort B2 will follow a 3+3 dose escalation design with dose levels defined in Table 15c. In addition to successfully completing B2:DL 4B (3+3), in order to advance patients ≥ 12 months of age and up to < 18 YOA to DL 5B on B2, Cohort A1 (single agent) at DL5 must have sufficient (n=6) evaluable patients enrolled and completed the DLT cycles to declare the single agent tolerable at that dose level.

Once the RP2D of lorlatinib as a single agent dose has been established in Cohort A2, patients $\geq$ 18 YOA and up to $\leq$ 30 YOA can enroll on B2 at the A2 RP2D in combination with chemotherapy. No dose escalation is planned for patients $\geq$ 18 YOA on B2. After Amendment 10, this cohort will enroll at DL 3A (100 mg/day) while adding 5 additional patients also treated at DL 3A to the Cohort A2 expansion. Although we would attempt to do a 3+3 dose evaluation in this cohort, since this is a rare population, if the study is otherwise completed this cohort may close after discussion with the study management committee.

At the time of preparing Amendment 7, Cohort A1 has completed 4 doses levels (see Table 15a in Section 4.2) and began accrual to DL 5. In Cohort A2, the 1st dose level (DL 3A) is complete and

the 2nd dose level (DL 4A) needs one more patient. The table below summarizes the current status of this trial and the text below summarizes the expected number of patients.

Table 26. Status of Trial with Activation of Amendment 7

Cohort	Description	Age Group	Current Status / Lorlatinib Dose Level (DL)	Future Dose Levels / Accrual	Expected Number of (Future) Patients
A1	Single Agent Dose Escalation	Age: ≥12 mos. & < 18 yrs.	Open at **DL 5**: 115 mg/m^2/day	No more dose levels. DL 5 currently open & if 0-1/6 pts have DLT then this will be the RP2D. Otherwise DL 4 (95 mg/m^2/day) will be RP2D (see Table 15a).	Up to 6 more patients at DL 5 (based on 3+3 rules). May back fill DL 4 with 1 more patient if DL 4 is RP2D.
A2	Single Agent Dose Escalation	Adult: ≥ 18 yrs.	Open at **DL 4A**: 150 mg/day	No more dose levels (see Table 15b). Currently 1/5 with DLT & will enroll 1 more pt. If 1/6 with DLT, then this (DL 4A) will be the adult RP2D. Otherwise DL 3A (100 mg/day) will be RP2D	1 more patient.
		Age: ≥12 mos. & < 18 yrs.	With DL5 in A1, dose is no longer capped based on BSA	No more accrual	0
A2	Single Agent Expansion	Adult: ≥ 18 yrs. & who are not eligible for B2	Waiting for A2 RP2D to be determined	Lorlatinib dose will be RP2D based on A2: DL 4A or DL 3A	6-12 more patients
B1	Single Agent Expansion	Age: ≥12 mos. & < 18 yrs. & who are not eligible for B2	Waiting for A1 RP2D to be determined	Lorlatinib dose will be RP2D based on A1: DL 5 or DL 4	6-12 patients (to ensure that there are 12+ evaluable patients treated at the RP2D for A1)
B2	Combined with Chemotherapy	Age: ≥12 mos. & < 18 yrs.	Will open at **DL 4B**: 95 mg/m^2/day	- See Table 15c. - Enrolling concurrently with A1 dose escalation - If both A1 DL5 and B2 DL 4B are both well tolerated (i.e. 0-1/6 DLT's), then will escalate to DL 5B: 115 mg/m^2/day	Based on 3+3 rules with 9 – 12 patients and 6 – 12 additional patients for expansion
		Age: ≥ 18 yrs. & ≤30 yrs.	Waiting for A2 RP2D to be determined	Lorlatinib dose will be RP2D based on A2: DL 4a or DL 3a (no dose escalation in this age group but de-escalation possible – see Table 15d)	6-12 patients

Total Sample Size: Following Amendment 7, in Cohort A1, with DL 1, 2, 3 and 4 having been preliminarily completed (19 patients enrolled), 6 additional DLT evaluable patients will be required to complete dose-escalation with DL 5. In Cohort A2, with 5 patients having been treated at 100 mg (DL 3A) with no DLT, and 5 patients treated at 150mg (DL 4A), 4 of which had no DLT, therefore 1 DLT evaluable patient will be required to complete dose-escalation on Cohort A2. If an RP2D is established in Cohort A1, then an additional 6-12 DLT evaluable patients will be required in Cohort B1, 9-12 DLT evaluable patients will be required in Cohort B2 DL 4B and 5B, and 6-12 evaluable patients for Cohort B2 expansion. Hence, an additional 27-42 DLT evaluable pediatric patients will be required to complete Cohorts A1, B1 and B2 combined, and 7-13 to complete Cohort A2 (this includes escalation and expansion portion). In all cohorts with dose escalation, 6 DLT-evaluable patients will be required to be treated at a dose level before it can be declared the MTD/RP2D. Additional patients will be treated at the declared MTD/RP2D as described above to better describe toxicity and evaluate the anti-tumor activity of lorlatinib at the declared MTD/RP2D.

Study Duration: We anticipate that 2-3 patients per month will be available for enrollment in Cohorts A1, B1, and B2 and half this number for Cohort A2. Factoring in study suspension for DLT evaluation and a 5% non-evaluability rate, this study will likely require 24 to 36 months to complete after activation of Amendment 7.

10.1 ENDPOINTS

10.1.1 Primary Endpoints

Following Amendment #4, the primary endpoint for safety and dose-escalation/de-escalation decision is occurrence of **DLT***, which is defined as any DLT as defined in section 4.3 that occurs during Course 1, and any neuropsychology-related DLT as defined in section 4.3 that occurs during Course 2. DLTs per section 4.3 that occur during Course 2 that are *not* neuropsychology-related will not be considered occurrences of DLT*.

Evaluability for DLT*: In Cohorts A1, A2, and B1, patients are considered evaluable for DLT* if they receive at least 75% of the planned dose (i.e. at least 21 of the planned 28 doses) of lorlatinib (and for patients in cohort B2, they receive at least 75% of the planned doses of topotecan/cyclophosphamide chemotherapy backbone) during Course 1, and at least 75% of planned dose of lorlatinib (and for cohort B2 of backbone chemotherapy) in each of the Courses 1 and 2, or if they experience DLT*. Patients who are not evaluable for DLT* will be replaced (for Cohorts A1, A2, or B1).

Following Amendment #7, in Cohort B2, only course 1 will be used to define evaluability for DLT and 2nd course neuropsychology-related DLT's will no longer be counted in the decisisons to dose escalate, expand, or de-escalate.

Evaluability for 1st Course DLT: In **Cohort B2** patients are considered evaluable for 1st course DLT if they receive at least 75% of the planned dose (i.e. at least 21 of the planned 28 doses) of lorlatinib and they receive at least 75% of the planned doses of topotecan/cyclophosphamide chemotherapy backbone during Course 1, or if they experience a 1st course DLT. Patients in Cohort B2 who are not evaluable for 1st course DLT will be replaced.

An additional primary endpoint will be the plasma concentrations of lorlatinib measured in all patients during the 1st course according to the schedule provided in Section 8. Based on these measurements, the following PK parameters will be estimated (among others): area under curve (AUC), clearance, C_{max}, T_{max}, and terminal half-life.

10.1.2 Secondary/Clinical Endpoints

Secondary toxicity and safety, and efficacy endpoints include:

1. DLT (per section 4.3) occurring during any course of treatment
2. CTCAE v4 toxicity occurring during any course of treatment
3. Tumor response per NANT response criteria (section 11)
4. Event-free survival (EFS), defined as the time from study entry until disease relapse, disease progression, second malignancy, or death from any cause, or until last follow-up for patients not experiencing any of these events.
5. Overall survival (OS), defined as the time from study entry until death from any cause, or until last follow-up for patients who are alive at last contact.

10.1.3 Endpoints based on Exploratory Aims

For each patient:

10.1.3.1 *Circulating Tumor DNA (ctDNA)*
Circulating tumor DNA will be extracted from the plasma (from peripheral blood) at baseline and at the time of each disease evaluation. The frequency of cell-free ctDNA, as well as the profile of acquired somatic mutations will be measured.

10.1.3.2 *ALK Alterations and Expression*
Where possible, matched tumor samples (at initial diagnosis and at time of most recent recurrence) will be analyzed for ALK alterations (presence of mutations, translocations, copy number changes).

10.1.3.3 *Detection of Minimal Residual Disease*
To quantify tumor cells in the blood and/or bone marrow before, during and at the end of therapy using the NB5, 5-gene Taqman Low Density Array (TLDA) assay.

In addition, every attempt will be made to establish patient-derived xenografts from the patient tumor tissue (obtained at recurrence). These will become a resource for future study.

10.2 STUDY DESIGN

10.2.1 Cohort A1: Dose Escalation / Phase 1

Cohort A1 is designed as a dose escalation with 5 dose levels. Cohort A1 will be closed to accrual once the single agent RP2D of lorlatinib is defined for patients under 18 years of age.

After Amendment #4, the primary endpoint for dose escalation/de-escalation is DLT* (section 10.1.1).

The standard 3+3 rules for dose escalation will be used.The maximum tolerated dose (MTD) will be the highest dose level tested at which 0/6 or 1/6 patients experience DLT*, with at least 2 patients experiencing DLT* at the next higher dose. If a higher dose level does not exist, then this dose will be referred to as the RP2D. The RP2D may be further refined by a comprehensive review and comparison of the toxicity, response and PK data of the patients treated at the same dose level during dose escalation or expansion.

The 3+3 Dose Escalation Rules Are:

1. Three new patients will be enrolled at the current dose level.

2. If 0/3 patients experiences DLT*, then up to 3 patients will be enrolled at the next higher dose level if a higher dose level exists. If no higher dose level exists, up to 3 additional patients will be enrolled at the current dose level.

3. If 1/3 experiences DLT* at current dose level, then up to three additional patients will be accrued at the same level.

    a. if 0/3 of the additional patients experience DLT* then up to 3 patients will be enrolled at the next higher dose level, if a higher dose level exists. If no higher dose level exists, the current dose level is the highest tested dose (HTD).

    b. If one or more of these three additional patients experiences DLT*, then patient entry at that dose level is stopped, the MTD has been exceeded and dose escalation will be stopped. Up to three additional patients will be treated at the next lower dose level. If 6 patients have already been treated at that prior dose,

then enrollment will be halted and the lower dose level is the MTD.

4. If 2 or 3 out of 3 experiences DLT*, then the MTD has been exceeded and up to 3 patients will be treated at the next lower dose level, unless 6 patients have already been treated at that dose or if no lower dose level exists. If no lower dose level exists, then dose escalation/de-escalation will be halted and no MTD exists.

Only patients who are evaluable for DLT* will be included in the application of the 3+3 rules above. Patients who are not evaluable will be replaced..

Following determination of the MTD and, following comprehensive review of all patients, and provided that other safety considerations are acceptable, it is likely that the MTD or HTD will also be labeled the recommended Phase 2 dose (RP2D) and used in cohorts B1 and B2.

Justification of the Use of the Phase 1 Design with the 3+3 Rules. Given the experience of lorlatinib in the treatment of adults, there is knowledge of the drug disposition and potential toxicities. This allows for a rational choice of a limited number of doses. Thus a design with 5 dose levels (and one back-up level: Dose Level -1) based on the adult experience is in keeping with the recommendations of Lee, Skolnick and Adamson[37]. In addition, simulation studies have shown that on average the 3+3 design selects an MTD that has a 10% to 20% chance of DLT[38,39]. Taken together, the proposed 3+3 design has a reasonable probability of selecting a dose with a low true DLT rate (in the 10% to 20%). The expansion cohort will further evaluate the probability of DLT at the RP2D.

10.2.2 Cohort A2: Inclusion of Older Patients (≥ 18 years of age) or Younger Patients with BSA ≥ 1.73 m^2

With Amendment #4 initiated the dose escalation of Cohort A2. Cohort A2 will have 2 stages: a dose escalation stage and an expansion stage. Cohort A2 (expansion) opened at the time that Cohort A1 was opened and will continue to enroll while Cohorts B1 and B2 are enrolling.

Initially, Cohort A2 treated all patients with single agent lorlatinib at 100 mg/day, with the provision that toxicities, as well as DLT's, will be reviewed on a per patient basis as well as summarized per dose in the aggregate and for patients < 18 years of age and for patients ≥ 18 years – and compared to those observed in cohorts A1 and B1.

A2 Escalation: Post Amendment 4, Cohort A2 was planned to have a dose escalation of 2 doses; DL 4A (150mg/day) and DL 5A (200mg/day). Dose escalation was to follow the standard 3+3 rules (described in 10.2.1). Once 6 patients are treated at the RP2D (with 0-1/6 DLTs) in this cohort (likely to be either DL 4A or 5A), the escalation portion will be completed. Post Amendment 7 due to toxicity observed on DL 4A, no more dose escalation beyond DL 4A was planned and DL 5A was eliminated. With Amendment 7, DL 5A will not be tested.

A2 Expansion: Once the escalation stage is complete, additional patients can be enrolled in the A2 expansion cohort at the RP2D from A2 escalation, if they are ≥ 18 YOA. Toxicities, as well as DLT's, will be reviewed on a per patient basis as well as summarized per dose in the aggregate by age group and combined. As of Amendment 10, 5 additional patients will be enrolled at DL 3A to collect additional PK, toxicity and response data in order to help determine RP2D.

Justification of Number of Patients in Cohort A2. It is expected that the A2 cohort will enroll a total of 20 evaluable patients prior to determination of RP2D. A2 expansion cohort at the RP2D may enroll 6 or fewer patients. If 2 or more of the 1st 6 patients experience a DLT*, this will lead to a discussion of the suitability of this dose in these patients with relapsed/refractory neuroblastoma. The ages of these patients will also be examined. Table 27 below summarizes the probability of observing 2+ patients with DLT* (exact binomial calculations – identical to those for cohort B1); if

the true probability of DLT* is 0.40 or greater, then there is a high probability (0.77 or more) of observing 2+ patients with DLT*, suggesting that the proposed dose may be higher than desired.

Table 27: Probability of 2+ Patients with DLT During Cohort A2 Expansion (with 6 DLT-Evaluable Patients)										
True Probability of DLT	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50
Probability of Observing 2+ DLTs in 6 Patients	0.03	0.11	0.22	0.34	0.47	0.58	0.68	0.77	0.84	0.89

10.2.3 Cohort B1: Expansion Cohort at the RP2D in Patients < 18 Years of Age: Single Agent, Lorlatinib

Cohort B1 will open once the single agent lorlatinib RP2D is established based on Cohort A1. Based on data available at the time of Amendment #7, this dose is likely to be either Dose Level 4 (95 mg/m^2/day with 150 mg/day max) or Dose Level 5 (115 mg/m^2/day).

In Cohort B1, the 6 new patients will serve to confirm that lorlatinib at the RP2D established in Cohort A1 does not have excessive toxicities. Once the acceptable toxicity profile is confirmed, then these 6 patients and the 6 patients treated at the RP2D during Cohort A1 will be combined (for a total of 12 DLT*-evaluable patients – and accounting for those patients who were not "evaluable for DLT*") to summarize toxicities overall and anti-tumor activity.

Toxicity Monitoring. In the expansion cohort, we will continue to monitor toxicities and DLT*'s. Therefore, if 2+ patients experience DLT* then toxicity data at the RP2D (including all patients), as well as at other doses will be reviewed to decide whether the dose, schedule, or the associated supportive care requirements should be modified or not. If a change is made, the protocol will be amended.

Justification of Number of Patients in the Expansion Cohort. The Cohort B1 expansion cohort will enroll 6 additional DLT* evaluable patients at the RP2D defined in the dose escalation Cohort A1 of the study. If 2 or more of these 6 patients experience a DLT* this will lead to a discussion of the suitability of the RP2D for the treatment of future patients. Table 28 below summarizes the probability of observing 2+ patients with DLT* (exact binomial calculations); if the true probability of DLT* is 0.40 or greater, then there is a high probability (0.77 or more) of observing 2+ patients with DLT*, suggesting that the proposed dose may be higher than desired.

Table 28: Probability of 2+ Patients with DLT During Cohort B1 (with 6 DLT-Evaluable Patients)										
True Probability of DLT	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50
Probability of Observing 2+ DLTs in 6 Patients	0.03	0.11	0.22	0.34	0.47	0.58	0.68	0.77	0.84	0.89

The data from all patients treated at the RP2D (in Cohort A1 and in Cohort B1), will be combined for a final summary and listing of toxicities observed. With 12 patients there is an 86% and 93%

chance that we will observe a toxicity that occurs in at least 15% and 20% of patients, respectively. Thus, with the expansion cohort we will be able to observe common toxicities associated with lorlatinib given daily as a single agent.

Similarly, with 12 patients treated at the RP2D, there is a 93% chance that at least one patient will experience an objective response, if the true response rate is 20% or greater. Stated differently, if none of the 12 patients experience a response, then we will conclude that the true response rate is less than 20% (with a 7% error rate of falsely rejecting lorlatinib as active).

10.2.4 Cohort B2: Combining Lorlatinib with Topotecan/Cyclophosphamide

With Amendment #7, cohort B2 will open and patients < 18 years of age and ≥ 12 months of age will be treated at Dose level B2 4B: Lorlatinib at 95 mg/m^2/day max, and cyclophosphamide and topotecan at fixed doses. There is one possible dose level escalation in this cohort to Dose level B2 5B: Lorlatinib at 115 mg/m^2/day with 200 mg/day max, and cyclophosphamide and topotecan at the standard fixed doses.

Patients 18-30 years of age will initiate B2 once the RP2D from cohort A2 is identified. No dose escalation will be planned for that age group in the B2. With Amendment 10, this cohort will be enrolled at DL 3A concurrently with the enrollment of A2 monotherapy expansion cohort at DL 3A.

Escalation to Dose Level B2 5B for patients < 18 years of age and ≥ 12 months of age when both of the following conditions are met:

- Only 0/3 or 1/6 patients experiences DLT at Dose Level B2-4B (reflecting the 3+3 rules), AND
- In Cohort A1, Lorlatinib at 115 mg/m^2/day is established as the RP2D for patients ≥12 months up to < 18 years of age,

Additonal patients, up to 6 (for a total of 12), can be treated at Dose Level B2 4B, if the RP2D in Cohort A1is not yet established and the following criteria below are NOT met:

- If 2+ patients in the 1st 6 evaluable patients experience a DLT at Dose level B2 4B
- If 3+ patients in the 1st 9 evaluable patients experience a DLT at Dose level B2 4B
- If 4+ patients in the 1st 12 evaluable patients experience a DLT at Dose level B2 4B

If any of these criteria are met, the cumulative data will be reviewed and a decision will be made to (a) continue, (b) modify the regimen, or (c) expand the dose level. If the regimen is modified, the protocol will be amended with monitoring rules updated. Operationally, during the 1st 6 patients, accrual will be paused to ensure that no more than 3 patients are at risk for DLT; in the 2nd group of 6 patients, if there are 2 DLT's, accrual will be paused to ensure that no more than 3 patients are at risk for DLT.

Table 28 below summarizes the probability of observing an excessive number of DLT's as described above (exact binomial calculations); if the true probability of DLT is 0.35 or greater, then there is a high probability (0.79 or more) of observing an excessive number of patients with DLT, suggesting that the proposed doses may be higher than desired.

Table 29: Probability of an Excessive Number of DLT's During Cohort B2

True Probability of DLT	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45	0.50
Probability of Observing 2+ DLTs in 6, 3+ DLTs in 9, or 4+ DLTs in 12 patients	0.03	0.13	0.26	0.41	0.56	0.69	0.79	0.87	0.93	0.96

10.2.5 Monitoring Plan for Deaths within 30 Days of Last Treatment

Each death after initiating protocol therapy and within 30 days of completion of protocol therapy not due to tumor will be reviewed by the NANT Study Management Committee (SMC), reported to NANT DSMB and a decision, in consultation with NANT DSMB and IND sponsor, will be made to close the trial, modify the trial, or continue unchanged; in addition, it will be determined if the event requires that new information be added to the informed consent. Each death occurring within 30 days of completing the last dose of lorlatinib regardless of cause will be reviewed and reported to the NANT DSMB and to the FDA according to standard procedure.

10.3 Statistical Analysis

All patients who begin treatment will be accounted for; basic demographic and clinical baseline data, number of courses begun, number of courses completed, reason off treatment, reason off study, total amounts of lorlatinib received, dose delays and reductions, toxicities (grade, type, course, and attribution) experienced, best response, and time to progression will be listed for each patient and summarized using standard descriptive methods.

10.3.1 Toxicity

All patients who begin treatment with lorlatinib will be included in the analyses of toxicity and (in cohort A1) the selection of the RP2D. Only the application of the 3+3 rules (Cohort A1 and A2) and the toxicity monitoring guidelines (Cohorts B1, and B2), will be restricted to the patients who are “evaluable for DLT” or “evaluable for DLT*”.

Toxicities will be tabulated and reported according to cohort, dose level, grade, type, course, and attribution. Cumulative incidence curves will be used to estimate the proportion of patients who will discontinue therapy for reasons of toxicity or general inability to tolerate the regimen. In a descriptive analysis, the association between toxicity (highest grade hematologic and highest grade non-hematologic experienced, hypercholesterolemia, and toxicities occurring in more than 20% of patients) and the PK levels measured and PK parameters estimated using graphical methods and logistic regression.

10.3.2 Anti-Tumor Activity

10.3.2.1 Tumor Response by NANT Criteria

Tumor response will be assessed according to standard NANT criteria (Section 11). The primary endpoint for response analysis will be Best Overall Response (BOR), defined as the best response observed prior to progression or start of another therapy. All eligible patients who receive any amount of lorlatinib will be evaluable for BOR and will be included in the primary analysis, except for patients who terminate protocol treatment or withdraw from the study for reasons unequivocally unrelated to either treatment tolerability or disease progression. Evaluable patients who withdraw before any post-enrollment disease evaluations will be considered non-responders in this analysis. Additional analyses may restrict to patients who receive at least 75% of prescribed lorlatinib dose in the first cycle and have at least one post-enrollment disease evaluation. Point estimates for the response rate (proportion of patients who have BOR of PR or better will be calculated, together with exact 95% confidence intervals. In addition, BOR of minor response or better will also be calculated with exacty 95% confidence intervals. These will include cohorts A1 and B1 combined, for cohort B2, and for cohort A2. In addition, multivariable logistic regression analysis will be performed to simultaneously assess the influence of age, BSA, dose, and single agent or combination treatment.

10.3.2.2 Event-Free Survival (EFS)

All eligible patients who receive any amount of lorlatinib will be included in the analysis of EFS; initially EFS will be summarized in 3 groups: patients treated on Levels 1 & 2 combined (if numbers permit) in cohort A1, patients treated at the RP2D in cohorts A1 and B1, and patients enrolled in cohort B2. The Kaplan-Meier product limit estimates of the EFS over time will be calculated and plotted. Point estimates and 95% confidence intervals will also be calculated. If numbers permit, EFS will be summarized for patients in cohort A2, in a similar fashion.

10.3.2.3 Overall Survival (OS)

All eligible patients who receive any amount of lorlatinib will be included in the analysis of OS; initially OS will be summarized in 3 groups: patients treated on Levels 1 & 2 combined in cohort A1 (if numbers permit), patients treated at the RP2D in cohorts A1 and B1, and patients enrolled in cohort B2. The Kaplan-Meier product limit estimates of the OS over time will be calculated and plotted. Point estimates and 95% confidence intervals will also be calculated. If numbers permit, OS will be summarized for patients in cohort A2, in a similar fashion.

10.3.3 Pharmacokinetic (PK) Data, and ALK Gene Status (ALK fusion protein, ALK mutation or ALK amplification)

The association between PK results and ALK gene status with tumor response, as well as the associations between PK results with selected toxicities, will be summarized with standard descriptive methods (scatterplots, exact logistic regression, contingency tables). Although p-values will be calculated to assess the strengths of the observed associations, because of the relatively small numbers, all patterns will require confirmation.

Routine pharmacokinetic parameters for lorlatinib will be determined using standard methods and reported descriptively in aggregate and by assigned dose level. Parameters to be determined include Area under the Curve (AUC), clearance, C_{max}, T_{max}, and terminal half-life.

The correlative biology studies (in cell-free ctDNA and tumor tissue) are also considered descriptive. For the evaluation of pharmacodynamic markers, the relative change from baseline will be reported in aggregate for each marker (predominantly, ctDNA frequency, ALK status in ctDNA or tumor tissue) and also by lorlatinib dose level. Association between modulation of these markers and occurrence of any DLT and any clinical response (partial response or better) will then be examined qualitatively.

For molecular profiling studies, patients will be grouped into sub-categories according to the underlying activating ALK alteration). Association between sub-category and clinical response category (partial response or better vs. non-responder) will then be examined qualitatively.

10.3.3.1 Analysis of NB5 Assay

NB5 assay by TLDA will be used as a measure of tumor load in patients at baseline and while on therapy. For each patient, at each evaluation, the TLDA score (with 40 corresponding to undetectable tumor and lower values associated with detectable tumor cells) will be calculated. For TLDA scores based on blood and on bone marrow (separately), the baseline values will be summarized for all patients and according to amount of tumor measured by longest diameter, Curie score, and routine bone marrow morphology (positive or negative). Standard descriptive summaries as well as scatterplots will be used. Changes (from baseline) in the TLDA scores over the course of treatment will be plotted and summarized by dose level and course. The association between the changes in TLDA scores and overall tumor response will also be summarized graphically and quantitatively. If numbers permit, patients will be grouped into sub-categories according to the underlying activating ALK alteration).

10.3.4 Cognitive and Behavioral Outcomes at Baseline and Changes with Treatment

These will be descriptive analyses to summarize the status of patients at baseline and then to record the changes at the end of Courses 1, 2, 4, 6 and every 4 courses thereafter (see Section 7.12. and Table 24 above for the specific variables). Standard descriptive statistics will be used; plots of individual patients over time as well as in the aggregate will be presented. For the majority of these standardized tests, parametric methods can be used; if the distribution of the data suggests otherwise, nonparametric methods will be used. Of particular interest will be the baseline values, the magnitude of changes (if any) and the patient-to-patient variability. In exploratory analysis, we will examine the patterns of cognitive and behavioral functioning and the association of relevant demographic and medical variables with change in performance over time. Scatterplots, correlations, and regression models (if appropriate) will be used to display and summarize patterns.

10.4 Inclusion of Women and Minorities

The study is open to all participants regardless of gender or ethnicity. Review of accrual to past NANT studies of new agents demonstrates the accrual of both genders and all NIH-identified ethnicities to such studies. Although we will summarize selected endpoints by gender and race/ethnicity, the relatively small number of patients entered into this trial will not permit formal comparisons.

Since this is a Phase I study, the exact total number of patients cannot be known in advance. However, our best guess is that we will enroll about 66 patients.

Table 30: PLANNED ENROLLMENT – N015-02 – Based on 66 Patients

Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	0
Asian	**2**	**3**	0	0	**5**
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	**2**	**2**	0	0	**4**
White	**16**	**30**	0	0	**46**
More Than One Race	0	0	0	0	0
Hispanic	0	0	**5**	**6**	**11**
Other	0	0	0	0	0
Unknown	0	0	0	0	0
Total	**20**	**35**	**5**	**6**	**66**

11.0 NANT RESPONSE CRITERIA V2.0

Overall response will incorporate all three parameters: Soft Tissue Response, Bone Response, and Bone Marrow Response with Overall Response defined as outlined in Section 11.6. Response for each parameter and overall response will be reported by the treating site using the criteria below. However, the final statistical analysis of response will utilize responses as graded by central review, using the same criteria below.

11.1 Soft Tissue Response Criteria

Soft tissue lesions will be evaluated by CT/MRI, using the definitions of measurable disease from the Response Evaluation Criteria in Solid Tumors (RECIST 1.1; European Journal Cancer 45: 228-247, 2009) modified per the criteria below to define target lesions (lesions which are measurable AND evaluable for response).

Note that the response criteria for lymph nodes measured by short axis will only be applied to discrete lymph nodes that are not adjacent to the primary site and are not composed of a coalesced mass of multiple lymph nodes. Coalesced masses of lymph nodes should be assessed using non-lymph node criteria and measured using longest dimension.

11.1.1 DEFINITION OF SOFT TISSUE TARGET LESIONS:

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Soft tissue target lesions that will be followed for response must meet criteria 1 and 2 OR criteria 3 below:

1. A target lesion must be measurable, defined as a soft tissue lesion that can be accurately measured in at least one dimension with a longest diameter ≥ 10mm, or for discrete lymph nodes ≥ 15mm on short axis. (The short axis is measured after identifying the longest diameter of a lymph node, and then measuring the longest perpendicular diameter to that as the short axis). For coalesced masses of multiple lymph nodes, the longest diameter will be used.
2. A target lesion must also be MIBG avid OR FDG-PET avid (if tumor known to be MIBG non-avid), and have a biopsy if required in the eligibility criteria. If one avid soft tissue or bone lesion present at enrollment is biopsied showing neuroblastoma or ganglioneuroblastoma at any time point prior to enrollment, then all other avid soft tissue lesions present at enrollment are considered target lesions.
3. A lesion that is measurable but does not have either MIBG or FDG-PET uptake will be considered a target lesion if a biopsy done at any time prior to enrollment demonstrates neuroblastoma and/or ganglioneuroblastoma.

NOTE: Soft tissue components of bone lesions will be considered measurable soft tissue lesions if ≥ 10mm in at least one dimension, and target lesions evaluable for response if MIBG avid (or FDG-PET-avid if tumor known to be MIBG non-avid).

Serial measurements of target lesions are to be done with the same method of assessment (either CT or MRI) used to characterize each lesion reported at baseline. The sum of diameters (longest for non-nodal lesions and coalesced masses of multiple lymph node, short axis for discrete nodal lesions) for all target soft tissue lesions will be calculated and reported as the **sum of diameters**.

11.1.2 DEFINITION OF NON-TARGET SOFT TISSUE LESIONS:

1. Leptomeningeal tumor and tumor in cerebrospinal fluid cytology.
2. Lesions that are considered likely to be active tumor by the treating physician based on clinical correlation (for example, hepatic and pulmonary nodules)

11.1.3 The following lesions will NOT be followed to evaluate response either as target lesions or non-target lesions, if they meet the criteria below **AND** the treating physician feels they are unlikely to represent active tumor (an exception for active tumor will be made for c. below):

1. Measurable non-lymph node and coalesced masses of lymph node soft tissue lesions ≥ 10mm and discrete lymph nodes ≥15 mm that are not MIBG avid or FDG-PET avid (if tumor known to be MIBG non-avid) such as tumor at surgical site and if biopsied did not show neuroblastoma or ganglioneuroblastoma.
2. Non-measurable non-lymph node soft tissue lesions < 10mm or non-measurable discrete lymph nodes (defined as lymph nodes >10 to <15mm on short axis).
3. Intramedullary bone lesions will not be followed for CT/MRI response even though they are felt to represent active tumor since they will be evaluated with MIBG scans (or FDG-PET scans if MIBG non-avid), and since bone changes on CT/MRI are known to persist after resolution of active tumor.

11.1.4 SOFT TISSUE RESPONSE CRITERIA:

11.1.4.1 Complete Response (CR)

All target and non-target soft tissue lesions have longest diameter < 10 mm. Discrete lymph nodes identified as target lesions must decrease to a short axis < 15 mm. Resolution of all MIBG uptake (FDG-PET uptake if tumor known to be MIBG non-avid).

11.1.4.2 Partial Response (PR)

At least a 30% decrease in sum of diameters of target soft tissue lesions (using longest diameter for non-nodal and coalesced masses of lymph node lesions and short axis for discrete lymph node lesions), taking as reference the measurement of target lesions performed at study enrollment. Non-target soft tissue lesions must be stable to smaller in size. No new lesions. MIBG (FDG-PET for MIBG non-avid tumors) uptake may still be present in lesions positive at enrollment.

11.1.4.3 Progressive Disease (PD)

At least a 20% increase in sum of diameters of target soft tissue lesions (using longest dimension for non-nodal and coalesced masses of lymph node lesions and short axis for discrete lymph node lesions) taking as reference the smallest sum of diameters while on study (this includes the baseline if that is the smallest while on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of 5 mm. A new target or non-target soft tissue lesion seen on CT/MRI without MIBG or PET uptake is considered PD, but may be biopsied to rule out PD. An overall substantial worsening of non-target soft tissue lesions is also considered as a criteria for PD (guidance for substantial includes a 73% increase in volume, or sufficient worsening of overall non-target disease such that the treating physician feels a change in therapy is indicated).

New uptake of MIBG (or FDG-PET for MIBG non-avid tumors) at target and/or non-target soft tissue lesions which are stable in size, will also be considered PD. Biopsy of such lesions can be done to rule out PD for the MIBG (or FDG-PET) response.

11.1.4.4 Stable disease (SD)

(Applies only to patients with target soft tissue lesions)

Neither sufficient shrinkage in sum of diameters to qualify for PR nor does the patient meet any criteria for PD. No new soft tissue lesions. Non-target soft tissue lesions must be stable to smaller in size.

11.1.4.5 Stable disease-no target lesions (SD-NTL)

(Applies to patients with non-target soft tissue lesions only)

Non-target soft tissue lesions are still present; may be smaller or stable in size, and do not meet criteria for PD. No new soft tissue lesions and no new uptake of MIBG (FDG-PET if tumor known to be MIBG non-avid) at existing non-target soft tissue lesions. New lesions or lesions with new MIBG (FDG-PET) uptake may be biopsied to rule out PD.

11.1.4.6 Not involved (NI): No target or non-target soft tissue lesions

11.1.4.7 Not evaluable (NE)

CT/MRI scans and/or MIBG scans (FDG-PET if tumor known to be MIBG non-avid) are of inadequate quality as assessed by central reviewer, or scans are not repeated of all anatomic sites with tumor documented at entry. (Note that patients not evaluable at a given time point may be evaluable for response at later time points if all scans done with adequate quality at later time point) or if based on Study Management Committee / PI review it is deemed that there is insufficient data to grade response.

11.1.4.8 Not done (ND)

No CT/MRI scans were done at the given time point.

11.2 Bone Marrow Response Criteria

Methodology:

1. Routine morphology with immunohistochemistry will be used for all bone marrow evaluations. Immunohistochemistry (with antibodies that are used per local site's standard procedure) is recommended for evaluating percentage of tumor but it is not required. If immunohistochemistry is not done on the baseline bone marrow, then BM response should be graded based on routine morphology only at all time points.
2. The percentage of tumor in the bone marrow at study entry (baseline) and all subsequent time points reported will use the highest tumor percentage noted among the four samples (bilateral aspirates and biopsies).
3. The percentage of tumor in an aspirate will be calculated as the number of tumor cells divided by the number of total nucleated cells.
4. The percentage of tumor in a biopsy will be calculated as the percent of tumor cells (including neuroblasts, mature and maturing ganglion cells) based on the bone marrow parenchymal surface area examined. Schwannian stroma only is considered negative.

Bone marrow response will be graded using the bone marrow done at study entry as the reference point, except for PD, which is graded based on comparison to the most recent bone marrow evaluation. The baseline bone marrow must include an attempt to obtain bilateral aspirates and biopsies, and will be considered as evaluable if at least one biopsy sample is adequate to determine the percentage tumor involvement. At baseline, or any subsequent time point, the percentage tumor from the unilateral evaluable biopsy will be used to grade bone marrow response. Patients with ≤ 5% tumor (including patients with tumor seen by immunohistochemistry only) on all samples of the bilateral bone marrow aspirate and biopsies at the baseline evaluation will be evaluable for bone marrow response, but defined separately from patients with > 5% at study entry as outlined below.

Central review will be performed on bilateral biopsies only, unless BM tumor is seen only on aspirates. If a patient meets protocol criteria for central review of BM response, morphology slides will be requested.

11.2.1 Complete Response (CR)

Greater than 5% tumor at study entry, with no tumor seen at one subsequent time point

11.2.2 Complete Response Minimal Disease (CR-MD)

≤ 5% tumor at study entry, with no tumor seen at one subsequent time point.

11.2.3 Partial Response (PR)

Greater than 20% tumor at study entry, with >0 to ≤ 5% tumor at a subsequent time point.

11.2.4 Minimal Disease (MD)

One of the following:

1. No tumor at study entry, with >0 to ≤5% tumor at a subsequent time point
2. >0 to ≤5% tumor at study entry, with >0 to ≤5% tumor at a subsequent time point
3. >5% tumor at study entry, with >0 to ≤5% at a subsequent time point.

11.2.5 Progressive Disease (PD)

Patients with any amount of tumor in the bone marrow at study entry will be considered to have PD if one subsequent evaluation shows >20% tumor on any one bone marrow sample AND there is a greater than 2 times increase in the amount of tumor compared to study entry.

Patients with ≤ 5% tumor at study entry must increase to > 20% tumor to have PD; a patient with 30% tumor at study entry must increase to ≥60% tumor. If patients have an increase in tumor amount which is less than the amount specified for PD, the response will be classified as SD.

Patients with no tumor at study entry will be considered PD if ONE subsequent evaluation shows >5% tumor.

Patients who are deemed to have bone marrow progression based on review of prior bone marrows by physician assessment and confirmed by the study management committee.

11.2.6 Stable Disease (SD)

Persistence of an amount of tumor in the bone marrow that does not meet criteria for progressive disease or PR or MD, and is > 5%.

11.2.7 Not Evaluable (NE)

Patients for whom follow-up bone marrow evaluations do not include an attempt to obtain bilateral aspirates and biopsies and do not have at least one adequate biopsy sample, as assessed by local site's pathology report for that time point or if based on Study Management Committee / PI review it is deemed that there is insufficient data to grade response.

11.2.8 Not involved (NI)

Patients with no evidence of neuroblastoma in the bone marrow at study entry, and bone marrow remains negative on any subsequent evaluations.

11.2.9 Not done (ND)

Bone marrow evaluation not done at a given time point.

11.2.10 EXAMPLES OF GRADING BONE MARROW RESPONSE:

BASELINE	Time Point 1 or any subsequent time point*	BM Response
0	0	NI
0	>0-<=5	MD
0	>5	PD
>0-<=5	0	CR-MD
>0-<=5	>0-<=5	MD
>0-<=5	>5-20	SD
>0-<=5	>-20	PD
>5-20	0	CR
>5-20	>0-<=5	MD
>5-20	>5-20	SD
>5-20	>-20 and doubled compared to baseline	PD
>20	0	CR
>20	>0-<=5	PR
>20	>5-20	SD
>20	>20 but not doubled compared to baseline	SD
>20	>-20 and doubled compared to baseline	PD

11.3. Bone Response Criteria using MIBG scans (for MIBG avid tumors)

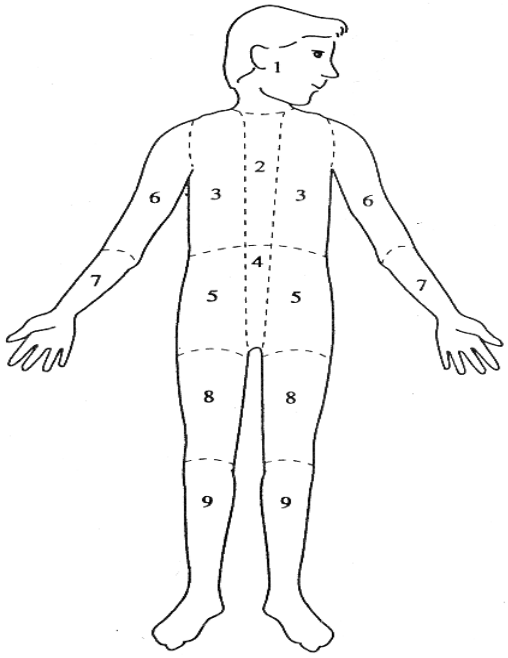
Bone response will be evaluated using MIBG scans for MIBG avid tumors. FDG-PET scans (see section 11.4) may be substituted for MIBG scans to assess bone response only if the tumor is known to be MIBG non-avid. Bone response will be graded using a modification of the Curie scoring scale (Eur J Cancer 1995;31A:256-261). The treating site will report the Bone Response using MIBG scoring done at local site, however the statistical endpoint of Bone Response will utilize the MIBG score from the central reviewer.

MIBG scans will be scored for 9 anatomic regions for bone metastases only, MIBG uptake in soft tissue disease will NOT be included, since this uptake is utlized as part of evaluating Soft Tissue Response. SPECT scans are strongly encouraged to be used for MIBG scoring, if SPECT is available at baseline and subsequent time points. If SPECT scans are not available at all time points, then conjugate planar imaging alone should be used to score each region, and SPECT may be used only as an adjunct to help delineate the location of the MIBG avid lesion.

Each of the 9 regions will be given a score of 0-3, as defined below.

Table 32: Scoring of Bone Disease Regions 1 – 9

Scoring	MIBG uptake
0	No MIBG uptake
1	1 focal lesion
2	> 1 focal lesion
3	> 50% of a region



The **absolute extension score** is obtained by adding the scores of all nine regions. The presence of a MIBG avid lesion, and NOT the "intensity" of MIBG-avidity, determines the scoring within a particular region.

REGIONS 1 – 9 / BONE DISEASE: Cranio-facial disease is scored in Region 1, cervico-thoracic spine in Region 2, ribs / sternum / clavicles / scapula in Region 3, lumbar-sacral spine in Region 4, pelvis in Region 5, humeri in Region 6, distal upper extremities in Region 7, femurs in Region 8, and distal lower extremities in Region 9 (see figure above).

The **relative score** is calculated by dividing the absolute score of bone lesions at each time by the corresponding pre-treatment overall absolute score. The relative score of each patient is calculated at each response assessment and classified as below:

a. Complete response: all areas of bone uptake on MIBG scan completely resolved.
b. Partial response: Relative score ≥ 0.1 to ≤ 0.5
c. Stable disease: Relative score > 0.5 to < 1.2
d. Progressive disease: New bone lesions on MIBG scan compared to most recent prior MIBG scan OR a relative score ≥ 1.2. Biopsy of new lesions may be done to rule out progressive disease. If biopsy is negative for tumor (neuroblastoma and/or ganglioneuroblastoma), patient will not meet definition of PD.
e. Not evaluable (NE): MIBG scan of inadequate quality as assessed by central reviewer.
f. Not involved (NI): No MIBG avid bone lesions at study entry and subsequent response time points.
g. Not done (ND): MIBG scan not done at a given response time point

11.4 Bone Response Criteria using FDG-PET scans (only for MIBG non-avid tumors)

Patients known to be non-avid for MIBG should have FDG-PET scans performed for monitoring bone response. FDG-PET avid bone lesions will be scored by the presence or absence of a lesion with uptake that is two times above background. For MIBG non-avid patients, uptake of FDG-PET in soft tissue lesions will be utilized in the Soft Tissue Response (see section 11.1).

11.4.1 Complete response (CR)
Resolution of all FDG-PET uptake in all FDG-PET avid bone lesions identified at baseline and no new FDG-PET avid bone lesions.

11.4.2 Partial response (PR)
Reduction of number of bone lesions by FDG-PET by ≥ 50%. No new FDG-PET avid bone lesions.

11.4.3 Stable disease (SD)
Changes that do not meet the criteria for PR or PD.

11.4.4 Progressive disease (PD)
New bone lesions on FDG-PET scan. Note: biopsy may be done to exclude causes of FDG-PET uptake other than tumor. If biopsy of the new lesion is negative for tumor (neuroblastoma and/or ganglioneuroblastoma), patient will not meet definition of PD.

11.4.5 Not evaluable (NE)
FDG-PET scan of inadequate quality to evaluate bone response or if based on Study Management Committee / PI review it is deemed that there is insufficient data to grade response.

11.4.6 Not involved (NI)
No FDG-PET uptake in bone sites that is two times above background.

11.4.7 Not done (ND)
FDG-PET scan not done at a given time point.

On central review, FDG-PET avid bone lesions will be evaluated by both the MIBG scoring method outlined in Section 11.3 and also by enumeration of lesions to grade bone response.

11.5 Urine Catecholamines

Due to variance with diet and concomitant medications, frequently missing dopamine levels, and lack of standardized methodology for this assay, urine catecholamines will not be utilized in grading response. Results of urine catecholamines will not be requested.

11.6 Definition of Overall Response

The criteria below will be used to define the overall response for each patient, with consideration of all three individual response parameters: Soft tissue Response, Bone Response, and Bone Marrow Response.

11.6.1 Complete Response (CR)

Response of CR or NI for soft tissue and bone, soft tissue with bone marrow response of CR or CR-MD.

11.6.2 Complete Response MD (CR-MD)

Soft tissue and bone response are both NI, with BM response of CR-MD

11.6.3 Partial Response (PR) includes any one of the following:

1. Response of PR for soft tissue, bone response of PR, and BM response of CR, CR-MD, PR, MD, or NI.
2. Response of CR, SD-NTL or NI for soft tissue, with bone response of PR, and BM response of CR, CR-MD, PR, MD, or NI.
3. Soft tissue response of PR; with bone response of CR or NI; and BM response of CR, CR-MD, PR, MD, or NI.
4. CR for soft tissue and bone response, with MD for bone marrow response

11.6.4 Progressive Disease (PD) includes either one of the following:

1. PD for at least one response parameter, including soft tissue, bone, and bone marrow response. If PD is found by one parameter, the other two parameters are not required to be evaluated to define an overall response of PD.
2. Treating physician grades patient as progressive disease based on clinical assessment without radiographic or bone marrow evaluations.

11.6.5 Stable disease (SD)

Response of stable disease for at least one parameter, with response of SD, NI, MD, or SD-NTL for other parameters.

11.6.6 Stable disease-Non-target lesions (SD-NTL)

Response of SD-NTL for soft tissue, with response of NI for bone and bone marrow.

11.6.7 Minor response (MR)

Complete response, Complete-MD response, and/or partial response for one parameter (i.e. soft tissue, bone, or bone marrow), with response of stable disease for a second parameter and any response other than PD for third parameter.

11.6.8 Minimal disease (MD)

Soft tissue and bone marrow responses are both NI, with bone marrow response of MD.

11.6.9 Not evaluable (NE)

Response of Not evaluable for one or more response parameters including soft tissue, bone, or bone marrow for any parameter that had sites evaluable for response at study enrollment. However, if one parameter is done and demonstrates PD this is defined as an overall response of PD. The SMC will review all patients where one or more parameters were graded as not evaluable, and make the final determination if the overall response is evaluable at that time point. In addition, response may be declared not evaluable if review by the Study Management Committee (SMC) that there is insufficient

data to grade response. The SMC may also declare response at a given time point evaluable if only one parameter is missing and was not involved at study enrollment.

11.6.10 No progression

Baseline status at enrollment was NI for soft tissue response, NI for bone marrow response, NI for bone response, and there has NOT been PD for any of the three parameters since on protocol therapy

11.6.11 Not done (ND)

Response not assessed at this time point. If only one parameter is not done at a given response time point, the SMC and PI will review and make the final determination if the overall response is evaluable at that time point.

11.6.12 Summary

The overall response as assessed at any particular time point based on consideration of each of the three parameters as defined above is summarized in the following table:

TABLE 33: RESPONSE CATEGORIZATION

SOFT TISSUE RESPONSE	BONE RESPONSE	BONE MARROW RESPONSE	OVERALL RESPONSE
CR	CR	CR	CR
NI	CR	CR	CR
CR	NI	CR	CR
NI	NI	CR	CR
CR	CR	CR-MD	CR
NI	CR	CR-MD	CR
CR	NI	CR-MD	CR
CR	CR	NI	CR
NI	CR	NI	CR
CR	NI	NI	CR
NI	NI	CR-MD	CR-MD
PR	CR	CR	PR
SD-NTL	CR	CR	PR
CR	PR	CR	PR
SD-NTL	PR	CR	PR
NI	PR	CR	PR
PR	NI	CR	PR
SD-NTL	NI	CR	PR
PR	CR	CR-MD	PR
SD-NTL	CR	CR-MD	PR
CR	PR	CR-MD	PR
PR	PR	CR-MD	PR
SD-NTL	PR	CR-MD	PR
NI	PR	CR-MD	PR
PR	NI	CR-MD	PR
SD-NTL	NI	CR-MD	PR
CR	CR	PR	PR
PR	CR	PR	PR
SD-NTL	CR	PR	PR
PR	PR	CR	PR
NI	CR	PR	PR
CR	PR	PR	PR
PR	PR	PR	PR
SD-NTL	PR	PR	PR
NI	PR	PR	PR
CR	NI	PR	PR
PR	NI	PR	PR
SD-NTL	NI	PR	PR
NI	NI	PR	PR
CR	CR	MD	PR
PR	CR	MD	PR
SD-NTL	CR	MD	PR
NI	CR	MD	PR
CR	PR	MD	PR

SOFT TISSUE RESPONSE	BONE RESPONSE	BONE MARROW RESPONSE	OVERALL RESPONSE
PR	PR	MD	PR
SD-NTL	PR	MD	PR
NI	PR	MD	PR
CR	NI	MD	PR
PR	NI	MD	PR
PR	CR	NI	PR
PR	PR	NI	PR
SD-NTL	CR	NI	PR
CR	PR	NI	PR
SD-NTL	PR	NI	PR
NI	PR	NI	PR
PR	NI	NI	PR
SD	CR	CR	MINOR
SD	PR	CR	MINOR
CR	SD	CR	MINOR
PR	SD	CR	MINOR
SD	SD	CR	MINOR
SD-NTL	SD	CR	MINOR
NI	SD	CR	MINOR
SD	NI	CR	MINOR
SD	CR	CR-MD	MINOR
SD	PR	CR-MD	MINOR
CR	SD	CR-MD	MINOR
PR	SD	CR-MD	MINOR
SD	SD	CR-MD	MINOR
SD-NTL	SD	CR-MD	MINOR
NI	SD	CR-MD	MINOR
SD	NI	CR-MD	MINOR
SD	CR	PR	MINOR
SD	PR	PR	MINOR
CR	SD	PR	MINOR
PR	SD	PR	MINOR
SD	SD	PR	MINOR
SD-NTL	SD	PR	MINOR
NI	SD	PR	MINOR
SD	NI	PR	MINOR
SD	CR	MD	MINOR
SD	PR	MD	MINOR
CR	SD	MD	MINOR
PR	SD	MD	MINOR
CR	CR	SD	MINOR
PR	CR	SD	MINOR
SD	CR	SD	MINOR
SD-NTL	CR	SD	MINOR
NI	CR	SD	MINOR
CR	PR	SD	MINOR
PR	PR	SD	MINOR
SD	PR	SD	MINOR
SD-NTL	PR	SD	MINOR
NI	PR	SD	MINOR
CR	SD	SD	MINOR
PR	SD	SD	MINOR
CR	NI	SD	MINOR
PR	NI	SD	MINOR
SD	CR	NI	MINOR
SD	PR	NI	MINOR
CR	SD	NI	MINOR
PR	SD	NI	MINOR
NI	NI	MD	MD
SD	SD	MD	SD
SD-NTL	SD	MD	SD
NI	SD	MD	SD
SD	NI	MD	SD
SD-NTL	NI	MD	MD
SD	SD	SD	SD

SOFT TISSUE RESPONSE	BONE RESPONSE	BONE MARROW RESPONSE	OVERALL RESPONSE
SD-NTL	SD	SD	SD
NI	SD	SD	SD
SD	NI	SD	SD
SD-NTL	NI	SD	SD
NI	NI	SD	SD
SD	SD	NI	SD
SD-NTL	SD	NI	SD
NI	SD	NI	SD
SD	NI	NI	SD
SD-NTL	NI	NI	SD-NTL
NI	NI	NI	NO PROGRESSION
PD	ANY	ANY	PD
ANY	PD	ANY	PD
ANY	ANY	PD	PD
NOT EVALUABLE	ANY EXCEPT PD	ANY EXCEPT PD	NOT EVALUABLE*
ANY EXCEPT PD	NOT EVALUABLE	ANY EXCEPT PD	NOT EVALUABLE*
ANY EXCEPT PD	ANY EXCEPT PD	NOT EVALUABLE	NOT EVALUABLE*
NOT EVALUABLE	NOT EVALUABLE	NOT EVALUABLE	NOT EVALUABLE*
NOT DONE	NOT DONE	NOT DONE	NOT DONE*
NOT DONE (and required at this time point)	ANY EXCEPT PD	ANY EXCEPT PD	NOT DONE*
ANY EXCEPT PD	NOT DONE (and required at this time point)	ANY EXCEPT PD	NOT DONE*
ANY EXCEPT PD	ANY EXCEPT PD	NOT DONE (and required at this time point)	NOT DONE*

** The Study Management Committee will review patients with overall response of Not Evaluable and/or Not Done to make the final determination of overall response.

12.0 ADVERSE EVENT REPORTING REQUIREMENTS

12.1 Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Please follow directions for routine reporting provided in the data collection packet for this protocol). Additionally, certain adverse events must be reported in an expedited manner to allow for timelier monitoring of patient safety and care. The following sections provide information about expedited reporting through the use of a written IND safety report (MedWatch) to the Food and Drug Administration (FDA).

Adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 4. A copy of the CTCAEv4 can be downloaded from the CTEP home page (http://ctep.cancer.gov).

12.2 Definitions

Adverse Event (AE): An adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected Adverse Reaction: Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the adverse event.

Unexpected Adverse Event or Unexpected Suspected Adverse Reaction: An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not available, is not consistent with the risk information described in the general investigational plan.

Serious Adverse Events (SAE) or Serious Suspected Adverse Reactions: An adverse event or suspected adverse reaction is considered serious if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

Table 34: Severe Adverse Events or Reactions	
Death of Patient	An event that results in the death of a patient.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization	An event that results in an admission to the hospital for any length of time. This does not include an emergency room visit or admission to an outpatient facility.
Prolongation of Hospitalization	An event that occurs while the study patient is hospitalized and prolongs the patient's hospital stay.
Congenital Anomaly	An anomaly detected at or after birth or any anomaly that result in fetal loss.

Persistent or Significant Disability/ Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study patient. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, or accidental trauma (*e.g.,* sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the patient and may require medical or surgical intervention to prevent any of the outcomes listed above (*i.e.,* death of patient, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Each death after initiating protocol therapy and within 30 days of completion of protocol therapy not due to tumor will be submitted to the NANT OPS as an SAE within 48 hours of learning of the death.

SAE reporting is required within 30 days after patient comes off protocol therapy regardless of attribution to protocol therapy.

12.3 Expedited Serious Adverse Event Reporting to NANT Operations

For any serious adverse event, both **expected and unexpected**:

1. Contact the Study Chairperson and the NANT Operations Center to alert them to the existence of the serious adverse event within 24 hours of learning of the event.
2. Within 48 hours of learning of the event, complete the NANT SAE form online through Medidata Rave. If access to Medidata Rave is unavailable for some reason, use the paper SAE form found on the NANT website (see NANT website (www.nant.org) and email to NANTstaff@chla.usc.edu.
3. Follow-up information should be submitted online in an updated report through Medidata Rave as soon as relevant information is available.

Copies of all serious adverse event reports will be kept on file in the NANT Operations Center. All NANT institutions are to file SAE reports with their Institutional Review Boards according to local institutional policy**.**

12.4 Expedited Adverse Event Reporting to the FDA

Per CFR 312.32 (c), the sponsor of the IND, Araz Marachelian, MD, must notify the FDA and all participating investigators in a written IND safety report of any adverse experience **associated with use of the drug** that is **both serious and unexpected.** Each written notification shall be made as soon as possible, and in no event later than **15 calendar** days after the sponsor's initial receipt of the information. Each written notification may be submitted on FDA Form 3500A (MedWatch) or in a narrative format and must bear prominent identification of its contents, i.e., "IND Safety Report". Follow-up information to a safety report should be submitted as soon as the relevant information is available.

The sponsor must also notify FDA **by telephone** or by **facsimile** transmission of any **unexpected fatal or life-threatening experience associated with use of the drug** in the clinical studies conducted under the IND as soon as possible but in no event later than **7 calendar** days after initial receipt of the information.

Each telephone call or facsimile transmission to the FDA shall be transmitted to the FDA division that has responsibility for review of the IND; a specific contact person is assigned to each IND at the time the application is filed, and this will be included in the FDA's correspondence acknowledging receipt of the IND application.

12.5 NANT Operations Center Role in Expedited Adverse Event Reporting to the FDA and Participating Sites

For purposes of this protocol, the MedWatch Report Form (FDA 3500A) will be submitted to the FDA by NANT on behalf of the IND sponsor, Araz Marachelian, MD. These forms will be submitted to the appropriate FDA division and will serve as the written IND safety report. The NANT Operations Center will file all expedited adverse event reports as well as other adverse events with the FDA and other relevant authorities or investigators. The IND sponsor, Araz Marachelian, MD, has also delegated to the NANT Operations Center the telephone/facsimile FDA notification responsibilities for unexpected fatal or life-threatening experiences. All IND submissions will be maintained in a master file at the NANT Operations Center.

<u>For Adverse Events associated with the use of the drug that are both Serious and Unexpected:</u>

1. The MedWatch form will be drafted by the NANT Operations Center based on the SAE form within 10 days of the adverse event and reviewed with PI at treating site and the study chair. Final MedWatch form will be submitted to FDA by NANT Operations Center. Electronic version of MedWatch form is available from NANT Operations Center or MedWatch website www.fda.gov/medwatch. NANT will forward the completed report to the FDA and other relevant authorities or investigators on behalf of the IND Sponsor, Araz Marachelian, MD.

2. Follow-up information should be submitted as soon as relevant information is available.

<u>For Adverse Events associated with the use of the drug that are Unexpected or Life Threatening:</u>

1. Notify the NANT Operations Center (who will notify the FDA and other relevant authorities and investigators) by telephone or fax as soon as possible but no later than 7 calendar days from the occurrence of the event.

   FDA PHONE: 1-800-332-1088
   FDA FAX: 1-800-332-0178

2. The MedWatch form will be drafted by the NANT Operations Center based on the SAE form within 10 days of the adverse event and reviewed with PI at treating site and the study chair. Final Medwatch form will be submitted to FDA and other relevant authorities or investigators by NANT Operations Center on behalf of the IND Sponsor, Araz Marachelian, MD.
3. Follow-up information should be submitted as soon as relevant information is available.

A cover letter to accompany the MedWatch report will be prepared by the NANT Operations Center in collaboration with the IND sponsor, Araz Marachelian, MD. The cover letter will be submitted with MedWatch report to the FDA and other NANT institutions and relevant authorities. Contents will include:

1. An assessment of the adverse event and its significance/relevance to the study. And the impact on the risk/benefit ratio of the study.
2. A statement as to whether this adverse event has been reported previously, and if so, whether the frequency is considered unusually high.
3. A statement as to whether the protocol and/or informed consent should reflect changes in the potential risks involved.

Copies of all adverse event reports will be kept on file in the NANT Operations Center. All NANT institutions are to file AE reports with their Institutional Review Boards according to local institutional policy.

12.6 Adverse event reporting requirements for Pfizer Inc.

NANT Operations Center will notify Pfizer, Inc. of all serious adverse events, both expected and unexpected, and a copy of all MedWatch forms and related correspondence within 24 hours of first awareness of an SAE.

12.7 Reporting Secondary AML/MDS

Within two weeks of an AML/MDS diagnosis or other secondary malignancy following treatment for cancer, submit the following to the NANT Operations Center:

1. A completed NANT SAE Form
2. A copy of the pathology report confirming the AML/MDS or other malignancy
3. A copy of the cytogenetics report (if applicable)

The NANT Operations Center will submit the form and accompanying reports to the FDA via MedWatch and to Araz Marachelian, MD (IND Sponsor). All NANT institutions are to file the secondary malignancy reports with their Institutional Review Boards according to local institutional policy.

12.8 Procedures for Reporting Drug Exposure during Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and must permanently discontinue study drug(s). All pregnancies and suspected pregnancies will be reported to by the NANT Operations Center (see Section 12.4 for contact information) immediately. If a female partner of a male patient becomes pregnant during the male patient's participation in this study, this must be reported to by the NANT Operations Center immediately.

13.0 RECORDS AND REPORTING

See separate Data Forms Packet which includes the data submission schedule in the member section on the NANT web site (www.NANT.org).

The following are required to be submitted for all patients entered:

1. Study case report forms, bone marrow reports (including aspirate and biopsy reports), urine catecholamine reports, and radiology reports (CT/MRI/MIBG/PET scans). Study case report form data is collected and accessed remotely through Medidata Rave. Disease response reports detail reports (CT/MRI, MIBG/PET, Bone marrow, urine catecholamines) are sent by email as electronic files to NANTCRF@chla.usc.edu at the end of each course of therapy.
2. For all patients on study, CT/MRI and MIBG/PET scans and bone marrow biopsy slides done as baseline tumor evaluation at study entry may be submitted for central review upon the request of the NANT Operations Center. Bone marrow aspirate slides will be submitted only upon the request of the NANT Operations Center.
3. For all patients who report an overall response of Complete Response and Partial Response, will submit all CT/MRI scans, MIBG scans, PET scans, and bone marrow biopsy slides done, for central review upon request by NANT Operations Center. For all patients who report an overall response of Minor Response and Stable Disease will submit the aforementioned imaging scans and bone marrow biopsy slides of involved disease sites for central review upon request by NANT Operations Center. Additional scans and bone marrow aspirate slides may also be requested by the NANT Operations Center to clarify response.
4. Radiology scans are submitted into NANT PACS electronic repository, which is managed by the ICL (Imaging Core Lab) at Children's Hospital Los Angeles. The Imaging CoreGrid DICOM Dropbox software is functional at all NANT sites and is used for all NANT clinical trials for central review of tumor response. (See NANT SOP regarding Central Review of Response Procedures for details).

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APPENDIX I: PERFORMANCE STATUS SCALES/SCORES

Performance Status Criteria Karnofsky and Lansky performance scores are intended to be multiples of 10					
ECOG (Zubrod)		**Karnofsky**		**Lansky***	
Score	Description	Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease	100	Fully active, normal.
		90	Able to carry on normal activity, minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours	60	Required occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play, able to participate in all quiet play and activities.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

*The conversion of the Lansky to ECOG scales is intended for NCI reporting purposes only.

APPENDIX II: BLOOD VOLUME SUMMARY FOR CORRELATIVE STUDIES

Blood volumes below are maximum values. For patients with a weight below the minimum required to tolerate all blood draws requested for correlative studies, please consult with study chair to determine prioritization of samples.

	Lorlatinib Pharmacokinetics			**Pharmacodynamic Studies (ctDNA)****	**Biology Study (NB5 Assay)***
	3.0 mL in K_2EDTA (lavender top)			8.5 mL in Streck Cell-Free DNA BCT tube	Refer to N04-05 protocol for collection requirements
Course	**Day**	**Sample Time Points**			
Entry (baseline)				17 mL	Blood & bone marrow aspirate
1	1	0 hour (pre-dose)	3.0 mL		
	1	1 hour	3.0 mL		
	1	2 hour	3.0 mL		
	2	24 hour (pre-2nd dose)	3.0 mL		
	15	Pre-dose; 1 hr; 2hr; 4hr; 6hr	3.0 mL		
2	End of course			17 mL	Blood & bone marrow aspirate
4	End of course			17 mL	Blood & bone marrow aspirate
6+ (corresponding with disease evaluations)	End of course			17 mL	Blood & bone marrow aspirate
End of therapy					Blood & bone marrow aspirate

*If > 10kg: four green tops (16ml); if < 10kg: three green tops (12ml). Bone marrow = two green tops (one for each side)

**When ctDNA and biology samples coincide, the priority is to collect the ctDNA first and if maximum volume of blood patient consented has not surpassed then collect biology sample.

APPENDIX III: DOSING NOMOGRAMS

Lorlatinib Dose Assignment:

Dose level -1

30 mg/m^2

(available in 5 mg, 25 mg tablets)

Daily Dose Given to a Patient			Number of Pills		
BSA (m^2)	Daily Dose (mg)	Equivalent Dose (mg/m^2)	#Pills 5 mg	#Pills 25 mg	#Pills Total
0.50 - 0.58	15	25.9-30	3	0	3
0.59 - 0.74	20	27 – 33.9	4	0	4
0.75 - 0.91	25	27.5-33.3	0	1	1
0.92-1.08	30	27.8-32.6	1	1	2
1.09-1.24	35	28.2-32.1	2	1	3
1.25-1.41	40	28.4-32	3	1	4
1.42-1.58	45	28.5-31.7	4	1	5
1.59-1.72	50	29.1-31.4	0	2	2
≥1.73	100	≤57.8	Treat on Cohort A2		

Lorlatinib Dose Assignment: Dose level 1

45 mg/m^2

(available in 5 mg, 25 mg tablets)

Daily Dose Given to a Patient			Number of Pills		
BSA (m^2)	**Daily Dose (mg)**	**Equivalent Dose (mg/m^2)**	**#Pills 5 mg**	**#Pills 25 mg**	**#Pills Total**
0.50 - 0.61	25	41.0 - 50.0	0	1	1
0.62 - 0.72	30	41.7 - 48.4	1	1	2
0.73 - 0.83	35	42.2 - 47.9	2	1	3
0.84 - 0.94	40	42.6 - 47.6	3	1	4
0.95 - 1.05	45	42.9 - 47.4	4	1	5
1.06 - 1.16	50	43.1 - 47.2	0	2	2
1.17 - 1.27	55	43.3 - 47.0	1	2	3
1.28 - 1.38	60	43.5 - 46.9	2	2	4
1.39 - 1.49	65	43.6 - 46.8	3	2	5
1.50 - 1.61	70	43.5 - 46.7	4	2	6
1.62 - 1.72	75	43.6 - 46.3	0	3	3
≥1.73	100	< 57.8	Treat on Cohort A2		

Lorlatinib Dose Assignment: Dose level 2

60 mg/m^2

(available in 5 mg, 25 mg tablets)

Daily Dose Given to a Patient			Number of Pills		
BSA (m^2)	**Daily Dose (mg)**	**Equivalent Dose (mg/m^2)**	**#Pills 5 mg**	**#Pills 25 mg**	**#Pills Total**
0.50 - 0.54	30	55.6 - 60.0	1	1	2
0.55 - 0.62	35	56.5 - 63.6	2	1	3
0.63 - 0.70	40	57.1 - 63.5	3	1	4
0.71 - 0.79	45	57.0 - 63.4	4	1	5
0.80 - 0.87	50	57.5 - 62.5	0	2	2
0.88 - 0.95	55	57.9 - 62.5	1	2	3
0.96 - 1.04	60	57.7 - 62.5	2	2	4
1.05 - 1.12	65	58.0 - 61.9	3	2	5
1.13 - 1.20	70	58.3 - 61.9	4	2	6
1.21 - 1.29	75	58.1 - 62.0	0	3	3
1.30 - 1.37	80	58.4 - 61.5	1	3	4
1.38 - 1.45	85	58.6 - 61.6	2	3	5
1.46 - 1.54	90	58.4 - 61.6	3	3	6
1.55 - 1.62	95	58.6 - 61.3	4	3	7
1.63 - 1.72	100	57.8 - 61.3	0	4	4
≥1.73	100	< 57.8	Treat on Cohort A2		

Lorlatinib Dose Assignment: Dose level 3

75 mg/m^2

(available in 5 mg, 25 mg tablets)

Daily Dose Given to a Patient			Number of Pills		
BSA (m^2)	**Daily Dose (mg)**	**Equivalent Dose (mg/m^2)**	**#Pills 5 mg**	**#Pills 25 mg**	**#Pills Total**
0.50 - 0.56	40	71.4 - 80.0	3	1	4
0.57 - 0.63	45	71.4 - 78.9	4	1	5
0.64 - 0.69	50	72.5 - 78.1	0	2	2
0.70 - 0.76	55	72.4 - 78.6	1	2	3
0.77 - 0.83	60	72.3 - 77.9	2	2	4
0.84 - 0.89	65	73.0 - 77.4	3	2	5
0.90 - 0.96	70	72.9 - 77.8	4	2	6
0.97 - 1.03	75	72.8 - 77.3	0	3	3
1.04 - 1.10	80	72.7 - 76.9	1	3	4
1.11 - 1.16	85	73.3 - 76.6	2	3	5
1.17 - 1.23	90	73.2 - 76.9	3	3	6
1.24 - 1.29	95	73.6 - 76.6	4	3	7
1.30 - 1.42	100	70.4 - 76.9	0	4	4
1.43 – 1.72	100	58.1 – 69.9	Treat on Cohorts A2 (only when A1 is open to dose level 3) or B1 or B2		
≥1.73	100	< 57.8	Treat on Cohort A2		

Lorlatinib Dose level 4 and 4B: 95 mg/m^2 (available in 5 mg, 25 mg tablets)

Daily Dose Given to a Patient			Number of Pills		
BSA (m^2)	Daily Dose (mg)	Equivalent Dose (mg/m^2)	#Pills 5 mg	#Pills 25 mg	#Pills Total
0.50 – 0.55	50	90.9 - 100	0	2	2
0.56 – 0.60	55	91.7 – 98.2	1	2	3
0.61 – 0.65	60	92.3 – 98.4	2	2	4
0.66 – 0.71	65	91.6 – 98.5	3	2	5
0.72 – 0.76	70	92.1 – 97.2	4	2	6
0.77 – 0.81	75	92.6 – 97.4	0	3	3
0.82 – 0.86	80	93.0 – 97.6	1	3	4
0.87 – 0.92	85	92.4 – 97.7	2	3	5
0.93 – 0.97	90	92.8 – 96.8	3	3	6
0.98 – 1.02	95	93.1 – 96.9	4	3	7
1.03 – 1.07	100	93.5 – 97.1	0	4	4
1.08 – 1.13	105	92.9 – 97.2	1	4	5
1.14 – 1.18	110	93.2 – 96.5	2	4	6
1.19 – 1.23	115	93.5 – 96.6	3	4	7
1.24 – 1.28	120	93.75 – 96.8	4	4	8
1.29 – 1.34	125	93.3 – 96.9	0	5	5
1.35 – 1.39	130	93.5 – 96.3	1	5	6
1.40 – 1.44	135	93.8 – 96.4	2	5	7
1.45 – 1.50	140	93.3 – 96.6	3	5	8
1.51 – 1.55	145	93.5 – 96.0	4	5	9
≥1.56	150	≤ 96.2	0	6	6

Lorlatinib Dose Level 5 and 5B: 115 mg/m^2 (available in 5 mg, 25 mg tablets)

Daily Dose Given to a Patient			Number of Pills		
BSA (m^2)	Daily Dose (mg)	Equivalent Dose (mg/m^2)	#Pills 5 mg	#Pills 25 mg	#Pills Total
0.50 – 0.54	60	111.1 – 120	2	2	4
0.55 – 0.58	65	112.1 – 118.2	3	2	5
0.59 – 0.63	70	111.1 – 118.6	4	2	6
0.64 – 0.67	75	111.9 – 117.2	0	3	3
0.68 – 0.71	80	112.7 – 117.6	1	3	4
0.72 – 0.76	85	111.8 – 118.1	2	3	5
0.77 – 0.80	90	112.5 – 116.9	3	3	6
0.81 – 0.84	95	113.1 – 117.3	4	3	7
0.85 – 0.89	100	112.4 – 117.6	0	4	4
0.90 – 0.93	105	112.9 – 116.7	1	4	5
0.94 – 0.97	110	113.4 – 117.0	2	4	6
0.98 – 1.02	115	112.7 – 117.3	3	4	7
1.03 – 1.06	120	113.2 – 116.5	4	4	8
1.07 – 1.10	125	113.6 – 116.8	0	5	5
1.11 – 1.15	130	113.0 – 117.1	1	5	6
1.16 – 1.19	135	113.4 – 116.4	2	5	7
1.20 – 1.23	140	113.8 – 116.7	3	5	8
1.24 – 1.28	145	113.3 – 116.9	4	5	9
1.29 – 1.32	150	113.6 – 116.3	0	6	6
1.33 – 1.36	155	114.0 – 116.6	1	6	7
1.37 – 1.41	160	113.5 – 116.8	2	6	8
1.42 – 1.45	165	113.8 – 116.2	3	6	9
1.46 – 1.50	170	113.3 – 116.4	4	6	10
1.51 – 1.54	175	113.6 – 115.9	0	7	7
1.55 – 1.58	180	114.0 – 116.1	1	7	8
1.59 – 1.63	185	113.5 – 116.4	2	7	9
1.64 – 1.67	190	113.8 – 115.9	3	7	10
1.68 – 1.71	195	114.0 – 116.1	4	7	11
≥1.72	200	≤ 116.3	0	8	8

APPENDIX IV: NEUROPSYCHOLOGICAL ADMINISTRATION PROCEDURES BY AGE GROUP

Age at Testing (Years: Months)	**Patient Testing/Self Report**	**Parent Report**	**Duration of Testing for Parents**	**Duration of Testing for Patients**
1:1 to 1:11	1. Bayley-III **(only at baseline, end of course 2, 6, 10 and then every 8 courses +/-5 days for duration of treatment)*	1. ABAS-3 *Parent/Primary Caregiver Form (Ages 0-5)* 2. PedsQL *Infant Scales (13-24 months)* *(standard neuropsych observation schedule)	~ 20 minutes	~ 60 - 90 minutes
2:0 – 2:11	1. Bayley-III **(only at baseline, end of course 2, 6, 10, and then every 8 courses +/- 5 days for duration of treatment)*	1. ABAS-3 *Parent/Primary Caregiver Form (Ages 0-5)* 2. BASC-3 *Parent Rating Scales-Preschool (Ages 2-5)* 3. BRIEF- *Preschool Version* 4. PedsQL Generic Version *– Parent Report for Toddlers (Ages 2-4)* 5. PedsQL *Multidimensional Fatigue Parent Report for Toddlers (Ages 2-4)* **(standard neuropsych observation schedule)*	~ 50 minutes	~ 60 - 90 minutes
3:0 – 4:11	1. Cogstate *(Detection, Identification)*	1. ABAS-3 *Parent/Primary Caregiver Form (Ages 0-5)* 2. BASC-3 *Parent Rating Scales-Preschool (Ages 2-5)* 3. BRIEF- *Preschool Version* 4. PedsQL Generic Version *– Parent Report for Toddlers (Ages 2-4)* 5. PedsQL Multidimensional Fatigue *– Parent Report for Toddlers (Ages 2-4)*		~ 10 minutes
5:0 – 5:11	1. Cogstate *(Detection, Identification)*	1. ABAS-3 *Parent/Primary Caregiver Form (Ages 0-5)* 2. BASC-3 *Parent Rating Scales-Preschool (Ages 2-5)* 3. BRIEF- *Preschool Version* 4. PedsQL Generic Version *– Parent Report for Young Children (Ages 5-7)* 5. PedsQL Multidimensional Fatigue *– Parent Report for*		

		Young Children (Ages 5-7)		
6:0 – 6:11	1. Cogstate *(Detection, Identification, One Card Learning, One Back, Groton Maze Learning Task)*	1. ABAS-3 *Parent Form (Ages 5-21)* 2. BASC-3 *Parent Rating Scales-Child (Ages 6-11)* 3. BRIEF 4. PedsQL Generic Version – *Parent Report for Young Children (Ages 5-7)* 5. PedsQL Multidimensional Fatigue – *Parent Report for Young Children (Ages 5-7)*	~ 50 minutes	
7:0-7:11	1. Cogstate *(Detection, Identification, One Card Learning, One Back, Groton Maze Learning Task)*	1. ABAS-3 *Parent Form (Ages 5-21)* 2. BASC-3 *Parent Rating Scales-Child (Ages 6-11)* 3. BRIEF 4. PedsQL Generic Version – *Parent Report for Young Children (Ages 5-7)* 5. PedsQL Multidimensional Fatigue – *Parent Report for Young Children (Ages 5-7)* 6. CSSRS – Children's Version	~ 50 – 55 minutes	
8:0-9:11	1. Cogstate *(Detection, Identification, One Card Learning, One Back, Groton Maze Learning Task)*	1. ABAS-3 *Parent Form (Ages 5-21)* 2. BASC-3 *Parent Rating Scales-Child (Ages 6-11)* 3. BRIEF 4. PedsQL Generic Version – *Parent Report for Children (Ages 8-12)* 5. PedsQL Multidimensional Fatigue – *Parent Report for Children (Ages 8-12)* 6. CSSRS – Children's Version		~ 30-40 minutes
10:0-11:11	1. Cogstate *(International Shopping List, Detection, Identification, One Card Learning, One Back, Groton Maze Learning Task, International Shopping List Delayed)*	1. ABAS-3 *Parent Form (Ages 5-21)* 2. BASC-3 *Parent Rating Scales-Child (Ages 6-11)* 3. BRIEF 4. PedsQL Generic Version – *Parent Report for Children (Ages 8-12)* 5. PedsQL Multidimensional Fatigue – *Parent Report for Children (Ages 8-12)* 6. CSSRS – Children's Version		~ 35-45 minutes
12:0 – 12:11	1. Cogstate	1. ABAS-3 *Parent Form (Ages 5-21)*		

	(International Shopping List, Detection, Identification, One Card Learning, One Back, Groton Maze Learning Task, International Shopping List Delayed)	*2.* BASC-3 *Parent Ratings Scales – Adolescent (Ages 12-21)* 3. BRIEF *4.* PedsQL Generic Version – *Parent Report for Children (Ages 8-12)* *5.* PedsQL Multidimensional Fatigue – *Parent Report for Children (Ages 8-12)* 6. CSSRS	~ 50-55 minutes	~ 35-45 minutes
13:0 – 17:11	1. Cogstate *(International Shopping List, Detection, Identification, One Card Learning, One Back, Groton Maze Learning Task, International Shopping List Delayed)*	1. ABAS-3 *Parent Form (Ages 5-21)* *2.* BASC-3 *Parent Ratings Scales – Adolescent (Ages 12-21)* 3. BRIEF *4.* PedsQL Generic Version – *Parent Report for Teens (Ages 13-18)* *5.* PedsQL Multidimensional Fatigue – *Parent Report for Teens (Ages 13-18)* 6. CSSRS		
18:0 – 25:11	1. Cogstate *(International Shopping List, Detection, Identification, One Card Learning, One Back, Groton Maze Learning Task, International Shopping List Delayed)* 2. ABAS-3 *Adult Self-Report Form (Ages 16-89)* 3. BASC-3 *Self-Report College (Ages 18-25)* 4. BRIEF - *Adult Self Report* 5. PedsQL Generic Version - *Young Adult Report (Ages 18-25)* 6. PedsQL Multidimensional Fatigue - *Young Adult Report (Ages 18-25)* 7. BDI-II 8. CSSRS	No Parent Reports	N/A	~80-90 minutes
≥26:0	1. Cogstate *(International Shopping List, Detection, Identification, One Card Learning, One Back, Groton Maze Learning Task, International Shopping List Delayed)* 2. ABAS-3 *Adult Self-Report Form (Ages 16-89)* 3. BRIEF - *Adult Self Report* 4. PedsQL Generic Version - *Adult Report (Ages* ≥26) 5. PedsQL Multidimensional Fatigue - *Adult Report (Ages* ≥26) 6. BDI-II 7. CSSRS			

APPENDIX V: SAMPLE TEMPLATE OF NEUROPSYCHOLOGICAL STATUS REPORT

Study Patient ID: _____ Date: _____ Post Cycle: _____

NEUROPSYCHOLOGICAL STATUS REPORT

☐ **Stable** – No decline in neuropsychological functioning.

☐ **Concern for Decline** – Some areas of concern warranting more frequent monitoring.

☐ **Significant Decline** – Decline in neuropsychological functioning.

Domain	Evidence of Decline			Severity Grading		
Cognitive Functioning	From baseline	From previous screen*	No decline	Mild	Moderate	Severe
Cognitive Disturbance	☐	☐	☐	☐	☐	☐
Concentration Impairment	☐	☐	☐	☐	☐	☐
Memory Impairments	☐	☐	☐	☐	☐	☐
Behavioral/Emotional Functioning	From baseline	From previous screen*	No decline	Mild	Moderate	Severe
Agitation	☐	☐	☐	☐	☐	☐
Anxiety	☐	☐	☐	☐	☐	☐
Depression	☐	☐	☐	☐	☐	☐
Suicidal Ideation	☐	☐	☐	☐	☐	☐

*Worsening Decline: Further neuropsychological decline from previous screening, indicating ___ periods of decline out of ___ screenings.

☐ **Improvement** – Improved neuropsychological functioning from previous screen.

☐Continue every cycle monitoring ☐Revert back to standard retest interval

COMMENTS:

Data Reviewed by: _____ _____
Kimberly Kayser, PhD, Neuropsychologist (Sign) Date

Form Submitted by: _____ _____
Clinical Research Coordinator (Sign) Date

Version 0.4 (10/20/2016)

APPENDIX VI: DOSE ESCALATION AND EXPANSION COHORT (A1 & B1) SAMPLE CONSENT

NANT 2015-02: PHASE 1 STUDY OF LORLATINIB (PF-06463922), AN ORAL SMALL MOLECULE INHIBITOR OF ALK/ROS1, FOR PATIENTS WITH ALK-DRIVEN RELAPSED OR REFRACTORY NEUROBLASTOMA

PHASE 1 DOSE ESCALATION & EXPANSION COHORT (A1 & B1): FOR PATIENTS ONE YEAR OF AGE UP TO 18 YEARS OF AGE

A New Approaches to Neuroblastoma Therapy (NANT) treatment protocol.

The word "you" used throughout this document refers to you or your child.

WHAT IS THIS STUDY ABOUT?
This study is a clinical trial, a type of research study. Clinical trials include only patients who choose to take part. Please take your time to make your decision about participating. You may discuss your decision with your friends, family, and health care team. If you have any questions, you may ask your doctor.

You are being asked to participate in this study because you have a kind of cancer called neuroblastoma. It may be that your cancer went away for a while but has grown back (relapsed) or it may be that it has never gone away (persistent or resistant tumor) after standard treatment. Standard treatment may have included chemotherapy, surgery, radiation therapy, high-dose chemotherapy with a stem cell transplant and/or immunotherapy.

WHY IS THIS STUDY BEING DONE?

The purposes of this study are:

- To find the highest safe dose of lorlatinib that can be given to children and adolescents with refractory or relapsed neuroblastoma without causing severe side effects.
- To learn about the side effects of the drug lorlatinib given at different dose levels to children and adolescents 1-18 years of age.
- To determine if your tumor gets smaller after treatment with lorlatinib.
- To measure the levels of lorlatinib in the blood at different dose levels.
- To look at genetic changes in tumor DNA found in the blood during treatment with lorlatinib.
- To look at genetic changes in tumor tissue to see if they affect response to lorlatinib.
- To describe the amount of neuroblastoma tumor found in the blood and bone marrow by testing samples with a new test (called NB5 assay).

The research is being done because:
Currently there is no known effective treatment for your type of cancer. We are testing new experimental drugs such as lorlatinib in the hopes of finding a drug that may be effective against neuroblastoma tumors that have come back (relapsed) or that have never gone away (persistent/refractory) after treatment with standard therapy.

This study involves the use of an experimental drug called lorlatinib. In laboratory testing, lorlatinib blocks the Anaplastic Lymphoma Kinase (ALK). ALK may be important in the growth of certain types of cancer cells, such as neuroblastoma. Lorlatinib is considered experimental because it has not been proven to work in a

situation like yours. Lorlatinib has been approved by the United States Food and Drug Administration (FDA) to treat adults with non-small cell lung cancer, a different cancer than yours. It is not approved for neuroblastoma. Lorlatinib has been used only in a small number of adults so there is a lot we do not know about it yet. Lorlatinib has not previously been used in children and adolescents not enrolled on this study. This study is called a phase 1 study because the goal is to find the highest dose of lorlatinib that we can give safely. Once we have found out the highest dose of lorlatinib that can be given safely, we will treat more children and adolescents with neuroblastoma with this Lorlatinib dose.

All patients enrolled on this phase 1 study have been previously tested and are known to have a defect in the ALK gene in their tumor before they start treatment. You or your doctor should have the results of this test before enrolling on this study.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

There will be about 60-75 patients enrolling on the 4 study cohorts. You have been given this consent because the planned enrollment is on cohort A1 or B1. When you join the study, you will be assigned a certain lorlatinib dose. This study will test up to five lorlatinib doses in groups of 3-6 patients. The starting lorlatinib dose for the first group of patients was about 25% lower than what was given to adults who received lorlatinib without bad side effects. If this is tolerated without serious side effects, then the lorlatinib dose will be increased in groups of 3-6 patients until the fifth dose level or if serious side effects are seen. At that point, investigators will have found the highest dose of lorlatinib that can be given without bad side effects. This part of the trial is called cohort A1.

Once the maximum tolerated dose is determined, another group of 6 patients will be enrolled and treated at this dose of lorlatinib, known as the dose expansion part of the study (Cohort B1). The purpose of the dose expansion part of the study is to gather more information about side effects seen in patients treated at the maximum tolerated dose of lorlatinib. The dose expansion cohort (Cohort B1) will not enroll patients until the dose escalation part of the study (Cohort A1) is completed and the highest dose of lorlatinib that can be given safely without serious side effects is found.

WHAT WILL HAPPEN TO ME IF I TAKE PART IN THIS STUDY?

Before You Begin the Study

Your doctor will have previously sent your tumor for genetic testing and these results showed your tumor has a defect in the *ALK* gene which allows you to be considered for participation in this study (Cohorts A1 and B1).

You will need to have the following exams, tests or procedures to find out if you can take part in the study. Most of these exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. These tests will also be done at various times throughout the study and at the end of the study. The purpose of these tests is to see how well the treatment works and to measure the status of your neuroblastoma. If you have had some of them recently, they may not need to be repeated. This will be up to your doctor.

A medical history & physical exam	Bone marrow tests[3] to check your tumor
Blood tests[1]	Various scans[4] to check your tumor
Pregnancy test (urine or blood)[2]	Electrocardiogram (EKG) to check the heart rhythm[5]
	Neuropsychological testing[6]

[1]Some blood tests (cholesterol and fat digestion [triglycerides]) may need to be done on an empty stomach, so you cannot eat or drink anything other than water for 8 hours before these tests are done (called fasting). Your doctor or nurse will tell you if it is necessary for you to fast before these blood tests are done.

[2]If you are a female at least 10 years old or who could have children, you will have a pregnancy test done by the doctor the week before starting treatment and then before each cycle of treatment begins. Both you and your parent/legal guardian will be informed of a positive pregnancy test. All men and women who could have children must either agree to practice abstinence from heterosexual intercourse or use two effective methods of birth control for as long as they participate in this study.

[3]Bone marrow tests are done by inserting a needle into the hip bone to remove the marrow which is inside the bone.

[4]Various scans are done for diagnosis and checking the response of the tumor to treatment. These may include CT and /or MRI scans and MIBG or PET scans. We will recommend scans specific for your case and we will answer your questions about these scans.

[5]Electrocardiogram (EKG) to document your heart rhythm before beginning lorlatinib treatment.

[6] Central nervous system effects (speech, memory and mood changes) were seen in previous studies treating adults with lorlatinib. Neuropsychological testing will be done within one week of starting treatment and at different times during this study to monitor for any changes in thinking skills, behavior and mood. Please see the section on Neuropsychological testing below in "During the Study" for more details on what tests are done and when they are done during this study.

<u>During the Study</u>

If the exams, tests and procedures show that you can be in the study, and you choose to take part, lorlatinib will be given for 28 days. This entire period is called a cycle with each treatment cycle being 28 days long. You may continue to take lorlatinib for an unlimited number of cycles unless you develop serious side effects or your tumor worsens.

One Treatment Cycle (Cohort A1: dose escalation group and Cohort B1: dose expansion group)			
Week 1	Week 2	Week 3	Week 4
Days 1 – 7	Days 8 - 14	Days 15 - 21	Days 22 - 28
Lorlatinib once a day →			

Lorlatinib will be given by mouth once a day followed by a small glass of water. If you vomit lorlatinib within 20 minutes of taking the dose for the day, that dose can be repeated. This is the only time a dose of lorlatinib can be repeated.

Lorlatinib will be available as a tablet. If you are unable to swallow the tablets whole, you will be instructed on how to make a liquid lorlatinib solution at home by mixing the lorlatinib tablets with water and a flavoring agent (Ora-Plus®). Your nurse or doctor will help you decide what is best for you and will make sure you have the proper directions for taking this medication.

You will be given a patient diary at the beginning of each cycle of lorlatinib. Use the diary to record the date and time you take the drug, all vomited and missed doses, side effects that you experience and any other medications and supplements you are taking. The diary should be returned to clinic along with the medication bottle (even if it is empty) weekly during cycle 1 and then after each treatment cycle of lorlatinib. This will help us to know how much of the drug you take and how it made you feel.

During the study you will have tests and procedures done to check for side effects from taking lorlatinib and to see how your tumor is doing. Many of these tests are part of regular cancer care but you may have them done more often because you are on the study:

Physical exam	Electrocardiogram (EKG) to test heart rhythm [3]
Blood tests [1]	Bone marrow tests & various scans (CT/MRI, MIBG or PET) to check your tumor [4]
Pregnancy test (urine or blood) [2]	Neuropsychological testing[5]

[1] Some blood tests (cholesterol and fat digestion) may be done on an empty stomach, so patients cannot eat or drink anything other than water for 8-10 hours before these tests are done.

[2] A urine or blood pregnancy test will be done before each treatment cycle begins if you are a female at least 10 years old or who could have children. Both you and your parent/legal guardian will be informed of a positive pregnancy test. All men and women who could have children must continue to practice abstinence from heterosexual intercourse or use two effective methods of birth control for as long as they participate in this study.

[3] Electrocardiogram (EKG) done before starting study treatment will be repeated at certain times during the study to document if lorlatinib treatment has any effect on heart rhythm.

[4] Bone marrow tests and various scans are done for checking the response of your tumor to treatment. These tests will be done at certain times during the study to look at response to lorlatinib and check that your tumor has not gotten worse.

[5] **Neuropsychological Testing**

Neuropsychological evaluations try to understand how changes in the health of the brain may affect behavior or mood and how well a person is able to pay attention, remember things or solve problems. Since effects on speech, memory and mood were seen in a small number of adults receiving lorlatinib, neuropsychological testing will be done to monitor for changes in thinking skills, behavior and mood at different times during this study. A table at the end of the consent lists how often neuropsychological testing will be done during the study. Testing methods are based on the age of the patient and include computerized tests using an iPad, written questionnaires and evaluations by a licensed psychologist. Parents or legal guardians of patients less than 18 years of age will also participate by completing written questionnaires at the same time their child is being tested.

If the testing results show areas of concern, you may be given more frequent testing as well as referrals for other care if needed. During testing, patients may skip questions that are stressful and may stop taking the tests at any time. Testing can be done as part of the clinic visit. You will need to talk with your doctor and nurse about scheduling to do these tests at times that are workable for you and your child.

- All patients 3 years of age and older will do computerized tests using an iPad. While the patient is taking these tests, the patient's parent or legal guardian will complete written questionnaires about the patient's mood and emotions, behavior, daily living/functional skills and social skills with others. The parent/legal guardian can be in the same room during the testing but they cannot help their child with their tests.
- Patients 18 years of age will complete computerized tests using an iPad and their own written questionnaires. Parents/Legal guardians do not have testing to do with patients of this age.
- Patients under 3 years of age will have an evaluation of overall functioning including language, motor and cognitive development done by a licensed psychologist. This testing will take 60 to 90 minutes to complete. Parents/legal guardians will also complete written questionnaires at the same time.

Patient age at testing in years	Testing being done	Length of testing time for Patients	Length of testing time for Parents/legal guardians
1	Patient: licensed psychologist Parent/legal guardian: written questionnaires	~ 60 - 90 minutes	~ 20 minutes
2			~ 50 minutes
3 - 5	Patient: computerized tests using an iPad Parent/legal guardian: written questionnaires	~ 10 minutes	~ 50 minutes
6		~ 30 – 40 minutes	~ 50 minutes
7 - 9		~ 30 – 40 minutes	~ 50 - 55 minutes
10 - 17		~ 35 – 45 minutes	~ 50 - 55 minutes
18	Patient: computerized tests using an iPad and written questionnaires	~ 80 – 90 minutes	NA

NANT Biology Study (NANT 2004-05)

If you choose to participate in this research, you will also be asked to join a companion NANT biology study to collect blood, bone marrow and tumor tissue (if available) and reports from radiology scans from patients with neuroblastoma. The biology study also provides a place (called NANT biorepository) where any leftover samples of tumor tissue or bone marrow and blood collected on this study could be transferred and stored. While you will be asked to join the Biology Study (NANT 2004-05), the decision to store/bank any leftover samples is optional and will not affect your ability to participate in this treatment study with Lorlatinib. Your doctor will talk with you in detail about the NANT biology study and have you sign a separate consent form.

Additional Tests in this Study

We would like to do some extra tests called pharmacokinetic studies and biologic studies. These tests will help us learn more about lorlatinib and may help children and adolescents who receive this drug in the future. The information learned would not change the way you are treated and the results of these tests will not be given to you. Some of these tests are required but others are optional meaning you can decide whether you want to do them or not.

Pharmacokinetic Studies: Determining Blood Levels of Lorlatinib – Required

During this study blood samples will be collected to determine how much lorlatinib is in your blood (called pharmacokinetics). About 3mL (just over half a teaspoon) of blood will be drawn with each sample. A total of 9 blood samples will be obtained over 3 separate days during course 1 (Day 1, Day 2 and Day 15). The total amount of blood drawn for testing will be about 27 mL (almost 5 ½ teaspoons). If you have a central line (such as a port or a Broviac) these samples can be drawn through that line or through a small tube placed in a vein in your hand or arm. This amount of blood is considered safe to donate. Samples will be sent to a commercial laboratory contracted to perform these tests for the study. These samples will be the property of Pfizer and Pfizer may also use the PK Biological Samples for evaluation of the bioanalytical method.

Other Biology Research Tests in this Study - Optional

You will be asked if you want to participate in 3 optional research tests. You can decide not to let the doctors do these tests and still be able to be treated as part of this study. There are checkboxes at end of this form to mark whether you are willing to participate in these voluntary studies. The results of these research tests will not be shared with you or become part of your medical record. These results would also not be used to make decisions about your care while enrolled on this study.

- **Using extra blood to look for genetic changes seen in tumor cells.**
  Tumor cells often release small pieces of DNA into the blood stream where it can be detected by sensitive tests. For this study, researchers would like to take almost 4 additional teaspoons of blood (17mL) at study entry and at each time a disease evaluation is done (after cycle 2, 4, 6 and then every 4th cycle after that) to look at what genetic changes in your tumor can be seen in your blood over time. The blood will be sent to a commercial laboratory for genetic testing.

- **Comparing genetic changes between leftover tumor from a surgical procedure prior to tumor relapse (at diagnosis or when you had surgery done after diagnosis) to relapsed neuroblastoma tumor tissue and bone marrow aspirates and whether these changes affect how the tumor will respond to treatment with Lorlatinib.**
  Researchers would like to look at tumor tissue to determine if there are certain gene changes present that might make your neuroblastoma more or less likely to respond to the drug lorlatinib. These tests would be done on tumor tissue remaining from diagnosis, or any previous surgery where tumor tissue was removed (removal of primary tumor or removal of tumor at a relapse) in the past. The tissue and bone marrow aspirates will be sent to a research laboratory at Children's Hospital of Philadelphia for testing.

When You Have Finished Treatment with Lorlatinib

After you stop treatment on this study, you will continue to have tests and scans done (listed below) to measure how much tumor is left. If test results show you have abnormal organ function, tests are recommended by the study to be repeated monthly until test results are stable or normal. You doctor will tell you how often these tests and evaluations will be done.

Medical Tests after the Study:

Physical exam	Neuropsychological testing[1]
Blood tests	Bone marrow tests & various scans to check your tumor[2]
Electrocardiogram (EKG) to check the heart rhythm[3]	

[1]The same neuropsychological testing and evaluation done before starting study treatment will be done at the end of treatment with lorlatinib. The need for any further testing after this will be up to your doctor.

[2]Bone marrow tests and various scans (CT/MRI, MIBG or PET) are done for checking the response of your tumor to treatment. These tests will be done at the end of a course and at certain times following treatment to monitor your tumor status.

[3] Electrocardiogram (EKG) done at the end of the study to document if lorlatinib treatment has any effect on heart rhythm.

A table detailing the tests and procedures required before, during and after the study has been attached to the end of this consent (Consent Addendum 1).

HOW LONG WILL I BE ON THIS STUDY?

You can get an unlimited number of treatment cycles with lorlatinib as long as you are not having bad side effects and as long as your tumor is not getting worse.

After you stop treatment, you will continue to have tests and scans done to measure how much tumor is left. Your doctor will tell you how often these tests will be done. Researchers will continue to collect information about you for a lifetime. Information will be collected about whether you are still alive; whether your tumor has grown back and at what sites in the body; whether you have developed any side effects from the treatment;

or whether you have developed any additional cancer. Your doctor will give the researchers this information at regular intervals.

CAN I STOP BEING IN THE STUDY?
Yes. If you are thinking about stopping your participation on this study, you should talk to your doctor before making a final decision so he/she can tell you how to do this safely.

Your doctor may also stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow study rules; or if the study is stopped.

WHAT ARE THE RISKS OF THE STUDY?
This is a Phase 1 study. A Phase 1 study looks at how common and serious side effects can be for each patient at a specific dose of a drug. In a Phase 1 study, some patients may have very serious side effects and could die as a result of these side effects. You may be one of those patients who have serious side effects as a result of participating in this Phase 1 study.

In this study, researchers will be looking at side effects seen in patients taking different doses of lorlatinib. Since subjects will be assigned to different dose levels of lorlatinib, some subjects may receive doses that are too small to be effective while others may receive higher doses that may cause increased side effects.

Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Other drugs may be given to make side effects less serious and more comfortable (such as for nausea, headache or reaction to lorlatinib). Many side effects go away soon after you stop taking the study medications but it is always possible that side effects can be serious, long lasting or may never go away. There is also a risk of death. Patients are watched carefully and treatment will be stopped if bad side effects develop. There may also be risks we do not know about. You should talk to your doctor about any side effects that you have while taking part in this study.

While on the study, you are at risk for the side effects listed below:

Possible Risks of Lorlatinib

The following side effects are considered to be related to lorlatinib have been reported:

Very Common (may affect 10 or more in 100 people)	**Common** (may affect from 1 up to less than 10 in 100 people)
• Increase in cholesterol and triglycerides (fats in your blood) • Effects on mood (for example, irritability and mood swings) • Effects on memory (for example, confusion, memory loss and disturbance of attention) • Effects on the peripheral nerves which are those outside of the brain and spinal cord, including tingling, numbness or pain in hands and feet) • Changes in vision (including double vision, perceived flashes or floaters of light, light intolerance, vision blurred, vision sharpness reduced and visual impairment) • Hypertension • Diarrhea • Constipation • Joint pain • Build-up of fluid in the body or extremities causing swelling (edema) • Fatigue (feeling tired and exhausted) • Increase in body weight • Increase in blood sugar levels	• Hallucination and loss of contact with reality • Changes in mental status • Changes in speech (for example, slow speech or slurred speech) • Inflammation of the lungs (pneumonitis) which can cause shortness of breath and difficulty breathing. If severe, this can be life threatening.

The following events have also been reported in patients while they were taking lorlatinib, although the relationship to lorlatinib is uncertain:

Very common (may affect 10 or more in 100 people)

- Abnormalities in blood tests that may indicate liver damage
- Abnormal pancreas tests
- Decrease in hemoglobin in the blood that can cause weakness
- Headache
- Muscle pain
- Difficulty sleeping
- Rash

Common (may affect from 1 up to less than 10 in 100 people)

- Decrease of ejection fraction of the heart which may indicate severe heart problem
- A sudden and temporary loss of consciousness (syncope)
- Changes in the electrical activity of your heart that might lead to a heart rhythm problem and/or irregular heartbeat

Uncommon (may affect less than 1 in 100 people)

- Inflammation of the pancreas causing pain in the upper abdomen. This could become severe and may cause nausea and vomiting, fever and rapid heart rate. This could require hospitalization and may be life threatening
- Suicidal thoughts
- Psychosis

Lorlatinib has moderate influence on the ability to drive and use machines. Caution should be exercised when driving or operating machines as patients may experience CNS effects.

Possible Risks to Unborn Child

Patients who agree to participate in this study should not become pregnant while on this study. Lorlatinib may cause fetal harm when administered to a pregnant woman and is not recommended during pregnancy or for women of childbearing potential not using contraception. Women of childbearing potential should use nonhormonal methods of birth control. If a hormonal method of birth control is unavoidable, then a condom must be used in combination with the hormonal method. Female patients must continue to follow these birth control guidelines for 21 days after finishing the study. Male patients must wear condoms as one of their forms of birth control for the duration of the study and for 97 days after finishing the study. Further contraception use should be discussed with your personal physician. If you or your partner becomes pregnant while you are participating in this study, please notify your doctor immediately. For more information about risks and side effects, ask your doctor.

Possible Long Term Side Effects of Treatment with Lorlatinib
Side effects in adults treated with lorlatinib have occurred while patients have been receiving the drug or shortly after finishing the drug. It is not known if some side effects may be seen only after a long time after finishing treatment with lorlatinib.

Possible Risks from Having Blood Drawn
The risks from having your blood taken are minimal, but can include an infection or a blood clot. Experienced doctors or nurses will perform these blood draws to minimize this risk.

Unknown Risks
The treatment may have side effects that no one knows about yet. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?
There may or may not be direct medical benefit to you. The information learned from this study may or may not benefit other children or young people with solid cancers in the future.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THIS STUDY?
There are other options for you instead of this treatment. Instead of being in this study, you have these options:

- Treatment with other chemotherapy medicines
- Treatment with other experimental agents that may be available
- No neuroblastoma therapy at this time, with care to help you feel more comfortable

Please talk about these options with your doctor.

WILL MY MEDICAL INFORMATION BE KEPT PRIVATE?
We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance and data analysis include:

- New Approaches to Neuroblastoma Therapy (NANT) Consortium at Children's Hospital Los Angeles in Los Angeles, CA. The NANT Consortium identifies you by a number.
- Independent auditor evaluating quality assurance for the NANT Consortium.
- The National Cancer Institute (NCI) and other governmental agencies, like the Food and Drug Administration (FDA), Health Canada, or European regulatory agency(ies) involved in keeping research safe for people.
- Foundation Medicine, Inc. who is a collaborator on this study.
- Pfizer Inc., the pharmaceutical company which makes lorlatinib.

NANT has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. Information about the certificate is included at the end of this consent.

Because this study involves the treatment of a medical condition, a copy of this consent form will be placed in your medical record. This will allow the doctors that are caring for you to obtain information about what medications or procedures you are receiving in the study and treat you appropriately.

WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?
Taking part in this study may lead to added costs to your insurance company. Your health insurance company will be billed for many expenses associated with the costs of this study. These expenses include medications, treatments, hospital charges, and doctors' fees related to your participation in this study.

Lorlatinib and the flavoring agent (Ora-Plus®) are being provided free of charge for use in this study, but the costs associated with administering the drug is normally covered by your insurance company. The cost of doing a heart test called an EKG and neuropsychological testing at several time points during your participation in the study with lorlatinib is being done as part of research and will be paid for by the study. The special research blood and tissue studies will be done at no cost to you. However, you or your health plan may need to pay for the costs of the supplies and personnel who draw the blood from you for these tests.

You may have to pay for other things during this study, such as but not limited to, your time, the cost of food you buy while you are being treated at the hospital, car fare, travel to and from the hospital for treatment, parking, and baby sitter fees.
Taking part in this study may lead to added costs that may not be covered by your insurance company. Please ask about any expected added costs or insurance problems.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's website at http://cancer.gov/clinicaltrials/understanding/insurance-coverage . You can print a copy of the "Clinical Trials and Insurance Coverage" information from this website.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?
It is important that you tell your study doctor, _____ *[investigator's name(s)]* if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number].*

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

WHAT ARE MY RIGHTS AS A STUDY PARTICIPANT?
Taking part in this study is your choice. You may choose not to take part or not take part in the study. If you decide to take part in this study, you may remove yourself from the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. If you remove yourself from the study, we will still take care of you. We will explain what stopping the treatment may do and we will offer other treatments if they are available.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In case of injury resulting from this study, you do not lose any of you legal rights to seek payment by signing this form.

A Data Safety and Monitoring Board, an independent group of experts, will be reviewing data from this research throughout the study. We will tell you about new information from this Board or other studies that may affect your health or willingness to stay in the study.

WHO CAN ANSWER MY QUESTIONS ABOUT THE STUDY?
You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number].*
For questions about your rights while taking part in this study, call the _____ *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ *(telephone number).*

WHO IS FUNDING THIS RESEARCH STUDY?
This study is supported by Pfizer, Inc. Pfizer is a drug company that makes the drug being studied in this research project. Pfizer is giving money to Children's Hospital for some of the costs of the study. The results of the study will be reported to Pfizer. If the study shows that lorlatinib may be useful for a new purpose, this could benefit Pfizer financially.

The Children's Hospital Los Angeles/NANT is also providing funding for this study.

Dr. Mossé at Children's Hospital of Philadelphia, one of the principal investigators of this study, has served as a paid consultant to Pfizer. Her participation in this research has been reviewed and approved, subject to management, according to CHOP's/NANT Conflict of Interest Policy.

WHERE CAN I GET MORE INFORMATION?

You may call the NCI's **Cancer Information Service** at

1–800–4–CANCER (1–800–422–6237) or **TTY: 1–800–332–8615**

You may visit the NCI Web sites at http://cancer.gov/
For NCI's clinical trials information, go to http://cancer.gov/clinicaltrials/
For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

You will get a copy of this consent form. If you want more information about this study, ask your doctor.

CONSENT FOR EXTRA STUDIES FOR RESEARCH

The following tests are optional for all patients in the study. You may still participate in the study even if you do not agree to these tests.

1. **Using extra blood to look for genetic changes seen in tumor cells**

   Initial next to YES if you agree to let researchers take almost 4 extra teaspoons (17mL) at study entry and each time a disease evaluation is done) to look at what genetic changes in your tumor can be seen in your blood over time before and after treatment with lorlatinib. This blood would be drawn at a time when blood was being drawn for clinical purposes. The blood will be sent to Foundation Medicine Inc. for analysis who is a collaborator on the study. The results of these tests will be confidential and not made available to you or your treating physician.

   Initial next to NO, if you do not want researchers to take extra blood above what is needed for clinical purposes.

   _____Yes _____No

2. **Comparing genetic changes between tumor leftover from a surgical procedure prior to relapse (diagnosis or second look) to relapsed neuroblastoma tumor tissue and bone marrow aspirates and whether these changes affect how the tumor will respond to treatment with lorlatinib.**

   Initial next to YES, if you agree (and if there is tumor remaining) to let this tumor be sent to a laboratory so researchers can compare these samples and determine if there are certain gene changes present that might make your neuroblastoma more or less likely to respond to the drug lorlatinib. The results of these tests will be confidential and not made available to you or your treating doctor.

   Initial next to NO if you do not want leftover tumor from an earlier procedure to be sent to a research laboratory to look for certain gene changes that might make your neuroblastoma more or less likely to respond to the drug lorlatinib.

   _____Yes _____No

   Initial next to YES, if you agree to let extra bone marrow aspirates be collected to be sent to a laboratory so researchers can compare these samples and determine if there are certain gene changes present that might make your neuroblastoma more or less likely to respond to the drug lorlatinib. The results of these tests will be confidential and not made available to you or your treating doctor.

   Initial next to NO if you do not want these bone marrow aspirates collected to be sent to a research laboratory to look for certain gene changes that might make your neuroblastoma more or less likely to respond to the drug lorlatinib.

   _____Yes _____No

STATEMENT OF CONSENT

I have already read the information in this informed consent document. I have read all the attachments that were included with this informed consent document. I have asked all of my questions and I have gotten answers. I agree to enroll myself (my child) in this study.

_____
Print Patient Name

_____ _____/_____/_____
Print Name of Parent or Guardian Date

_____ _____/_____/_____
Signature of Parent or Guardian Date

_____ _____/_____/_____
Signature of Patient (If > 7 years old) Date

_____ _____/_____/_____
Signature of Physician or Date
Responsible Investigator

_____ ____/_____/_____
Signature of Witness Date

_____ ____/_____/_____
Signature of Translator Date

Consent Addendum I: Tests That Will Be Done On This Study

Observation	Before Entry	Cycle 1	Cycle 2	Subsequent Cycles	End of Therapy
Physical exam including neurological exam	X	Weekly	Start of cycle	Start of each cycle	X
Routine Blood tests** (Blood counts, electrolytes, liver, kidney function, function of pancreas- amylase/lipase)	X	Weekly	Weekly for blood counts and twice during cycle for all other blood tests	Start of each cycle	X
Routine Blood tests** (Fasting cholesterol, triglycerides, glucose)	X	Every other week	Start of cycle	Start of each cycle	X
Hemoglobin A1c (HbA1c)	X		Start of cycle	With Disease Evaluations in Courses 4 and 6 and after every 4 courses thereafter	X
Pregnancy test (All females 10 years of age and older)	X		Start of cycle	Start of each cycle	
Heart rhythm test (EKG)	X	One hour after day 1 treatment is finished	End of cycle	End of cycle (4,6 and every 4th cycle thereafter)	X
Neuropsychological Testing	Within one week before starting treatment	End of cycle	End of cycle	End of cycle (4,6 and every 4th cycle thereafter)	X
Neuropsychological evaluation with licensed psychologist for patients less than 3 years of age	Within one week before and up to two weeks after starting treatment		End of cycle	End of cycle 6, 10 and then every 8 cycles thereafter	X
Submit Patient Treatment Diaries		X	X	X	X
Blood for Lorlatinib drug level tests (PK - Required)		Day 1: 3 times Day 2: 1 time Day 15: 5 times			
Blood for circulating tumor cells (Optional)	X		With disease evaluation	End of cycle (4,6, and every 4th cycle thereafter)	
Bone Marrow Aspirate (Optional)	X		With disease evaluation	End of cycle (4,6, and every 4th cycle thereafter)	
Sampling of leftover tumor tissue (Optional)	Leftover tumor tissue can be sent at any time during the study				

	Tests done during Disease Evaluation				
Bone marrow aspirate and biopsy	X		Week 4	End of cycle (4,6 and every 4th cycle thereafter)	X
CT/MRI scans and/or MIBG/PET scans					
Blood and bone marrow for NANT Biology study[#]					

[#] Patients enrolled in the companion biology study may have additional samples of blood and bone marrow collected at study entry and with each disease evaluation time point. Please look at the biology study N04-05 consent form for more information

**Blood draws can be done more often if needed at the discretion of your study doctor

Consent Addendum II
Certificate of Confidentiality Information

NANT has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. The Certificate protects against the involuntary release of information about subjects collected during the course of our covered studies. The researchers involved in the studies cannot be forced to disclose the identity or any information collected in the study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, the subject or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if the subject or his/her guardian requests the release of information in writing, the Certificate does not protect against that voluntary disclosure. Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act. The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

APPENDIX VII: LORLATINIB IN COMBINATION WITH CONVENTIONAL CHEMOTHERAPY (COHORT B2) SAMPLE CONSENT

NANT 2015-02: PHASE 1 STUDY OF LORLATINIB, AN ORAL SMALL MOLECULE INHIBITOR OF ALK/ROS1, FOR PATIENTS WITH ALK-DRIVEN RELAPSED OR REFRACTORY NEUROBLASTOMA

LORLATINIB IN COMBINATION WITH CONVENTIONAL CHEMOTHERAPY (COHORT B2): FOR PATIENTS ONE YEAR OF AGE THROUGH 30 YEARS OF AGE

A New Approaches to Neuroblastoma Therapy (NANT) treatment protocol.

The word "you" used throughout this document refers to you or your child.

WHAT IS THIS STUDY ABOUT?
This study is a clinical trial, a type of research study. Clinical trials include only patients who choose to take part. Please take your time to make your decision about participating. You may discuss your decision with your friends, family, and health care team. If you have any questions, you may ask your doctor.

You are being asked to participate in this study because you have a kind of cancer called neuroblastoma. It may be that your cancer went away for a while but has grown back (relapsed) or it may be that it has never gone away (persistent or resistant tumor) after standard treatment. Standard treatment may have included chemotherapy, surgery, radiation therapy, high-dose chemotherapy with a stem cell transplant and/or immunotherapy.

WHY IS THIS STUDY BEING DONE?

The purposes of this study are:

- To find the highest safe dose of lorlatinib that can be given to children, adolescents and adults with refractory or relapsed neuroblastoma without causing severe side effects.
- To learn about the side effects of the drug lorlatinib when given in combination with cyclophosphamide and topotecan) in children, adolescents and adults.
- To determine if your tumor gets smaller after treatment with lorlatinib when given in combination with cyclophosphamide and topotecan.
- To measure the levels of lorlatinib in the blood when given together with cyclophosphamide and topotecan in children and adolescents.
- To look at genetic changes in tumor DNA found in the blood during treatment.
- To look at genetic changes in tumor tissue to see if they affect response to lorlatinib.
- To describe the amount of neuroblastoma tumor found in the blood and bone marrow by testing samples with a new test (called NB5 assay).

The research is being done because:
Currently there is no known effective treatment for your type of cancer. We are testing new experimental drugs such as lorlatinib in the hopes of finding a drug that may be effective against neuroblastoma tumors that have come back (relapsed) or that have never gone away (persistent/refractory) after treatment with standard therapy. This part of the study will combine three drugs: lorlatinib, cyclophosphamide and topotecan. You may have taken cyclophosphamide and/or topotecan before (but not all three together) for treatment of your neuroblastoma.

This study involves the use of an experimental drug called lorlatinib. In laboratory testing, lorlatinib blocks the Anaplastic Lymphoma Kinase (ALK). ALK may be important in the growth of certain types of cancer cells such as neuroblastoma. Lorlatinib is considered experimental because it has not been proven to work in a situation like yours. Lorlatinib has been approved by the United States Food and Drug Administration (FDA) to treat adults with non-small cell lung cancer, a different cancer than yours. It is not approved for neuroblastoma. Lorlatinib has been used only in a small number of adults so there is a lot we do not know about it yet. Lorlatinib has not previously been used in children and adolescents not enrolled on this study.

Cyclophosphamide and topotecan are chemotherapy drugs that are FDA-approved for the treatment of certain adult cancers, but have not been approved to treat children with neuroblastoma. These drugs have been used in combination to treat many children with neuroblastoma and in some patients this combination has reduced the amount of neuroblastoma present. Even if you have previously received treatment with cyclophosphamide and topotecan, you can still participate in this study.

All patients enrolled on this study are known to have a defect in the ALK gene in their tumor before they start treatment. You or your doctor should have the results of this test before being able to enroll on this study.

A dose of lorlatinib that can be given safely to children and adolescents was chosenfrom the dose escalation part of the study. Lorlatinib has not been given in combination with chemotherapy in patients with childhood tumors. In this part of the study, we will test the dose of lorlatinib that can be given safely in combination with cyclophosphamide and topotecan to children, adolescents and adults up to age 30 with relapsed/refractory neuroblastoma. After 4 cycles of chemotherapy, you and your physician may decide to stop the chemotherapy and continue lorlatinib without the chemotherapy.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?
There will be about 60-75 patients enrolling on the 4 study cohorts. Of this number, about 12-18 children and adolescents and adults up to age 30 will be enrolled on this part of the study where lorlatinib is given together with cyclophosphamide and topotecan).

WHAT WILL HAPPEN TO ME IF I TAKE PART IN THIS STUDY?

Before You Begin the Study
Your doctor will have previously sent your tumor for genetic testing and these results showed your tumor has a defect in the *ALK* gene which allows you to be considered for participation in this study (Cohort B2).

You will need to have the following exams, tests or procedures to find out if you can take part in the study. Most of these exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study.
These tests will also be done at various times throughout the study and at the end of the study. The purpose of these tests is to see how well the treatment works and to measure the status of your neuroblastoma. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

A medical history & physical exam	Bone marrow tests[3] to check your tumor
Blood tests[1]	Various scans[4] to check your tumor
Pregnancy test (urine or blood)[2]	Electrocardiogram (EKG) to check the heart rhythm[5]
	Neuropsychological testing[6]

[1]Some blood tests (cholesterol and fat digestion [triglycerides]) may need to be done on an empty stomach, so you cannot eat or drink anything other than water for 8 hours before these tests are done (called fasting). Your doctor or nurse will tell you if it is necessary for you to fast before these blood tests are done.

[2]If you are a female at least 10 years old or who could have children, you will have a pregnancy test done by the doctor the week before starting treatment and then before each cycle of treatment begins. Both you and your parent/legal guardian (if applicable) will be informed of a positive pregnancy test. All men and women who could have children must either agree to practice abstinence from heterosexual intercourse or use two effective methods of birth control for as long as they participate in this study.

[3]Bone marrow tests are done by inserting a needle into the hip bone to remove the marrow which is inside the bone.

[4]Various scans are done for diagnosis and checking the response of the tumor to treatment. These may include CT and /or MRI scans and MIBG or PET scans. We will recommend scans specific for your case and we will answer your questions about these scans.

[5]Electrocardiogram (EKG) to document your heart rhythm before beginning lorlatinib treatment.

[6]Central nervous system effects (speech, memory and mood changes) were seen in previous studies treating adults with Lorlatinib. Neuropsychological testing will be done at within one week of starting treatment and at different times during this study to monitor for any changes in thinking skills, behavior and mood. Please see the section on Neuropsychological testing below in "During the Study" for more details on what tests are done and when they are done during this study.

During the Study

If the exams, tests and procedures show that you can be in the study, and you choose to take part, lorlatinib will be given once a day for 28 days and will be given together with cyclophosphamide/topotecan on the first 5 days. This entire period is called a cycle with each treatment cycle being 28 days long. You may continue to receive treatment with lorlatinib and cyclophosphamide/topotecan for up to 24 cycles or indefinitely if you are no longer receiving chemotherapy unless you develop serious side effects or your tumor worsens.

One Treatment Cycle **Cohort B2: Lorlatinib with chemotherapy**									
Week 1							Week 2	Week 3	Week 4
Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Days 8-14	Days 15 -21	Days 22-28
***Lorlatinib once a day** →									
CPM	CPM	CPM	CPM	CPM					
TOPO	TOPO	TOPO	TOPO	TOPO	MGF				

CPM: Cyclophosphamide
TOPO: Topotecan
MGF: Myeloid growth factor
*Lorlatinib should be given at least one hour before chemotherapy on days 1-5 of each cycle.

Lorlatinib

Lorlatinib will be given by mouth once a day followed by a small glass of water. Lorlatinib should be given at least one hour before chemotherapy on days 1 – 5 of each cycle. If you vomit lorlatinib within 20 minutes of taking the dose for the day, that dose can be repeated. This is the only time a dose of lorlatinib can be repeated.

Lorlatinib will be available as a tablet. If you are unable to swallow the tablets whole, you will be instructed on how to make a liquid lorlatinib solution at home by mixing the lorlatinib tablets with water and a flavoring agent (Ora-Plus®). Your nurse or doctor will help you decide what is best for you and will make sure you have the proper directions for taking this medication.

You will be given a patient diary at the beginning of each cycle of lorlatinib. Use the diary to record the date and time you take the drug, all vomited and missed doses, side effects that you experience and any other medications and supplements you are taking. The diary should be returned to clinic along with the medication bottle (even if it is empty) weekly during cycle 1 and then at the end of each treatment cycle. This will help us to know how much of the drug you take and how it made you feel.

Cyclophosphamide & Topotecan

You will receive both cyclophosphamide and topotecan into the bloodstream (either through your central line or through a small tube placed in a vein in your hand or arm) on days 1 through 5 of each cycle. You will receive each medicine over 30 minutes and the cyclophosphamide will be given first. These medicines are typically given in the clinic. You may stop cyclophosphamide and topotecan after 4 courses after discussion with your physician if it is deemed to be in your interest.

Myeloid Growth Factor

In addition, you will be given a medicine to help boost your white blood cell count. White blood cells help fight infection and having low white blood cells can increase your risk of developing an infection. This drug will be started on day 6 of each treatment cycle if you receive chemotherapy. Filgrastim or G-CSF is a shot given into the skin each day until the white blood cell count increases. Pegfilgrastim is a long-acting version of Filgrastim that is given as shot into the skin just once on day 6 of the cycle. Your doctor will talk with you about which of these study drugs you will receive.

During the study you will have tests and procedures done to check for side effects from taking lorlatinib in combination with chemotherapy and to see how your tumor is doing. Many of these tests are part of regular cancer care but you may have them done more often because you are on the study:

Physical exam	Electrocardiogram (EKG) to test heart rhythm [3]
Blood tests [1]	Bone marrow tests & various scans (CT/MRI, MIBG or PET) to check your tumor [4]
Pregnancy test (urine or blood) [2]	Neuropsychological testing [5]

[1] Some blood tests (cholesterol and fat digestion) may be done on an empty stomach, so patients cannot eat or drink anything other than water for 8-10 hours before these tests are done.

[2] A urine or blood pregnancy test will be done before each treatment cycle begins if you are a female at least 10 years old or who could have children. Both you and your parent/legal guardian will be informed of a positive pregnancy test. All men and women who could have children must continue to practice abstinence from heterosexual intercourse or use two effective methods of birth control for as long as they participate in this study.

[3] Electrocardiogram (EKG) done before starting study treatment will be repeated at certain times during the study to document if lorlatinib treatment has any effect on heart rhythm.

[4] Bone marrow tests and various scans are done for checking the response of your tumor to treatment. These tests will be done at certain times during the study to look at response to lorlatinib and check that your tumor has not gotten worse.

[5]**Neuropsychological Testing**

Neuropsychological evaluations try to understand how changes in the health of the brain may affect behavior or mood and how well a person is able to pay attention, remember things or solve problems. Since effects on speech, memory and mood were seen in a small number of adults receiving lorlatinib, neuropsychological testing will be done to monitor for changes in thinking skills, behavior and mood at different times during this study. Testing methods are based on the age of the patient and include computerized tests using an iPad, written questionnaires and evaluations by a licensed psychologist. Parents or legal guardians of patients less than 18 years of age will also participate by completing written questionnaires at the same time their child is being tested.

The results of the neuropsychological testing will be told to your doctor and entered as part of your medical record. Neuropsychological results will be used to make decisions about your care while enrolled on this study. If the testing results show areas of concern, you may be given more frequent testing as well as referrals for other care if needed. During testing, patients may skip questions that are stressful and may stop taking the tests at any time. Testing can be done as part of the clinic visit. You will need to talk with your doctor and nurse about scheduling to do these tests at times that are workable for you and your child. Please see the table at the end of the consent form that tells how often these tests will be done during the study.

- All patients 3 years of age and older will do computerized tests using an iPad. While the patient is taking these tests, the patient's parent or legal guardian will complete written questionnaires about the patient's mood and emotions, behavior, daily living/functional skills and social skills with others. The parent/legal guardian can be in the same room during the testing but they cannot help their child with their tests.

- Patients 18 years of age will complete computerized tests using an iPad and their own written questionnaires. Parents/Legal guardians do not have testing to do with patients of this age.

- Patients under 3 years of age will have an evaluation of overall functioning including language, motor and cognitive development done by a licensed psychologist. Parents/legal guardians will also complete written questionnaires at the same time.

<table>
<tr><th>Patient age at testing in years</th><th>Testing being done</th><th>Length of testing time for Patients</th><th>Length of testing time for Parents/legal guardians</th></tr>
<tr><td>1</td><td rowspan="2">Patient: licensed psychologist
Parent/legal guardian: written questionnaires</td><td rowspan="2">~ 60 - 90 minutes</td><td>~ 20 minutes</td></tr>
<tr><td>2</td><td>~ 50 minutes</td></tr>
<tr><td>3 - 5</td><td rowspan="4">Patient: computerized tests using an iPad
Parent/legal guardian: written questionnaires</td><td>~ 10 minutes</td><td>~ 50 minutes</td></tr>
<tr><td>6</td><td>~ 30 – 40 minutes</td><td>~ 50 minutes</td></tr>
<tr><td>7 - 9</td><td>~ 30 – 40 minutes</td><td>~ 50 - 55 minutes</td></tr>
<tr><td>10 - 17</td><td>~ 35 – 45 minutes</td><td>~ 50 - 55 minutes</td></tr>
<tr><td>18</td><td>Patient: computerized tests using an iPad and written questionnaires</td><td>~ 80 – 90 minutes</td><td>NA</td></tr>
</table>

NANT Biology Study (NANT 2004-05)

If you choose to participate in this research, you will also be asked to join a companion NANT biology study to collect blood, bone marrow and tumor tissue (if available) and reports from radiology scans from patients with neuroblastoma. The biology study also provides a place (called NANT biorepository) where any leftover samples of tumor tissue or bone marrow and blood collected on this study could be transferred and stored. While you will be asked to join the Biology Study (NANT 2004-05), the decision to store/bank any leftover

samples is optional and will not affect your ability to participate in this treatment study with lorlatinib. Your doctor will talk with you in detail about the NANT biology study and have you sign a separate consent form.

Additional Tests in this Study

We would like to do some extra tests called pharmacokinetic studies and biologic studies. These tests will help us learn more about lorlatinib and may help children and adolescents who receive this drug in the future. The information learned would not change the way you are treated and the results of these tests will not be given to you. Some of these tests are required but others are optional meaning you can decide whether you want to do them or not.

Pharmacokinetic Studies: Determining Blood Levels of Lorlatinib – Required

During this study blood samples will be collected to determine how much lorlatinib is in your blood (called pharmacokinetics). About 3mL (just over half a teaspoon) of blood will be drawn with each sample. A total of 9 blood samples will be obtained over 3 separate days during course 1 (Day 1, Day 2 and Day 15). The total amount of blood drawn for testing will be about 27 mL (almost 5 ½ teaspoons). If you have a central line (such as a port or a Broviac) these samples can be drawn through that line or through a small tube placed in a vein in your hand or arm. This amount of blood is considered safe to donate. Samples will be sent to a commercial laboratory contracted to perform these tests for the study. These samples will be the property of Pfizer and Pfizer may also use the PK Biological Samples for evaluation of the bioanalytical method.

Other Biology Research Tests in this Study - Optional

You will be asked if you want to participate in 3 optional research tests. You can decide not to let the doctors do these tests and still be able to be treated as part of this study. There are checkboxes at end of this form to mark whether you are willing to participate in these voluntary studies. The results of these research tests will not be shared with you or become part of your medical record. These results would also not be used to make decisions about your care while enrolled on this study.

- **Using extra blood to look for genetic changes seen in tumor cells.**
  Tumor cells often release small pieces of DNA into the blood stream where it can be detected by sensitive tests. About 17mL (almost four teaspoons) of blood will be drawn at study entry and at each time disease evaluation testing is done (after cycles 2, 4, 6 and then every 4th cycle) to look at what genetic changes in your tumor may be seen over time from the small pieces of tumor DNA found in your blood. The blood will be sent to a commercial laboratory contracted to perform this testing for the study.

- **Comparing genetic changes between leftover tumor from a surgical procedure prior to tumor relapse (at diagnosis or when you had surgery done after diagnosis) to relapsed neuroblastoma tumor tissue and bone marrow aspirates and whether these changes affect how the tumor will respond to treatment with Lorlatinib.**
  Researchers would like to look at tumor tissue to determine if there are certain gene changes present that might make your neuroblastoma more or less likely to respond to the drug lorlatinib. These tests would be done on tumor tissue remaining from diagnosis, or any previous surgery where tumor tissue was removed (removal of primary tumor or removal of tumor at a relapse) in the past. The tissue and bone marrow aspirates will be sent to a research laboratory at Children's Hospital of Philadelphia for testing.

When You Have Finished Treatment with Lorlatinib

After you stop treatment on this study, you will continue to have tests and scans done (listed below) to measure how much tumor is left. If test results show you have abnormal organ functions, tests are recommended by the study to be repeated monthly until test results are stable or normal. You doctor will tell you how often these tests and evaluations will be done.

Medical Tests after the Study:

Physical exam	Neuropsychological testing[1]
Blood tests	Bone marrow tests & various scans (CT/MRI, MIBG or PET) to check your tumor[2]
Electrocardiogram (EKG) to check the heart rhythm[3]	

[1]The same neuropsychological testing and evaluation done before starting study treatment will be done at the end of treatment with lorlatinib. The need for any further testing after this will be up to your doctor.

[2]Bone marrow tests and various scans are done for checking the response of your tumor to treatment. These tests will be done at the end of a course and at certain times following treatment to monitor your tumor status.

[3]Electrocardiogram (EKG) done at the end of the study to document if lorlatinib treatment has any effect on heart rhythm.

A table detailing the tests and procedures required before, during and after the study has been attached to the end of this form (Consent Addendum 1).

HOW LONG WILL I BE ON THIS STUDY?
You can get up to 24 cycles with lorlatinib and chemotherapy or indefinitely if you are no longer receiving chemotherapy as long as you are not having bad side effects and as long as your tumor is not getting worse.

After you stop treatment, you will continue to have tests and scans done to measure how much tumor is left. Your doctor will tell you how often these tests will be done. Researchers will continue to collect information about you for a lifetime. Information will be collected about whether you are still alive; whether your tumor has grown back and at what sites in the body; whether you have developed any side effects from the treatment; or whether you have developed any additional cancer. Your oncologist or family doctor will give the researchers this information at regular intervals.

CAN I STOP BEING IN THE STUDY?
Yes. If you are thinking about stopping your participation on this study, you should talk to your doctor before making a final decision so he/she can tell you how to do this safely.

Your doctor may also stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow study rules; or if the study is stopped.

WHAT ARE THE RISKS OF THE STUDY?
This is a Phase 1 study. A Phase 1 study looks at how common and serious side effects can be for each patient at a specific dose of a drug. In a Phase 1 study, some patients may have very serious side effects and could die as a result of these side effects. You may be one of those patients who have serious side effects as a result of participating in this Phase 1 study.

In this study, researchers will be looking at side effects seen in patients taking different doses of lorlatinib as well as lorlatinib given together with chemotherapy.
Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Other drugs may be given to make side effects less serious and more comfortable. Many side effects go away soon after you stop taking the study medications but it is always possible that side effects can be serious, long lasting or may never go away. There is also a risk of death. Patients are watched carefully and treatment will be stopped

if bad side effects develop. There may also be risks we do not know about. You should talk to your doctor about any side effects that you have while taking part in this study.

While on the study, you are at risk for the side effects listed below:

Possible Risks of Lorlatinib:

The following side effects are considered to be related to lorlatinib have been reported:

Very Common (may affect 10 or more in 100 people)	**Common** (may affect from 1 up to less than 10 in 100 people)
• Increase in cholesterol and triglycerides (fats in your blood) • Effects on mood (for example, irritability and mood swings) • Effects on memory (for example, confusion, memory loss and disturbance of attention) • Effects on the peripheral nerves which are those outside of the brain and spinal cord, including tingling, numbness or pain in hands and feet) • Changes in vision (including double vision, perceived flashes or floaters of light, light intolerance, vision blurred, vision sharpness reduced and visual impairment) • Hypertension • Diarrhea • Constipation • Joint pain • Build-up of fluid in the body or extremities causing swelling (edema) • Fatigue (feeling tired and exhausted) • Increase in body weight • Increase in blood sugar levels	• Hallucination and loss of contact with reality • Changes in mental status • Changes in speech (for example, slow speech or slurred speech) • Inflammation of the lungs (pneumonitis) which can cause shortness of breath and difficulty breathing. If severe, this can be life threatening.

The following events have also been reported in patients while they were taking lorlatinib, although the relationship to lorlatinib is uncertain:

Very common (may affect 10 or more in 100 people)

- Abnormalities in blood tests that may indicate liver damage
- Abnormal pancreas tests
- Decrease in hemoglobin in the blood that can cause weakness
- Headache
- Muscle pain
- Difficulty sleeping
- Rash

Common (may affect from 1 up to less than 10 in 100 people)

- Decrease of ejection fraction of the heart which may indicate severe heart problem
- A sudden and temporary loss of consciousness (syncope)
- Changes in the electrical activity of your heart that might lead to a heart rhythm problem and/or irregular heartbeat

Uncommon (may affect less than 1 in 100 people)

- Inflammation of the pancreas causing pain in the upper abdomen. This could become severe and may cause nausea and vomiting, fever and rapid heart rate. This could require hospitalization and may be life threatening
- Suicidal thoughts
- Psychosis

Lorlatinib has moderate influence on the ability to drive and use machines. Caution should be exercised when driving or operating machines as patients may experience CNS effects.

Possible Side Effects of Cyclophosphamide:

Likely	Less Likely	Rare But Serious

• Loss of appetite
• Nausea
• Vomiting
• Fewer white blood cells in the blood.
  ○ A low number of white blood cells may make it easier to get infections.
• Hair loss
• Decreased ability of the body to fight infection
• Absence or decrease in the number of sperm which may be temporary or permanent which may decrease the ability to have children
	• Abdominal pain
	• Diarrhea
	• Fewer red blood cells and platelets in the blood
	  ○ A low number of red blood cells may make you feel tired and weak.
	  ○ A low number of platelets may cause you to bruise and bleed more easily.
	• Bleeding and inflammation of the urinary bladder
	• Absence or decrease monthly periods which may be temporary or permanent and which may decrease the ability to have children
		• Temporary blurred vision
		• Nasal stuffiness with fast IV infusions
		• Irregular heart rate with fast IV infusions
		• Skin rash
		• Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure, rapid heart rate chills and fever
		• Abnormal hormone function which may lower the level of salt in the blood
		• Heart muscle damage which may occur with very high doses and which may be fatal
		• Darkening of areas of the skin and finger nails
		• Fingernail changes
		• Slow healing of wounds
		• Infections
		• Infertility which is the inability to have children
		• Damage and scarring of lung tissue which may make you short of breath
		• A new cancer or leukemia resulting from this treatment.
		• Damage or scarring of urinary bladder tissue

Possible Side Effects of Topotecan:

Likely	Less Likely	Rare But Serious

• Diarrhea
• Nausea
• Vomiting
• Constipation
• Fewer white blood cells, red blood cells and platelets in the blood.
  ○ A low number of white blood cells can make it easier to get infections
  ○ A low number of red blood cells can make you feel tired and weak
  ○ A low number of platelets causes you to bruise and bleed more easily
• Fever including fever with a low white blood cell count which could indicate infection and may require hospitalization and treatment with antibiotics
• Pain which may be in your abdomen, back or bones
• A feeling of weakness and/or tiredness
• Temporary hair loss
	• Loss of appetite
	• Headache
	• Lack of muscle strength or weakness
	• Rash, hives, itching or a red bumpy rash
	• A mild lowering of the blood pressure which usually does not require treatment
	• Shortness of breath
	• Inflammation and/or sores in the mouth, throat and/or esophagus
	• Elevation in the blood of certain enzymes found in the liver which may indicate liver irritation or damage
	• An infection in the blood which will require admission to the hospital and treatment with antibiotics
		• Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure and a rapid heart rate
		• Severe allergic reaction which can be life threatening with rapid build-up of fluid under the skin, in the lining of the intestine and possibly in the throat or swelling of the tongue which could make it difficult to breath.
		• Chest pain
		• Shaking chills
		• Elevation in the blood of certain enzymes or bilirubin found in the liver which could indicate liver irritation or damage
		• Numbness and tingling in the fingers and toes
		• Muscle or joint aches and pains
		• Bleeding into the tumor which may cause damage depending on the location of the tumor
		• Small amount of blood and/or protein in the urine or an elevation in blood creatinine which may indicate mild kidney damage

Growth Factors are not anti-cancer medicines. It helps the growth of white blood cells that fight infection (filgrastim/pegfilgrastim).

Possible Side Effects of Neupogen (Filgrastim):

Likely (happens to 21-100 children out every 100 children)	**Less Likely** (happens to 5-20 children out every 100 children)	**Rare** (happens to < 5 children out every 100 children)
• Aching or pain in bones.	• Local irritation/pain at the site of the injection. • Higher than normal levels in the blood of uric acid and of liver enzymes which may indicate liver irritation or damage. • Fever • A low number of platelets in the blood which may cause you to bruise and bleed more easily.	• Allergic reactions which can be life threatening with shortness of breath, low blood pressure, rapid heart rate, hives, facial swelling. This reaction is very rare and has been associated mainly with intravenous administration. • If you are known to have sickle cell disease , this drug may cause sickle cell crises • Severe damage to the spleen (an organ in the abdomen which stores blood cells) which could lead to pain and loss of blood into the abdomen or rupture of the spleen. • Difficulty breathing and lung damage that may be due to the white blood cells, stimulated by Pegfilgrastim , travelling to the lungs when they are inflamed or infected (Adult Respiratory Distress Syndrome) • Bone marrow dysfunction (MDS) or secondary leukemia in patients with very bad ongoing low white cell counts that require prolonged administration of this drug. • Worsening of skin rashes • Low Fever • Inflammation of blood vessels leading to a raised purple rash and bruising • Higher than normal white blood count. • Low blood pressure and/or increased heart rate • Wheezing or shortness of breath • Skin rash, hives or facial swelling

Possible Side Effects of Neulasta (Pegfilgrastim):

Likely (happens to 21-100 children out every 100 children)	**Less Likely** (happens to 5-20 children out every 100 children)	**Rare** (happens to < 5 children out every 100 children)
• Aching or pain in bones.	• Local irritation at the site of the injection. • Headache • Higher than normal levels in the blood of uric acid and of liver enzymes which may indicate liver irritation or damage. • A low number of platelets in the blood which may cause you to bruise and bleed more easily.	• Low grade fever • Allergic reactions which can be life threatening with shortness of breath, low blood pressure, rapid heart rate, hives, facial swelling. This reaction is very rare and has been associated mainly with intravenous administration. • Redness and flushing of the face and body. • Enlarged spleen • Severe damage to the spleen (an organ in the abdomen which stores blood cells) which could lead to pain and loss of blood into the abdomen. • If you are known to have sickle cell disease , this drug may cause sickle cell crises • Markedly higher than normal white blood cell count which may be associated with fever and red, often painful patches on the skin (Sweet's syndrome). • Difficulty breathing and lung damage that may be due to the white blood cells, stimulated by Pegfilgrastim, travelling to the lungs when they are inflamed or infected (Adult Respiratory Distress Syndrome)

Possible Risks to Unborn Child

Patients who agree to participate in this study should not become pregnant while on this study. Lorlatinib may cause fetal harm when administered to a pregnant woman and is not recommended during pregnancy or for women of childbearing potential not using contraception. Women of childbearing potential should use nonhormonal methods of birth control. If a hormonal method of birth control is unavoidable, then a condom must be used in combination with the hormonal method. Female patients must continue to follow these birth control guidelines for 21 days after finishing the study. Male patients must wear condoms as one of their forms of birth control for the duration of the study and for 97 days after finishing the study. Further contraception use should be discussed with your personal physician. If you or your partner becomes pregnant while you are participating in this study, please notify your doctor immediately. For more information about risks and side effects, ask your doctor.

Possible Long Term Side Effects of This Treatment

Side effects in adults treated with lorlatinib have occurred while patients have been receiving the drug or shortly after finishing the drug. It is not known if some side effects may be seen only after a long time after finishing treatment with lorlatinib.

Possible Risks from Having Blood Drawn

The risks from having your blood taken are minimal, but can include an infection or a blood clot. Experienced doctors or nurses will perform these blood draws to minimize this risk.

Unknown Risks

The treatment may have side effects that no one knows about yet. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

There may or may not be direct medical benefit to you. The information learned from this study may or may not benefit other children or young people with solid cancers in the future.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THIS STUDY?
There are other options for you instead of this treatment. Instead of being in this study, you have these options:

- Treatment with other chemotherapy medicines
- Treatment with other experimental agents that may be available.
- No neuroblastoma therapy at this time, with care to help you feel more comfortable.

Please talk about these options with your doctor.

WILL MY MEDICAL INFORMATION BE KEPT PRIVATE?
We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance and data analysis include:

- New Approaches to Neuroblastoma Therapy (NANT) Consortium at Children's Hospital Los Angeles in Los Angeles, CA. The NANT Consortium identifies you by a number.
- Independent auditor evaluating quality assurance for the NANT Consortium.
- The National Cancer Institute (NCI) and other governmental agencies, like the Food and Drug Administration (FDA) or Health Canada, involved in keeping research safe for people.
- Foundation Medicine, Inc. who is a collaborator on this study.
- Pfizer Inc., the pharmaceutical company which makes lorlatinib.

NANT has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. Information about the certificate is included at the end of this consent.

Because this study involves the treatment of a medical condition, a copy of this consent form will be placed in your medical record. This will allow the doctors that are caring for you to obtain information about what medications or procedures you are receiving in the study and treat you appropriately.

WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?
Taking part in this study may lead to added costs to your insurance company. Your health insurance company will be billed for many expenses associated with the costs of this study. These expenses include medications, treatments, hospital charges, and doctors' fees related to your participation in this study.

Lorlatinib and the flavoring agent (Ora-Plus®) are being provided free of charge for use in this study, but the costs associated with administering the drug is normally covered by your insurance company. Cyclophosphamide and topotecan is normally covered by your insurance company. The cost of doing a heart test called an EKG and neuropsychological testing at several time points during your participation in the study with Lorlatinib is being done as part of research and will be paid for by the study.
The special research blood and tissue studies will be done at no cost to you. However, you or your health plan may need to pay for the costs of the supplies and personnel who draw the blood from you for these tests.

You may have to pay for other things during this study, such as but not limited to, your time, the cost of food you buy while you are being treated at the hospital, car fare, travel to and from the hospital for treatment, parking, and baby sitter fees.

Taking part in this study may lead to added costs that may not be covered by your insurance company. Please ask about any expected added costs or insurance problems.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage . You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?
It is important that you tell your study doctor, _____ *[investigator's name(s)],* if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number].*

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

WHAT ARE MY RIGHTS AS A STUDY PARTICIPANT?
Taking part in this study is your choice. You may choose not to take part or not take part in the study. If you decide to take part in this study, you may remove yourself from the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. If you remove yourself from the study, we will still take care of you. We will explain what stopping the treatment may do and we will offer other treatments if they are available.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In case of injury resulting from this study, you do not lose any of you legal rights to seek payment by signing this form.

A Data Safety and Monitoring Board, an independent group of experts, will be reviewing data from this research throughout the study. We will tell you about new information from this Board or other studies that may affect your health or willingness to stay in the study.

WHO CAN ANSWER MY QUESTIONS ABOUT THE STUDY?
You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number].*

For questions about your rights while taking part in this study, call the _____ *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ *(telephone number).*

WHO IS FUNDING THIS RESEARCH STUDY?
This study is supported by Pfizer, Inc. Pfizer is a drug company that makes the drug being studied in this research project. Pfizer is giving money to Children's Hospital for some of the costs of the study. The results of the study will be reported to Pfizer. If the study shows that lorlatinib may be useful for a new purpose, this could benefit Pfizer financially.

The Children's Hospital Los Angeles/NANT is also providing funding for this study.

Dr. Mossé at Children's Hospital of Philadelphia, one of the principal investigators of this study, has served as a paid consultant to Pfizer. Her participation in this research has been reviewed and approved, subject to management, according to CHOP's/NANT Conflict of Interest Policy.

WHERE CAN I GET MORE INFORMATION?

You may call the NCI's **Cancer Information Service** at

1–800–4–CANCER (1–800–422–6237) or **TTY: 1–800–332–8615**

You may visit the NCI Web sites at http://cancer.gov/
For NCI's clinical trials information, go to http://cancer.gov/clinicaltrials/
For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

You will get a copy of this consent form. If you want more information about this study, ask your doctor.

CONSENT FOR EXTRA STUDIES FOR RESEARCH

The following tests are optional for all patients in the study. You may still participate in the study even if you do not agree to these tests.

1. **Using extra blood to look for genetic changes seen in tumor cells**
   Initial next to YES if you agree to let researchers take almost 4 extra teaspoons (17mL) at study entry and each time a disease evaluation is done) to look at what genetic changes in your tumor can be seen in your blood over time before and after treatment with lorlatinib. This blood would be drawn at a time when blood was being drawn for clinical purposes. The blood will be sent to Foundation Medicine Inc. for analysis who is a collaborator on this study. The results of these tests will be confidential and not made available to you or your treating physician.

   Initial next to NO, if you do not want researchers to take extra blood above what is needed for clinical purposes.

   _____Yes _____No

2. **Comparing genetic changes between tumor leftover from a surgical procedure prior to relapse (diagnosis or second look) to relapsed neuroblastoma tumor tissue and bone marrow aspirates and whether these changes affect how the tumor will respond to treatment with Lorlatinib.**

   Initial next to YES, if you agree (and if there is tumor remaining) to let this tumor be sent to a laboratory so researchers can compare these samples and determine if there are certain gene changes present that might make your neuroblastoma more or less likely to respond to the drug lorlatinib. The results of these tests will be confidential and not made available to you or your treating doctor.

   Initial next to NO if you do not want leftover tumor from an earlier procedure to be sent to a research laboratory to look for certain gene changes that might make your neuroblastoma more or less likely to respond to the drug lorlatinib.

   _____Yes _____No

   Initial next to YES, if you agree to let extra bone marrow aspirates be collected to be sent to a laboratory so researchers can compare these samples and determine if there are certain gene changes present that might make your neuroblastoma more or less likely to respond to the drug lorlatinib. The results of these tests will be confidential and not made available to you or your treating doctor.

   Initial next to NO if you do not want these bone marrow aspirates collected to be sent to a research laboratory to look for certain gene changes that might make your neuroblastoma more or less likely to respond to the drug lorlatinib.

   _____Yes _____No

STATEMENT OF CONSENT

I have already read the information in this informed consent document. I have read all the attachments that were included with this informed consent document. I have asked all of my questions and I have gotten answers. I agree to enroll myself (my child) in this study.

_____
Patient Name

_____ _____/_____/_____
Print Name of Parent or Guardian Date

_____ _____/_____/_____
Signature of Parent or Guardian Date

_____ _____/_____/_____
Signature of Patient (If > 7 years old) Date

_____ _____/_____/_____
Signature of Physician or Date
Responsible Investigator

_____ ____/_____/_____
Signature of Witness Date

_____ ____/_____/_____
Signature of Translator Date

Consent Addendum I: Tests That Will Be Done On This Study

Observation	Before Entry	Cycle 1	Cycle 2	Subsequent Cycles	End of Therapy
Physical exam including neurological exam	X	Weekly	Start of cycle	Start of each cycle	X
Routine blood tests** (Blood counts, electrolytes, liver, kidney function, function of pancreas-amylase/lipase)	X	Weekly for other tests and twice weekly for blood counts	Weekly for blood counts and twice during cycle for all other blood tests	Start of each cycle and weekly for blood counts	X
Routine Blood tests** (Fasting cholesterol, triglycerides, glucose)	X	Every other week	Start of cycle	Start of each cycle	X
Hemoglobin A1c (HbA1c)	X		Start of cycle	With Disease Evaluations in Courses 4 and 6 and after every 4 courses thereafter	X
Blood tests for cholesterol, triglycerides and function of the pancreas (amylase/lipase)	X	Weekly	Start of cycle	Start of each cycle	X
Pregnancy test (All females10 years of age and older)	X		Start of cycle	Start of each cycle	
Heart rhythm test (EKG)	X	One hour after day 1 treatment is finished	End of cycle	End of cycle (4,6 and every 4th cycle thereafter)	X
Neuropsychological Testing	Within one week before starting treatment	End of cycle	End of cycle	End of cycle (4,6 and every 4th cycle thereafter)	X
Neuropsychological evaluation with licensed psychologist for patients less than 3 years of age	Within one week before and up to two weeks after starting treatment		End of cycle	End of cycle 6, 10 and then every 8 cycles thereafter	X
Submit Patient Treatment Diaries		X	X	X	X
Blood for Lorlatinib drug level tests (PK - Required)		Day 1: 3 times Day 2: 1 time Day 15: 5 times			
Blood for circulating tumor cells (Optional)	X		With disease evaluation	End of cycle (4,6 and every 4th cycle thereafter)	

Bone Marrow Aspirate (Optional)	X		With disease evaluation	End of cycle (4,6, and every 4th cycle thereafter)	
Sampling of leftover tumor tissue (Optional)	Leftover tumor tissue can be sent at any time during the study				
	Tests done at Disease Evaluation				
Bone marrow aspirate and biopsy CT/MRI scans and/or MIBG/PET scans Blood and bone marrow for NANT Biology study[#]	X		Week 4	End of cycle (4,6 and every 4th cycle thereafter)	X

[#] Patients enrolled in the companion biology study may have additional samples of blood and bone marrow collected at study entry and with each disease evaluation time point. Please look at the biology study (NANT 2004-05) consent form for more information.

**Blood draws can be done more often if needed at the discretion of your study doctor

Consent Addendum II

Certificate of Confidentiality Information

NANT has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. The Certificate protects against the involuntary release of information about subjects collected during the course of our covered studies. The researchers involved in the studies cannot be forced to disclose the identity or any information collected in the study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, the subject or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if the subject or his/her guardian requests the release of information in writing, the Certificate does not protect against that voluntary disclosure. Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act. The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

APPENDIX VIII: DOSE EXPANSION COHORT A2: PATIENTS ≥ 18 YEARS OF AGE SAMPLE CONSENT

NANT 2015-02: PHASE 1 STUDY OF LORLATINIB, AN ORAL SMALL MOLECULE INHIBITOR OF ALK/ROS1, FOR PATIENTS WITH ALK-DRIVEN RELAPSED OR REFRACTORY NEUROBLASTOMA

COHORT A2: PATIENTS 18 YEARS OF AGE AND OLDER

A New Approaches to Neuroblastoma Therapy (NANT) treatment protocol.

WHAT IS THIS STUDY ABOUT?
This study is a clinical trial, a type of research study. Clinical trials include only patients who choose to take part. Please take your time to make your decision about participating. You may discuss your decision with your friends, family, and health care team. If you have any questions, you may ask your doctor.

You are being asked to participate in this study because you have a kind of cancer called neuroblastoma. It may be that your cancer went away for a while but has grown back (relapsed) or it may be that it has never gone away (persistent or resistant tumor) after standard treatment. Standard treatment may have included chemotherapy, surgery, radiation therapy, high-dose chemotherapy with a stem cell transplant and/or immunotherapy.

WHY IS THIS STUDY BEING DONE?

The Purposes Of This Study Are:

- To find the highest dose of lorlatinib that can be given to adults with refractory or relapsed neuroblastoma without causing severe side effects.
- To learn about the side effects of the drug lorlatinib when given to adults.
- To determine if your tumor gets smaller after treatment with lorlatinib.
- To measure the levels of lorlatinib in the blood
- To look at genetic changes in tumor DNA found in the blood during treatment.
- To look at genetic changes in tumor tissue to see if they affect response to lorlatinib.
- To describe the amount of neuroblastoma tumor found in the blood and bone marrow by testing samples with a new test (called NB5 assay).

The Research Is Being Done Because:
Currently there is no known effective treatment for your type of cancer. We are testing new experimental drugs such as lorlatinib in the hopes of finding a drug that may be effective against neuroblastoma tumors that have come back (relapsed) or that have never gone away (persistent/refractory) after treatment with standard therapy.

This study involves the use of an experimental drug called lorlatinib. In laboratory testing, lorlatinib blocks the Anaplastic Lymphoma Kinase (ALK) gene. ALK may be important in the growth of certain types of cancer cells such as neuroblastoma. Lorlatinib is considered experimental because it has not been proven to work in a situation like yours. Lorlatinib has been approved by the United States Food and Drug Administration (FDA) to treat adults with non-small cell lung cancer, a different cancer than yours.It is not approved for neuroblastoma. Lorlatinib has been used only in a small number of adults so there is a lot we do not know about it yet. In these previous studies, the recommended dose of lorlatinib that can be given safely was

determined for adults. In this study, we are also studying higher dose levels. Adults will receive 2 dose levels of lorlatinib on this cohort. All patients enrolled on this study are known to have a defect in the ALK gene in their tumor before they start treatment.

In this study, the lorlatinib dose you will be given is higher than the recommended dose given to adults with other cancers who have been treated with lorlatinib. This is because based on laboratory studies, it is thought that higher levels of lorlatinib might be needed to have an effect on neuroblastoma. Other adults have been treated at similar higher dose levels in the past and side effects experienced were temporary and resolved after stopping or decreasing the dose of lorlatinib. You will be closely monitored for any side effects with this treatment.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?
There will be about 60-75 patients enrolling on the 4 study cohorts. You have been given this consent because the planned enrollment is on cohort A2. When you join the study, you will be assigned a certain lorlatinib dose. Cohort A2 will test up to 2 lorlatinib doses. There will be a a minimum of 20 patients enrolling on these two doses. Investigators are trying to decide the highest dose of lorlatinib that can be given without bad side effects.

WHAT WILL HAPPEN TO ME IF I TAKE PART IN THIS STUDY?

Before You Begin the Study
Your doctor will have previously sent your tumor for genetic testing and these results showed your tumor has a defect in the ALK gene which allows you to be considered for participation in this study.

You will need to have the following exams, tests or procedures to find out if you can take part in the study. Most of these exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. These tests will also be done at various times throughout the study and at the end of the study. The purpose of these tests is to see how well the treatment works and to measure the status of your neuroblastoma. If you have had some of them recently, they may not need to be repeated. This will be up to your doctor.

A medical history & physical exam	Bone marrow tests[3] to check your tumor
Blood tests[1]	Various scans[4] to check your tumor
Pregnancy test (urine or blood)[2]	Electrocardiogram (EKG) to check the heart rhythm[5]
	Neuropsychological testing[6]

[1]Some blood tests (cholesterol and fat digestion [triglycerides]) may need to be done on an empty stomach, so you cannot eat or drink anything other than water for 8-10 hours before these tests are done (called fasting). Your doctor or nurse will tell you if it is necessary for you to fast before these blood tests are done.

[2]If you are a female at least 10 years old or who could have children, you will have a pregnancy test done by the doctor the week before starting treatment and then before each cycle of treatment begins. Both you and your parent/legal guardian (if applicable) will be informed of a positive pregnancy test. All men and women who could have children must either agree to practice abstinence from heterosexual intercourse or use two effective methods of birth control for as long as they participate in this study.

[3]Bone marrow tests are done by inserting a needle into the hip bone to remove the marrow which is inside the bone.

[4]Various scans are done for diagnosis and checking the response of the tumor to treatment. These may include CT and /or MRI scans and MIBG or PET scans. We will recommend scans specific for your case and we will answer your questions about these scans.

[5]Electrocardiogram (EKG) to document your heart rhythm before beginning lorlatinib treatment.

[6]Central nervous system effects (speech, memory and mood changes) were seen in previous studies treating adults with Lorlatinib. Neuropsychological testing will be done at within one week of starting treatment and at different times during this study to monitor for any changes in thinking skills, behavior and mood. Please see the section on Neuropsychological testing below in "During this Study" for more details on what tests are done and when they are done during this study.

During the Study

If the exams, tests and procedures show that you can be in the study, and you choose to take part, lorlatinib will be given for 28 days. This entire period is called a cycle with each treatment cycle being 28 days long. You may continue to take lorlatinib for an unlimited number of cycles unless you develop serious side effects or your tumor worsens.

One Treatment Cycle (Cohort A2: adults and children/adolescents higher BSA group meeting adult dosing criteria)			
Week 1	Week 2	Week 3	Week 4
Days 1 - 7	Days 8 – 14	Days 15 - 21	Days 22 - 28
Lorlatinib once a day →			

Lorlatinib will be given by mouth once a day followed by a small glass of water. If you vomit lorlatinib within 20 minutes of taking the dose for the day, that dose can be repeated. This is the only time a dose of lorlatinib can be repeated.

Lorlatinib will be available as a tablet. If you are unable to swallow the tablets whole, you will be instructed on how to make a liquid lorlatinib solution at home by mixing the lorlatinib tablets with water and a flavoring agent (Ora-Plus®). Your nurse or doctor will help you decide what is best for you and will make sure you have the proper directions for taking this medication.

You will be given a patient diary at the beginning of each cycle of lorlatinib. Use the diary to record the date and time you take the drug, all vomited and missed doses, side affects you experience and any other medications and supplements you are taking. The diary should be returned to clinic along with the medication bottle (even if it is empty) weekly during cycle 1 and then after each treatment cycle of lorlatinib. This will help us to know how much of the drug you take and how it made you feel.

During the study you will have tests and procedures done to check for side effects from taking lorlatinib and to see how your tumor is doing. Many of these tests are part of regular cancer care but you may have them done more often because you are on the study:

Physical exam	Electrocardiogram (EKG) to test heart rhythm[3]
Blood tests[1]	Bone marrow tests & various scans (CT/MRI, MIBG or PET) to check your tumor[4]
Pregnancy test (urine or blood)[2]	Neuropsychological testing[5]

[1]Some blood tests (cholesterol and fat digestion) can only be done on an empty stomach, so patients cannot eat or drink anything other than water for 8-10 hours before these tests are done.

[2]A urine or blood pregnancy test will be done before each treatment cycle begins if you are a female who could have children. Both you and your parent/legal guardian will be informed of a positive pregnancy test.

All men and women who could have children must continue to practice abstinence from heterosexual intercourse or use two effective methods of birth control for as long as they participate in this study.

[3]Electrocardiogram (EKG) done before starting study treatment will be repeated at certain times during the study to document if lorlatinib treatment has any effect on heart rhythm.

[4]Bone marrow tests and various scans are done for checking the response of your tumor to treatment. These tests will be done at certain times during the study to look at response to lorlatinib and check that your tumor has not gotten worse.

[5]**Neuropsychological Testing**

Neuropsychological evaluations try to understand how changes in the health of the brain may affect behavior or mood and how well a person is able to pay attention, remember things or solve problems. Since effects on speech, memory and mood were seen in a small number of adults receiving lorlatinib, neuropsychological testing will be done to monitor for changes in thinking skills, behavior and mood at different times during this study. A table at the end of the consent lists how often neuropsychological testing will be done during the study. Testing methods are based on the age of the patient and include computerized tests using an iPad, written questionnaires and evaluations by a licensed psychologist. Parents or legal guardians of patients less than 18 years of age will also participate by completing written questionnaires at the same time their child is being tested.

The results of the neuropsychological testing will be told to your doctor and entered as part of your medical record. Neuropsychological results will be used to make decisions about your care while enrolled on this study. If the testing results show areas of concern, you may be given more frequent testing as well as referrals for other care if needed. During testing, patients may skip questions that are stressful and may stop taking the tests at any time. Testing can be done as part of the clinic visit. You will need to talk with your doctor and nurse about scheduling to do these tests at times that are workable for you and your child.

- Patients 18 years of age and older will complete computerized tests using an iPad and their own written questionnaires. Parents/Legal guardians do not have testing to do with patients of this age.

<table>
<tr><th>Patient age at testing in years</th><th>Testing being done</th><th>Length of testing time for Patients</th><th>Length of testing time for Parents/legal guardians</th></tr>
<tr><td>1</td><td rowspan="2">Patient: licensed psychologist
Parent/legal guardian: written questionnaires</td><td rowspan="2">~ 60 - 90 minutes</td><td>~ 20 minutes</td></tr>
<tr><td>2</td><td>~ 50 minutes</td></tr>
<tr><td>3 - 5</td><td rowspan="4">Patient: computerized tests using an iPad
Parent/legal guardian: written questionnaires</td><td>~ 10 minutes</td><td>~ 50 minutes</td></tr>
<tr><td>6</td><td>~ 30 – 40 minutes</td><td>~ 50 minutes</td></tr>
<tr><td>7 - 9</td><td>~ 30 – 40 minutes</td><td>~ 50 - 55 minutes</td></tr>
<tr><td>10 - 17</td><td>~ 35 – 45 minutes</td><td>~ 50 - 55 minutes</td></tr>
<tr><td>18 – 25</td><td rowspan="2">Patient: computerized tests using an iPad and written questionnaires</td><td rowspan="2">~ 80 - 90 minutes</td><td rowspan="2">NA</td></tr>
<tr><td>26+</td></tr>
</table>

NANT Biology Study (NANT 2004-05)

You will also be expected to join a companion NANT biology study to collect blood, bone marrow and tumor tissue (if available) and reports from radiology scans from patients with neuroblastoma. The biology study also provides a place (called NANT biorepository) where any leftover samples of tumor tissue or bone marrow and blood collected on this study could be transferred and stored. While you will be asked to join the Biology Study (NANT 2004-05), the decision to store/bank any leftover samples is optional and will not affect your ability to participate in this treatment study with Lorlatinib. Your doctor will talk with you in detail about the NANT biology study and have you sign a separate consent form.

Additional Tests in this Study

We would like to do some extra tests called pharmacokinetic studies and biologic studies. These tests will help us learn more about lorlatinib and may help children and adolescents who receive this drug in the future. The information learned would not change the way you are treated and the results of these tests will not be given to you. Some of these tests are required but others are optional meaning you can decide whether you want to do them or not.

Pharmacokinetic Studies: Determining Blood Levels of Lorlatinib – Required

During this study blood samples will be collected to determine how much lorlatinib is in your blood (called pharmacokinetics). About 3mL (just over half a teaspoon) of blood will be drawn with each sample. A total of 9 blood samples will be obtained over 3 separate days during course 1 (Day 1, Day 2 and Day 15). The total amount of blood drawn for testing will be about 27 mL (almost 5 ½ teaspoons). If you have a central line (such as a port or a Broviac) these samples can be drawn through that line or through a small tube placed in a vein in your hand or arm. This amount of blood is considered safe to donate. Samples will be sent to a commercial laboratory contracted to perform these tests for the study. These samples will be the property of Pfizer and Pfizer may also use the PK Biological Samples for evaluation of the bioanalytical method.

Other Biology Research Tests in this Study – Optional

You will be asked if you want to participate in 3 optional research tests. You can decide not to let the doctors do these tests and still be able to be treated as part of this study. There are checkboxes at end of this form to mark whether you are willing to participate in these voluntary studies. The results of these research tests will not be shared with you or become part of your medical record. These results would also not be used to make decisions about your care while enrolled on this study.

- **Using extra blood to look for genetic changes seen in tumor cells.**
  Tumor cells often release small pieces of DNA into the blood stream where it can be detected by sensitive tests. About 17mL (almost four teaspoons) of blood will be drawn at study entry and at each time disease evaluation testing is done (after cycles 2, 4, 6 and then every 4th cycle) to look at what genetic changes in your tumor may be seen over time from the small pieces of tumor DNA found in your blood. The blood will be sent to a commercial laboratory contracted to perform this testing for the study.

- **Comparing genetic changes between leftover tumor from an earlier procedure (diagnosis or second look) to relapsed neuroblastoma tumor tissue and bone marrow aspirates and whether these changes affect how the tumor will respond to treatment with Lorlatinib.**
  Researchers would like to look at tumor tissue to determine if there are certain gene changes present that might make your neuroblastoma more or less likely to respond to the drug lorlatinib. These tests would be done on tumor tissue remaining from diagnosis, or any previous surgery where tumor tissue was removed (removal of primary tumor or removal of tumor at a relapse) in the past. The tissue and bone marrow aspirates will be sent to a research laboratory at Children's Hospital of Philadelphia for testing.

When you have finished treatment with Lorlatinib
After you stop treatment on this study, you will continue to have tests and scans done (listed below) to measure how much tumor is left. If test results show you have abnormal organ functions, tests are recommended by the study to be repeated monthly until test results are stable or normal. You doctor will tell you how often these tests and evaluations will be done.

Medical Tests after the Study:

Physical exam	Neuropsychological testing[1]
Blood tests	Bone marrow tests and Various scans (CT/MRI, MIBG or PET) to check your tumor[2]
Electrocardiogram (EKG) to check the heart rhythm[3]	

[1]The same neuropsychological testing and evaluation done before starting study treatment will be done at the end of treatment with lorlatinib. The need for any further testing after this will be up to your doctor.

[2]Bone marrow tests and various scans are done for checking the response of your tumor to treatment. These tests will be done at the end of a course and at certain times following treatment to monitor your tumor status.

[3] Electrocardiogram (EKG) done at the end of the study to document if lorlatinib treatment has any effect on heart rhythm.

A table detailing the tests and procedures required before, during and after the study has been attached to the end of this form (Consent Addendum 1).

HOW LONG WILL I BE ON THIS STUDY?
You can get an unlimited number of treatment cycles with lorlatinib as long as you are not having bad side effects and as long as your tumor is not getting worse.

After you stop treatment, you will continue to have tests and scans done to measure how much tumor is left. Your doctor will tell you how often these tests will be done. Researchers will continue to collect information about you for a lifetime. Information will be collected about whether you are still alive; whether your tumor has grown back and at what sites in the body; whether you have developed any side effects from the treatment;

or whether you have developed any additional cancer. Your oncologist or family doctor will give the researchers this information at regular intervals.

CAN I STOP BEING IN THE STUDY?
Yes. If you are thinking about stopping your participation on this study, you should talk to your doctor before making a final decision so he/she can tell you how to do this safely.

Your doctor may also stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow study rules; or if the study is stopped.

WHAT ARE THE RISKS OF THE STUDY?
This is a Phase 1 study. A Phase 1 study looks at how common and serious side effects can be for each patient at a specific dose of a drug. In a Phase 1 study, some patients may have very serious side effects and could die as a result of these side effects. You may be one of those patients who have serious side effects as a result of participating in this Phase 1 study.

In this study, researchers will be looking at side effects seen in patients taking different doses of lorlatinib. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Other drugs may be given to make side effects less serious and more comfortable (such as for nausea, headache or reaction to lorlatinib). Many side effects go away soon after you stop taking the study medications but it is always possible that side effects can be serious, long lasting or may never go away. There is also a risk of death. Patients are watched carefully and treatment will be stopped if bad side effects develop. There may also be risks we do not know about. You should talk to your doctor about any side effects that you have while taking part in this study.

While on the study, you are at risk for the side effects listed below:

<u>Possible Risks of Lorlatinib</u>

The following side effects are considered to be related to lorlatinib have been reported:

Very Common (may affect 10 or more in 100 people)	**Common** (may affect from 1 up to less than 10 in 100 people)
• Increase in cholesterol and triglycerides (fats in your blood) • Effects on mood (for example, irritability and mood swings) • Effects on memory (for example, confusion, memory loss and disturbance of attention) • Effects on the peripheral nerves which are those outside of the brain and spinal cord, including tingling, numbness or pain in hands and feet) • Changes in vision (including double vision, perceived flashes or floaters of light, light intolerance, vision blurred,	• Hallucination and loss of contact with reality • Changes in mental status • Changes in speech (for example, slow speech or slurred speech) • Inflammation of the lungs (pneumonitis) which can cause shortness of breath and difficulty breathing. If severe, this can be life threatening.

vision sharpness reduced and visual impairment) • Hypertension • Diarrhea • Constipation • Joint pain • Build-up of fluid in the body or extremities causing swelling (edema) • Fatigue (feeling tired and exhausted) • Increase in body weight • Increase in blood sugar levels	

The following events have also been reported in patients while they were taking lorlatinib, although the relationship to lorlatinib is uncertain:

Very common (may affect 10 or more in 100 people)

- Abnormalities in blood tests that may indicate liver damage
- Abnormal pancreas tests
- Decrease in hemoglobin in the blood that can cause weakness
- Headache
- Muscle pain
- Difficulty sleeping
- Rash

Common (may affect from 1 up to less than 10 in 100 people)

- Decrease of ejection fraction of the heart which may indicate severe heart problem
- A sudden and temporary loss of consciousness (syncope)
- Changes in the electrical activity of your heart that might lead to a heart rhythm problem and/or irregular heartbeat

Uncommon (may affect less than 1 in 100 people)

- Inflammation of the pancreas causing pain in the upper abdomen. This could become severe and may cause nausea and vomiting, fever and rapid heart rate. This could require hospitalization and may be life threatening
- Suicidal thoughts
- Psychosis

Lorlatinib has moderate influence on the ability to drive and use machines. Caution should be exercised when driving or operating machines as patients may experience CNS effects.

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Possible Risks to Unborn Child
Patients who agree to participate in this study should not become pregnant while on this study. Lorlatinib may cause fetal harm when administered to a pregnant woman and is not recommended during pregnancy or for women of childbearing potential not using contraception. Women of childbearing potential should use nonhormonal methods of birth control. If a hormonal method of birth control is unavoidable, then a condom must be used in combination with the hormonal method. Female patients must continue to follow these birth control guidelines for 21 days after finishing the study. Male patients must wear condoms as one of their forms of birth control for the duration of the study and for 97 days after finishing the study. Further contraception use should be discussed with your personal physician. If you or your partner becomes pregnant while you are participating in this study, please notify your doctor immediately. For more information about risks and side effects, ask your doctor.

Possible Long Term Side Effects of Treatment with Lorlatinib
Side effects in adults treated with lorlatinib have occurred while patients have been receiving the drug or shortly after finishing the drug. It is not known if some side effects may be seen only after a long time after finishing treatment with lorlatinib.

Possible Risks from Having Blood Drawn
The risks from having your blood taken are minimal, but can include an infection or a blood clot. Experienced doctors or nurses will perform these blood draws to minimize this risk.

Unknown Risks
The treatment may have side effects that no one knows about yet. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?
There may or may not be direct medical benefit to you. The information learned from this study may or may not benefit other children, young people and adults with solid cancers in the future.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THIS STUDY?
There are other options for you instead of this treatment. Instead of being in this study, you have these options:

- Treatment with other chemotherapy medicines
- Treatment with other experimental agents that may be available.
- No neuroblastoma therapy at this time, with care to help you feel more comfortable.

Please talk about these options with your doctor.

WILL MY MEDICAL INFORMATION BE KEPT PRIVATE?
We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance and data analysis include:

- New Approaches to Neuroblastoma Therapy (NANT) Consortium at Children's Hospital Los Angeles in Los Angeles, CA. The NANT Consortium identifies you by a number.
- Independent auditor evaluating quality assurance for the NANT Consortium.
- The National Cancer Institute (NCI) and other governmental agencies, like the Food and Drug Administration (FDA) or Health Canada, involved in keeping research safe for people.
- Foundation Medicine, Inc. who is a collaborator on this study.
- Pfizer Inc., the pharmaceutical company which makes lorlatinib.

NANT has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. Information about the certificate is included at the end of this consent.

Because this study involves the treatment of a medical condition, a copy of this consent form will be placed in your medical record. This will allow the doctors that are caring for you to obtain information about what medications or procedures you are receiving in the study and treat you appropriately.

WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?
Taking part in this study may lead to added costs to your insurance company. Your health insurance company will be billed for many expenses associated with the costs of this study. These expenses include medications, treatments, hospital charges, and doctors' fees related to your participation in this study.

Lorlatinib and the flavoring agent (Ora-Plus®) are being provided free of charge for use in this study, but the costs associated with administering the drug is normally covered by your insurance company. The cost of doing a heart test called an EKG and neuropsychological testing at several time points during your participation in the study with lorlatinib is being done solely as part of research and will be paid for by the study.

The special research blood and tissue studies will be done at no cost to you. However, you or your health plan may need to pay for the costs of the supplies and personnel who draw the blood from you for these tests.

You may have to pay for other things during this study, such as but not limited to, your time, the cost of food you buy while you are being treated at the hospital, car fare, travel to and from the hospital for treatment, parking, and baby sitter fees.

Taking part in this study may lead to added costs that may not be covered by your insurance company. Please ask about any expected added costs or insurance problems.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's website at http://cancer.gov/clinicaltrials/understanding/insurance-coverage . You can print a copy of the "Clinical Trials and Insurance Coverage" information from this website.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?
It is important that you tell your study doctor, _____ *[investigator's name(s)],* if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number].*

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

WHAT ARE MY RIGHTS AS A STUDY PARTICIPANT?
Taking part in this study is your choice. You may choose not to take part or not take part in the study. If you decide to take part in this study, you may remove yourself from the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. If you remove yourself from the study, we will still take care of you. We will explain what stopping the treatment may do and we will offer other treatments if they are available.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In case of injury resulting from this study, you do not lose any of you legal rights to seek payment by signing this form.

A Data Safety and Monitoring Board, an independent group of experts, will be reviewing data from this research throughout the study. We will tell you about new information from this Board or other studies that may affect your health or willingness to stay in the study.

WHO IS FUNDING THIS RESEARCH STUDY?
This study is supported by Pfizer, Inc. Pfizer is a drug company that makes the drug being studied in this research project. Pfizer is giving money to Children's Hospital for some of the costs of the study. The results of the study will be reported to Pfizer. If the study shows that lorlatinib may be useful for a new purpose, this could benefit Pfizer financially.

The Children's Hospital Los Angeles/NANT is also providing funding for this study.

Dr. Mossé at Children's Hospital of Philadelphia, one of the principal investigators of this study, has served as a paid consultant to Pfizer. Her participation in this research has been reviewed and approved, subject to management, according to CHOP's/NANT Conflict of Interest Policy.

WHO CAN ANSWER MY QUESTIONS ABOUT THE STUDY?
You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number].*

For questions about your rights while taking part in this study, call the _____ *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ *(telephone number).*

WHERE CAN I GET MORE INFORMATION?

You may call the NCI's **Cancer Information Service** at

1–800–4–CANCER (1–800–422–6237) or **TTY: 1–800–332–8615**

You may visit the NCI Web sites at http://cancer.gov/
For NCI's clinical trials information, go to http://cancer.gov/clinicaltrials/
For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

You will get a copy of this consent form. If you want more information about this study, ask your doctor.

CONSENT FOR EXTRA STUDIES FOR RESEARCH

The following tests are optional for all patients in the study. You may still participate in the study even if you do not agree to these tests.

1. Using extra blood to look for genetic changes seen in tumor cells

Initial next to YES if you agree to let researchers take almost 4 extra teaspoons (17 mL) at study entry and each time a disease evaluation is done) to look at what genetic changes in your tumor can be seen in your blood over time before and after treatment with lorlatinib. This blood would be drawn at a time when blood was being drawn for clinical purposes. The blood will be sent to Foundation Medicine Inc. for analysis who is a collaborator on this study. The results of these tests will be confidential and not made available to you or your treating physician.

Initial next to NO, if you do not want researchers to take extra blood above what is needed for clinical purposes.

_____Yes _____No

2. Comparing genetic changes between tumor leftover from an earlier procedure (diagnosis or second look) to relapsed neuroblastoma tumor tissue and bone marrow aspirates and whether these changes affect how the tumor will respond to treatment with Lorlatinib.

Initial next to YES, if you agree (and if there is tumor remaining) to let this tumor be sent to a laboratory so researchers can compare these samples and determine if there are certain gene changes present that might make your neuroblastoma more or less likely to respond to the drug lorlatinib. The results of these tests will be confidential and not made available to you or your treating doctor.

Initial next to NO if you do not want left over tumor from an earlier procedure to be sent to a research laboratory to look for certain gene changes that might make your neuroblastoma more or less likely to respond to the drug lorlatinib.

_____Yes _____No

Initial next to YES, if you agree to let extra bone marrow aspirates be collected to be sent to a laboratory so researchers can compare these samples and determine if there are certain gene changes present that might make your neuroblastoma more or less likely to respond to the drug lorlatinib. The results of these tests will be confidential and not made available to you or your treating doctor.

Initial next to NO if you do not want these bone marrow aspirates collected to be sent to a research laboratory to look for certain gene changes that might make your neuroblastoma more or less likely to respond to the drug lorlatinib.

_____Yes _____No

STATEMENT OF CONSENT

I have already read the information in this informed consent document. I have read all the attachments that were included with this informed consent document. I have asked all of my questions and I have gotten answers. I agree to enroll myself (my child) in this study.

_____
Print Patient Name

_____ _____/_____/_____
Signature of Patient Date

_____ _____/_____/_____
Signature of Physician or Responsible Investigator Date

_____ ____/_____/_____
Signature of Witness Date

_____ ____/_____/_____
Signature of Translator Date

Consent Addendum I: Tests that will be done on this study.

Observation	Before Entry	Cycle 1	Cycle 2	Subsequent Cycles	End of Therapy
Physical exam including neurological exam	X	Weekly	Start of cycle	Start of each cycle	X
Routine blood tests** (Blood counts, electrolytes, liver, kidney function, , function of pancreas-amylase/lipase)	X	Weekly	Weekly for blood counts and twice during cycle for all other blood tests	Start of each cycle	X
Routine Blood tests** (Fasting cholesterol, triglycerides, glucose)	X	Every other week	Start of cycle	Start of each cycle	X
Hemoglobin A1c (HbA1c)	X		Start of cycle	With Disease Evaluations in Courses 4 and 6 and after every 4 cycles thereafter	X
Pregnancy test (All females 10 years of age and older)	X		Start of cycle	Start of each cycle	
Heart rhythm test (EKG)	X	One hour after day 1 treatment is finished	End of cycle	End of cycle (4,6 and every 4th cycle thereafter)	X
Neuropsychological Testing	Within one week before starting treatment	End of cycle	End of cycle	End of cycle (4, 6 and every 4th cycle thereafter)	X
Neuropsychological evaluation with licensed psychologist for patients less than 3 years of age	Within one week before and up to one week after starting treatment		End of cycle	End of cycle 6, 10 and then every 8 cycles thereafter	X
Submit Patient Treatment Diaries		X	X	X	X
Blood for Lorlatinib drug level tests (PK - Required)		Day 1: 3 times Day 2: 1 time Day 15: 5 times			
Bone Marrow Aspirate (Optional)	X		With disease evaluation	End of cycle (4,6, and every 4th cycle thereafter)	
Blood for circulating tumor cells (Optional)	X		With disease evaluation	End of cycle (4,6 and every 4th cycle thereafter)	
Sampling of leftover tumor tissue (Optional)	Leftover tumor tissue can be sent at any time during the study				
	Tests done at Disease Evaluation				
Bone marrow aspirate and biopsy	X		Week 4	End of cycle (4,6 and every 4th cycle thereafter)	X
CT/MRI scans and/or MIBG/PET scans					
Blood and bone marrow for NANT Biology study[#]					

[#] Patients enrolled in the companion biology study may have additional samples of blood and bone marrow collected at study entry and with each disease evaluation time point. Please look at the biology study N04-05 consent form for more information.

**Blood draws can be done more often if needed at the discretion of your study doctor

Consent Addendum 2

Certificate of Confidentiality Information

NANT has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. The Certificate protects against the involuntary release of information about subjects collected during the course of our covered studies. The researchers involved in the studies cannot be forced to disclose the identity or any information collected in the study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, the subject or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if the subject or his/her guardian requests the release of information in writing, the Certificate does not protect against that voluntary disclosure. Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act. The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

APPENDIX IX: SAMPLE ASSENT FORM COHORTS A1 AND B1

NANT 2015-02: PHASE 1 STUDY OF PF-06463922 (LORLATINIB), AN ORAL SMALL MOLECULE INHIBITOR OF ALK/ROS1, FOR PATIENTS WITH ALK-DRIVEN RELAPSED OR REFRACTORY NEUROBLASTOMA

Cohorts A1 and B1: Taking Lorlatinib only

A New Approaches to Neuroblastoma Therapy (NANT) treatment protocol

INVESTIGATOR [Insert Name of Investigator]
[Insert Name of Institution]

[Insert Address (include City, State and Zip Code)]
[Insert Telephone/Fax Numbers]
[Insert Email]

1. Dr. _____ is doing a research study about using other medicines to get rid of Neuroblastoma.

2. You have a kind of cancer called **neuroblastoma.** We are doing a study about this kind of cancer. It may be that your cancer went away for a while but has come back. Or it may be that it has never gone away. We are asking you to take part in a research study because doctors want to learn more about treating neuroblastoma using a medicine called **lorlatinib** to see what effects (both good and bad) this medicine has on patients and their cancer. Lorlatinib is a medicine that is given by mouth either as a pill (tablet) or a liquid. The doctors think that giving this drug may help get rid of neuroblastoma cancer cells.

3. **If you agree to be in this study this is what will happen:**
   You will take lorlatinib by mouth every day followed by a small glass of water. Lorlatinib is given in cycles that last about one month (28 days). You can continue taking lorlatinib for as many cycles as you can unless there are side effects or your tumor gets worse. Lorlatinib works differently than some of the other medicines you have gotten before to treat your neuroblastoma. Before this study started, the doctors sent a sample of your tumor to a laboratory for testing and found out there is a change in the ALK gene. The ALK gene is a gene that when it has been changed, can help your neuroblastoma tumor to grow. Lorlatinib works on the ALK gene. Researchers hope it will stop your neuroblastoma tumor from growing.

   Coming to See the Doctors:
   During and after you have finished the treatment, you will have appointments with the doctors who are taking care of you. This is called "**Follow-Up**". This is to see how well the treatment has worked so far. The doctors will want to do some special tests to find this information out. They will include;

   - Blood tests (we will do this twice each week to start with, and then less often). You may need to fast (not eat anything and not drink anything other than water) for 8 hours before certain blood tests. This will happen once per week in the first month of treatment and then just once per month during the rest of treatment.
   - A heart test called an EKG that shows the doctors your heart beat. This is done by attaching wires from an EKG machine to your chest with sticky pads. It takes less than 5 minutes to do this test once all the wires are attached.
   - MRI, CT, and MIBG Scans (special pictures of your tumor)
   - Bone marrow test (to look for tumor in your bone marrow)
   - Feel your belly, look into your eyes and ears, and listen to your heart and lungs.
   - Ask you and your parents a lot of questions about how you are feeling, how you are doing in school, and any problems you might be having.

- The doctors will have you answer questions about how you are doing using an iPad. This should take about 30 minutes to do. At the same time you are using your iPad; your parents will also answer questions about how you are doing using pen and paper. This testing will be done at the beginning then monthly to every other month for a year then less often after that. Your doctor will let you know if any of these testing needs to be done more often.

- You will come to visit your doctor every week or so to start with, then less often if everything is going well.
- To measure the amount of medicine in your blood, we will draw 9 blood samples (about 5 teaspoons total) over the first 2 days of treatment with lorlatinib. We can use your central line to draw these blood samples. If you don't have a central line, you will need to have a needle poke or a small plastic tube placed in a vein of your hand or arm to collect these samples.

4. **When you are in a research study, sometimes good things and bad things can happen.**
Sometimes things happen to kids in research studies that may make them feel bad. These are called "risks". Some of the risks of this study are:
    - You may feel lightheaded, jittery, irritable or hungry while you are fasting before certain tests
    - You may have swelling in your arms and legs
    - You may have tingling, or prickly feeling or numbness in your hands and feet
    - You may have a hard time concentrating, remembering things or talking to others.
    - You may feel tired
    - You may feel sick to your stomach and you may throw up
    - You may not feel like eating
    - You may get diarrhea or constipation
    - You may feel difficulty breathing
    - You may gain weight
    - The treatments may not work and your tumor may grow, or it might come back again after the treatment has finished. If this happens, we will try other ways to stop the tumor from growing.
    - You could get a different kind of cancer, this doesn't happen often, but can happen years later.
    - It is possible you could die from the treatment or cancer.

Not all of these things may happen to you. It's possible that none of them will happen. Or bad things may happen that we don't know about yet.

- Things that happen to children in research studies that are good are called "benefits". Some of the good things for this research study could be:
    - This treatment might make your neuroblastoma tumor stay the same size or get smaller for some time.
    - We hope to learn more about this new treatment which could help other children with neuroblastoma

5. We will do everything possible to keep your information private and prevent people outside of the study from seeing information about you.

6. Please talk this over with your parents before you decide whether or not to be in this study. We will also ask your parents to give their permission for you to take part in this study. But even if your parents say "yes" <u>you</u> can still decide not to do this.

7. You do not have to be in this study if you don't want to. You may stop being in this study at any time. Remember, being in this study is up to <u>you</u>.

8. You can ask any questions that you have about the study. If you have a question later that you didn't think of now, you can call me or ask me next time you see me.

- Study doctor's phone number: _____

9. **Special Study Tests:**

   You will have blood tests done to measure the amount of lorlatinib in your blood. This blood test will be done 9 times over 3 days in the first course. A central line can be used to draw these blood samples. Otherwise you may need to have a needle poke or a small plastic tube placed in a vein of your hand or arm for these samples.

   There are extra tests on this study that are optional meaning that you can say no to doing these tests and still be part of the main study. Please discuss this with your family. These extra tests are done for research only so the results won't be told to your doctor or to you.

   #1: Almost 4 teaspoons of extra blood will be taken at the same time blood will be drawn as part of your normal neuroblastoma care. This would be done when you start the study and then every time after when you have tests and scans to look at how your tumor is doing (called a disease evaluation).

   #2: The doctors will compare old and new tumor samples and bone marrow aspirates collected from you as part of your normal neuroblastoma care. They will be looking at changes in the ALK gene in these tumor samples.

Signing your name at the bottom means that you agree to be in this study. You and your parents will be given a copy of this form after you have signed it.

Name of Patient: _____

_____ Yes, I want to be in the study.

_____ No, I do not want to be in the study.

_____ _____
Signature of Patient **Date**

_____ _____
Name of Physician or Responsible Investigator **Date**

_____ _____
Signature of Physician or Responsible Investigator **Date**

APPENDIX X: SAMPLE ASSENT FORM COHORT A2

NANT 2015-02: PHASE 1 STUDY OF PF-06463922 (LORLATINIB), AN ORAL SMALL MOLECULE INHIBITOR OF ALK/ROS1, FOR PATIENTS WITH ALK-DRIVEN RELAPSED OR REFRACTORY NEUROBLASTOMA

Cohort A2: Taking Lorlatinib only

A New Approaches to Neuroblastoma Therapy (NANT) treatment protocol

INVESTIGATOR [Insert Name of Investigator]
[Insert Name of Institution]

[Insert Address (include City, State and Zip Code)]
[Insert Telephone/Fax Numbers]
[Insert Email]

1. Dr. _____ is doing a research study about using other medicines to get rid of Neuroblastoma.

2. You have a kind of cancer called **neuroblastoma.** We are doing a study about this kind of cancer. It may be that your cancer went away for a while but has come back. Or it may be that it has never gone away. We are asking you to take part in a research study because doctors want to learn more about treating neuroblastoma using a medicine called **lorlatinib** to see what effects (both good and bad) this medicine has on patients and their cancer. Lorlatinib is a medicine that is given by mouth either as a pill (tablet) or a liquid. The doctors think that giving this drug may help get rid of neuroblastoma cancer cells.

3. **If you agree to be in this study this is what will happen:**
You will take lorlatinib by mouth every day followed by a small glass of water. Lorlatinib is given in cycles that last about one month (28 days). You can continue taking lorlatinib for as many cycles as you can unless there are side effects or your tumor gets worse. Lorlatinib works differently than some of the other medicines you have gotten before to treat your neuroblastoma. Before this study started, the doctors sent a sample of your tumor to a laboratory for testing and found out there is a change in the ALK gene. The ALK gene is a gene that when it has been changed, can help your neuroblastoma tumor to grow. Lorlatinib works on the ALK gene. Researchers hope it will stop your neuroblastoma tumor from growing.

Coming to See the Doctors:
During and after you have finished the treatment, you will have appointments with the doctors who are taking care of you. This is called "**Follow-Up**". This is to see how well the treatment has worked so far. The doctors will want to do some special tests to find this information out. They will include;

- Blood tests (we will do this twice each week to start with, and then less often). You may need to fast (not eat anything and not drink anything other than water) for 8 hours before certain blood tests. This will happen once per week in the first month of treatment and then just once per month during the rest of treatment.
- A heart test called an EKG that shows the doctors your heart beat. This is done by attaching wires from an EKG machine to your chest with sticky pads. It takes less than 5 minutes to do this test once all the wires are attached.
- MRI, CT, and MIBG Scans (special pictures of your tumor)
- Bone marrow test (to look for tumor in your bone marrow)
- Feel your belly, look into your eyes and ears, and listen to your heart and lungs.

- Ask you and your parents a lot of questions about how you are feeling, how you are doing in school, and any problems you might be having.
    - The doctors will have you answer questions about how you are doing using an iPad. This should take about 30 minutes to do. At the same time you are using your iPad; your parents will also answer questions about how you are doing using pen and paper. This testing will be done at the beginning then monthly to every other month for a year then less often after that. Your doctor will let you know if any of these testing needs to be done more often.
- You will come to visit your doctor every week or so to start with, then less often if everything is going well.
- To measure the amount of medicine in your blood, we will draw 9 blood samples (about 5 teaspoons total) over the first 2 days of treatment with lorlatinib. We can use your central line to draw these blood samples. If you don't have a central line, you will need to have a needle poke or a small plastic tube placed in a vein of your hand or arm to collect these samples.

4. **When you are in a research study, sometimes good things and bad things can happen.**
Sometimes things happen to kids in research studies that may make them feel bad. These are called "risks". Some of the risks of this study are:
    a. You may feel lightheaded, jittery, irritable or hungry while you are fasting before certain tests
    b. You may have swelling in your arms and legs
    c. You may have tingling, or prickly feeling or numbness in your hands and feet
    d. You may have a hard time concentrating, remembering things or talking to others.
    e. You may feel tired
    f. You may feel sick to your stomach and you may throw up
    g. You may not feel like eating
    h. You may get diarrhea or constipation
    i. You may feel difficulty breathing
    j. You may gain weight
    k. The treatments may not work and your tumor may grow, or it might come back again after the treatment has finished. If this happens, we will try other ways to stop the tumor from growing.
    l. You could get a different kind of cancer, this doesn't happen often, but can happen years later.
    m. It is possible you could die from the treatment or cancer.

    Not all of these things may happen to you. It's possible that none of them will happen. Or bad things may happen that we don't know about yet.
    - Things that happen to children in research studies that are good are called "benefits". Some of the good things for this research study could be:
        - This treatment might make your neuroblastoma tumor stay the same size or get smaller for some time.
        - We hope to learn more about this new treatment which could help other children with neuroblastoma

5. We will do everything possible to keep your information private and prevent people outside of the study from seeing information about you.

6. Please talk this over with your parents before you decide whether or not to be in this study. We will also ask your parents to give their permission for you to take part in this study. But even if your parents say "yes" <u>you</u> can still decide not to do this.

7. You do not have to be in this study if you don't want to. You may stop being in this study at any time. Remember, being in this study is up to <u>you</u>.

8. You can ask any questions that you have about the study. If you have a question later that you didn't think of now, you can call me or ask me next time you see me.
   - Study doctor's phone number: _____

9. **Special Study Tests:**

You will have blood tests done to measure the amount of lorlatinib in your blood. This blood test will be done 9 times over the 3 days in the first course. A central line can be used to draw these blood samples. Otherwise you may need to have a needle poke or a small plastic tube placed in a vein of your hand or arm for these samples.

There are extra tests on this study that are optional meaning that you can say no to doing these tests and still be part of the main study. These extra tests are done for research only so the results won't be told to your doctor or to you.

#1: Almost 4 teaspoons of extra blood will be taken at the same time blood will be drawn as part of your normal neuroblastoma care. Please discuss this with your family. This would be done when you start the study and then every time after when you have tests and scans to look at how your tumor is doing (called a disease evaluation).

#2: The doctors will compare old and new tumor samples and bone marrow aspirates collected from you as part of your normal neuroblastoma care. They will be looking at changes in the ALK gene in these tumor samples.

Signing your name at the bottom means that you agree to be in this study. You and your parents will be given a copy of this form after you have signed it.

Name of Patient: _____

_____ Yes, I want to be in the study.
_____ No, I do not want to be in the study.

_____ _____
Signature of Patient **Date**

_____ _____
Name of Physician or Responsible Investigator **Date**

_____ _____
Signature of Physician or Responsible Investigator **Date**

APPENDIX XI: SAMPLE ASSENT FORM COHORT B2

NANT 2015-02: PHASE 1 STUDY OF PF-06463922 (LORLATINIB), AN ORAL SMALL MOLECULE INHIBITOR OF ALK/ROS1, FOR PATIENTS WITH ALK-DRIVEN RELAPSED OR REFRACTORY NEUROBLASTOMA

Cohort B2: Taking Lorlatinib combined with chemotherapy (cyclophosphamide/topotecan)

A New Approaches to Neuroblastoma Therapy (NANT) treatment protocol

INVESTIGATOR [Insert Name of Investigator]
[Insert Name of Institution]

[Insert Address (include City, State and Zip Code)]
[Insert Telephone/Fax Numbers]
[Insert Email]

1. Dr. _____ is doing a research study about using other medicines to get rid of Neuroblastoma.

2. You have a kind of cancer called **neuroblastoma.** We are doing a study about this kind of cancer. It may be that your cancer went away for a while but has come back. Or it may be that it has never gone away. We are asking you to take part in a research study because doctors want to learn more about treating neuroblastoma using three experimental medicines called **lorlatinib, cyclophosphamide and topotecan** and to see what effects (both good and bad) these medicines has on patients and their cancer. Lorlatinib is a medicine that is given by mouth either as a pill (tablet) or a liquid. Cyclophosphamide and topotecan are medicines that are given into the bloodstream either through your central line or a small tube placed in a vein in your hand or arm. The doctors think that giving these three drugs together may help get rid of neuroblastoma cancer cells.

3. **If you agree to be in this study this is what will happen:**

   The medicines will be given in cycles that each last about one month (28 days). Your doctor will explain the schedule for each cycle to you and your parents. You can continue to get this treatment unless you have bad side effects or your tumor gets worse. These medicines work differently than some of the other medicines you have gotten before to treat your neuroblastoma.

   Before this study started, the doctors sent a sample of your tumor to a laboratory for testing and found out there is a change in the ALK gene. The ALK gene is a gene that when it has been changed, can help your neuroblastoma tumor to grow. Lorlatinib works on the ALK gene. Researchers hope it will stop your neuroblastoma tumor from growing when used together the chemotherapy medinces cyclophosphamide and topotecan.

   Lorlatinib:
   You will take lorlatinib by mouth every day followed by a small glass of water.

   Cyclophosphamide and topotecan:
   You will take cyclophosphamide and topotecan by I.V. once a day for the first 5 days of every cycle. You will be in the clinic on those days. You do not need to be in the hospital to get these chemotherapy medicines.

Other medicines (not chemotherapy):

You will need to take Neupogen (given once a day as an injection) or Neulasta (given once each cycle as an injection). These medicines are given to help your normal blood cells get better after getting chemotherapy medicines like cyclophosphamide and topotecan.

Coming to See the Doctors:

During and after you have finished the treatment, you will have appointments with the doctors who are taking care of you. This is called "**Follow-Up**". This is to see how well the treatment has worked so far. The doctors will want to do some special tests to find this information out. They will include;

- Blood tests (we will do this twice each week to start with, and then less often). You may need to fast (not eat anything and not drink anything other than water) for 8 hours before certain blood tests. This will happen once per week in the first month of treatment and then just once per month during the rest of treatment.
- A heart test called an EKG that shows the doctors your heart beat. This is done by attaching wires from an EKG machine to your chest with sticky pads. It takes less than 5 minutes to do this test once all the wires are attached.
- MRI, CT, and MIBG Scans (special pictures of your tumor)
- Bone marrow test (to look for tumor in your bone marrow)
- Feel your belly, look into your eyes and ears, and listen to your heart and lungs.
- Ask you and your parents a lot of questions about how you are feeling, how you are doing in school, and any problems you might be having.
    - The doctors will have you answer questions about how you are doing using an iPad. This should take about 30 minutes to do. At the same time you are using your iPad; your parents will also answer questions about how you are doing using pen and paper. This testing will be done at the beginning then monthly to every other month for a year then less often after that. Your doctor will let you know if any of these testing needs to be done more often.
- You will come to visit your doctor every week or so to start with, then less often if everything is going well.
- To measure the amount of medicine in your blood, we will draw 9 blood samples (about 5 teaspoons total) over the first 2 days of treatment with lorlatinib. We can use your central line to draw these blood samples. If you don't have a central line, you will need to have a needle poke or a small plastic tube placed in a vein of your hand or arm to collect these samples.

4. **When you are in a research study, sometimes good things and bad things can happen.**

Sometimes things happened to children in research studies that may make them feel bad. These are called "risks". Some of the risks of this study are:

- You may feel lightheaded, jittery, irritable or hungry while you are fasting before certain tests
- You may have swelling in your arms and legs
- You may have tingling, or prickly feeling or numbness in your hands and feet
- You may have a hard time concentrating, remembering things or talking to others.
- You may feel tired
- You may feel sick to your stomach and you may throw up
- You may not feel like eating
- You might have a fever and maybe an infection where you will need to be in the hospital to get medicines to treat the infection. You may feel tired and weak and need a blood transfusion or you may get bruises or have bleeding (most often a nosebleed) and need a platelet transfusion.
- You may get sores in your mouth that makes it difficult to eat and drink. If this happens, you may need some pain medicines and you may need to stay in the hospital.
- You may get diarrhea or constipation.

- You may feel difficulty breathing
- You may gain weight
- The treatments may not work, and your tumor may grow, or it might come back again after the treatment has finished. If this happens we will try other ways to stop the tumor from growing
- You could get a different kind of cancer, this doesn't happen often, but can happen years later
- It is possible that you could die from the treatment or cancer

Not all of these things may happen to you. It's possible that none of them will happen. Or bad things may happen that we don't know about yet.

Things that happen to children in research studies that are good are called "benefits". Some of the good things for this research study could be:

- This treatment might make your neuroblastoma tumor stay the same size or get smaller for some time.
- We hope to learn more about this new treatment which could help other children with neuroblastoma

5. We will do everything possible to keep your information private and prevent people outside of the study from seeing information about you.

6. Please talk this over with your parents before you decide whether or not to be in this study. We will also ask your parents to give their permission for you to take part in this study. But even if your parents say "yes" you can still decide not to do this.

7. You do not have to be in this study if you don't want to. You may stop being in this study at any time. Remember, being in this study is up to you.

8. You can ask any questions that you have about the study. If you have a question later that you didn't think of now, you can call me or ask me next time you see me.

    - Study doctor's phone number: _____

9. **Special Study Tests:**

You will have blood tests done to measure the amount of lorlatinib in your blood. This blood test will be done 9 times over 3 days in the first course. A central line can be used to draw these blood samples. Otherwise you may need to have a needle poke or a small plastic tube placed in a vein of your hand or arm for these samples.

There are extra tests on this study that are optional meaning that you can say no to doing these tests and still be part of the main study. Please discuss this with your family. These extra tests are done for research only so the results won't be told to your doctor or to you.

#1: Almost 4 teaspoons of extra blood will be taken at the same time blood will be drawn as part of your normal neuroblastoma care. This would be done when you start the study and then every time after when you have tests and scans to look at how your tumor is doing (called a disease evaluation).

#2: The doctors will compare old and new tumor samples and bone marrow aspirates collected from you as part of your normal neuroblastoma care. They will be looking at changes in the ALK gene in these tumor samples.

Signing your name at the bottom means that you agree to be in this study. You and your parents will be given a copy of this form after you have signed it.

Name of Patient: _____

_____ Yes, I want to be in the study.

_____ No, I do not want to be in the study.

_____ _____
Signature of Patient **Date**

_____ _____
Name of Physician or Responsible Investigator **Date**

_____ _____
Signature of Physician or Responsible Investigator **Date**

APPENDIX VI: DOSE ESCALATION AND EXPANSION COHORT (A1 & B1) SAMPLE CONSENT

NANT 2015-02: PHASE 1 STUDY OF LORLATINIB (PF-06463922), AN ORAL SMALL MOLECULE INHIBITOR OF ALK/ROS1, FOR PATIENTS WITH ALK-DRIVEN RELAPSED OR REFRACTORY NEUROBLASTOMA

PHASE 1 DOSE ESCALATION & EXPANSION COHORT (A1 & B1): FOR PATIENTS ONE YEAR OF AGE UP TO 18 YEARS OF AGE

A New Approaches to Neuroblastoma Therapy (NANT) treatment protocol.

The word "you" used throughout this document refers to you or your child.

WHAT IS THIS STUDY ABOUT?
This study is a clinical trial, a type of research study. Clinical trials include only patients who choose to take part. Please take your time to make your decision about participating. You may discuss your decision with your friends, family, and health care team. If you have any questions, you may ask your doctor.

You are being asked to participate in this study because you have a kind of cancer called neuroblastoma. It may be that your cancer went away for a while but has grown back (relapsed) or it may be that it has never gone away (persistent or resistant tumor) after standard treatment. Standard treatment may have included chemotherapy, surgery, radiation therapy, high-dose chemotherapy with a stem cell transplant and/or immunotherapy.

WHY IS THIS STUDY BEING DONE?

The purposes of this study are:

- To find the highest safe dose of lorlatinib that can be given to children and adolescents with refractory or relapsed neuroblastoma without causing severe side effects.
- To learn about the side effects of the drug lorlatinib given at different dose levels to children and adolescents 1-18 years of age.
- To determine if your tumor gets smaller after treatment with lorlatinib.
- To measure the levels of lorlatinib in the blood at different dose levels.
- To look at genetic changes in tumor DNA found in the blood during treatment with lorlatinib.
- To look at genetic changes in tumor tissue to see if they affect response to lorlatinib.
- To describe the amount of neuroblastoma tumor found in the blood and bone marrow by testing samples with a new test (called NB5 assay).

The research is being done because:
Currently there is no known effective treatment for your type of cancer. We are testing new experimental drugs such as lorlatinib in the hopes of finding a drug that may be effective against neuroblastoma tumors that have come back (relapsed) or that have never gone away (persistent/refractory) after treatment with standard therapy.

This study involves the use of an experimental drug called lorlatinib. In laboratory testing, lorlatinib blocks the Anaplastic Lymphoma Kinase (ALK). ALK may be important in the growth of certain types of cancer cells, such as neuroblastoma. Lorlatinib is considered experimental because it has not been proven to work in a

situation like yours. Lorlatinib has been approved by the United States Food and Drug Administration (FDA) to treat adults with non-small cell lung cancer, a different cancer than yours. It is not approved for neuroblastoma. Lorlatinib has been used only in a small number of adults so there is a lot we do not know about it yet. Lorlatinib has not previously been used in children and adolescents not enrolled on this study. This study is called a phase 1 study because the goal is to find the highest dose of lorlatinib that we can give safely. Once we have found out the highest dose of lorlatinib that can be given safely, we will treat more children and adolescents with neuroblastoma with this Lorlatinib dose.

All patients enrolled on this phase 1 study have been previously tested and are known to have a defect in the ALK gene in their tumor before they start treatment. You or your doctor should have the results of this test before enrolling on this study.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

There will be about 60-75 patients enrolling on the 4 study cohorts. You have been given this consent because the planned enrollment is on cohort A1 or B1. When you join the study, you will be assigned a certain lorlatinib dose. This study will test up to five lorlatinib doses in groups of 3-6 patients. The starting lorlatinib dose for the first group of patients was about 25% lower than what was given to adults who received lorlatinib without bad side effects. If this is tolerated without serious side effects, then the lorlatinib dose will be increased in groups of 3-6 patients until the fifth dose level or if serious side effects are seen. At that point, investigators will have found the highest dose of lorlatinib that can be given without bad side effects. This part of the trial is called cohort A1.

Once the maximum tolerated dose is determined, another group of 6 patients will be enrolled and treated at this dose of lorlatinib, known as the dose expansion part of the study (Cohort B1). The purpose of the dose expansion part of the study is to gather more information about side effects seen in patients treated at the maximum tolerated dose of lorlatinib. The dose expansion cohort (Cohort B1) will not enroll patients until the dose escalation part of the study (Cohort A1) is completed and the highest dose of lorlatinib that can be given safely without serious side effects is found.

WHAT WILL HAPPEN TO ME IF I TAKE PART IN THIS STUDY?

Before You Begin the Study

Your doctor will have previously sent your tumor for genetic testing and these results showed your tumor has a defect in the *ALK* gene which allows you to be considered for participation in this study (Cohorts A1 and B1).

You will need to have the following exams, tests or procedures to find out if you can take part in the study. Most of these exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. These tests will also be done at various times throughout the study and at the end of the study. The purpose of these tests is to see how well the treatment works and to measure the status of your neuroblastoma. If you have had some of them recently, they may not need to be repeated. This will be up to your doctor.

A medical history & physical exam	Bone marrow tests[3] to check your tumor
Blood tests[1]	Various scans[4] to check your tumor
Pregnancy test (urine or blood)[2]	Electrocardiogram (EKG) to check the heart rhythm[5]
	Neuropsychological testing[6]

[1]Some blood tests (cholesterol and fat digestion [triglycerides]) may need to be done on an empty stomach, so you cannot eat or drink anything other than water for 8 hours before these tests are done (called fasting). Your doctor or nurse will tell you if it is necessary for you to fast before these blood tests are done.

[2]If you are a female at least 10 years old or who could have children, you will have a pregnancy test done by the doctor the week before starting treatment and then before each cycle of treatment begins. Both you and your parent/legal guardian will be informed of a positive pregnancy test. All men and women who could have children must either agree to practice abstinence from heterosexual intercourse or use two effective methods of birth control for as long as they participate in this study.

[3]Bone marrow tests are done by inserting a needle into the hip bone to remove the marrow which is inside the bone.

[4]Various scans are done for diagnosis and checking the response of the tumor to treatment. These may include CT and /or MRI scans and MIBG or PET scans. We will recommend scans specific for your case and we will answer your questions about these scans.

[5]Electrocardiogram (EKG) to document your heart rhythm before beginning lorlatinib treatment.

[6] Central nervous system effects (speech, memory and mood changes) were seen in previous studies treating adults with lorlatinib. Neuropsychological testing will be done within one week of starting treatment and at different times during this study to monitor for any changes in thinking skills, behavior and mood. Please see the section on Neuropsychological testing below in "During the Study" for more details on what tests are done and when they are done during this study.

<u>During the Study</u>

If the exams, tests and procedures show that you can be in the study, and you choose to take part, lorlatinib will be given for 28 days. This entire period is called a cycle with each treatment cycle being 28 days long. You may continue to take lorlatinib for an unlimited number of cycles unless you develop serious side effects or your tumor worsens.

One Treatment Cycle (Cohort A1: dose escalation group and Cohort B1: dose expansion group)			
Week 1	Week 2	Week 3	Week 4
Days 1 – 7	Days 8 - 14	Days 15 - 21	Days 22 - 28
Lorlatinib once a day →			

Lorlatinib will be given by mouth once a day followed by a small glass of water. If you vomit lorlatinib within 20 minutes of taking the dose for the day, that dose can be repeated. This is the only time a dose of lorlatinib can be repeated.

Lorlatinib will be available as a tablet. If you are unable to swallow the tablets whole, you will be instructed on how to make a liquid lorlatinib solution at home by mixing the lorlatinib tablets with water and a flavoring agent (Ora-Plus®). Your nurse or doctor will help you decide what is best for you and will make sure you have the proper directions for taking this medication.

You will be given a patient diary at the beginning of each cycle of lorlatinib. Use the diary to record the date and time you take the drug, all vomited and missed doses, side effects that you experience and any other medications and supplements you are taking. The diary should be returned to clinic along with the medication bottle (even if it is empty) weekly during cycle 1 and then after each treatment cycle of lorlatinib. This will help us to know how much of the drug you take and how it made you feel.

During the study you will have tests and procedures done to check for side effects from taking lorlatinib and to see how your tumor is doing. Many of these tests are part of regular cancer care but you may have them done more often because you are on the study:

Physical exam	Electrocardiogram (EKG) to test heart rhythm [3]
Blood tests [1]	Bone marrow tests & various scans (CT/MRI, MIBG or PET) to check your tumor [4]
Pregnancy test (urine or blood) [2]	Neuropsychological testing[5]

[1] Some blood tests (cholesterol and fat digestion) may be done on an empty stomach, so patients cannot eat or drink anything other than water for 8-10 hours before these tests are done.

[2] A urine or blood pregnancy test will be done before each treatment cycle begins if you are a female at least 10 years old or who could have children. Both you and your parent/legal guardian will be informed of a positive pregnancy test. All men and women who could have children must continue to practice abstinence from heterosexual intercourse or use two effective methods of birth control for as long as they participate in this study.

[3] Electrocardiogram (EKG) done before starting study treatment will be repeated at certain times during the study to document if lorlatinib treatment has any effect on heart rhythm.

[4] Bone marrow tests and various scans are done for checking the response of your tumor to treatment. These tests will be done at certain times during the study to look at response to lorlatinib and check that your tumor has not gotten worse.

[5] **Neuropsychological Testing**

Neuropsychological evaluations try to understand how changes in the health of the brain may affect behavior or mood and how well a person is able to pay attention, remember things or solve problems. Since effects on speech, memory and mood were seen in a small number of adults receiving lorlatinib, neuropsychological testing will be done to monitor for changes in thinking skills, behavior and mood at different times during this study. A table at the end of the consent lists how often neuropsychological testing will be done during the study. Testing methods are based on the age of the patient and include computerized tests using an iPad, written questionnaires and evaluations by a licensed psychologist. Parents or legal guardians of patients less than 18 years of age will also participate by completing written questionnaires at the same time their child is being tested.

If the testing results show areas of concern, you may be given more frequent testing as well as referrals for other care if needed. During testing, patients may skip questions that are stressful and may stop taking the tests at any time. Testing can be done as part of the clinic visit. You will need to talk with your doctor and nurse about scheduling to do these tests at times that are workable for you and your child.

- All patients 3 years of age and older will do computerized tests using an iPad. While the patient is taking these tests, the patient's parent or legal guardian will complete written questionnaires about the patient's mood and emotions, behavior, daily living/functional skills and social skills with others. The parent/legal guardian can be in the same room during the testing but they cannot help their child with their tests.
- Patients 18 years of age will complete computerized tests using an iPad and their own written questionnaires. Parents/Legal guardians do not have testing to do with patients of this age.
- Patients under 3 years of age will have an evaluation of overall functioning including language, motor and cognitive development done by a licensed psychologist. This testing will take 60 to 90 minutes to complete. Parents/legal guardians will also complete written questionnaires at the same time.

<table>
<tr><th>Patient age at testing in years</th><th>Testing being done</th><th>Length of testing time for Patients</th><th>Length of testing time for Parents/legal guardians</th></tr>
<tr><td>1</td><td rowspan="2">Patient: licensed psychologist
Parent/legal guardian: written questionnaires</td><td rowspan="2">~ 60 - 90 minutes</td><td>~ 20 minutes</td></tr>
<tr><td>2</td><td>~ 50 minutes</td></tr>
<tr><td>3 - 5</td><td rowspan="4">Patient: computerized tests using an iPad
Parent/legal guardian: written questionnaires</td><td>~ 10 minutes</td><td>~ 50 minutes</td></tr>
<tr><td>6</td><td>~ 30 – 40 minutes</td><td>~ 50 minutes</td></tr>
<tr><td>7 - 9</td><td>~ 30 – 40 minutes</td><td>~ 50 - 55 minutes</td></tr>
<tr><td>10 - 17</td><td>~ 35 – 45 minutes</td><td>~ 50 - 55 minutes</td></tr>
<tr><td>18</td><td>Patient: computerized tests using an iPad and written questionnaires</td><td>~ 80 – 90 minutes</td><td>NA</td></tr>
</table>

NANT Biology Study (NANT 2004-05)

If you choose to participate in this research, you will also be asked to join a companion NANT biology study to collect blood, bone marrow and tumor tissue (if available) and reports from radiology scans from patients with neuroblastoma. The biology study also provides a place (called NANT biorepository) where any leftover samples of tumor tissue or bone marrow and blood collected on this study could be transferred and stored. While you will be asked to join the Biology Study (NANT 2004-05), the decision to store/bank any leftover samples is optional and will not affect your ability to participate in this treatment study with Lorlatinib. Your doctor will talk with you in detail about the NANT biology study and have you sign a separate consent form.

Additional Tests in this Study

We would like to do some extra tests called pharmacokinetic studies and biologic studies. These tests will help us learn more about lorlatinib and may help children and adolescents who receive this drug in the future. The information learned would not change the way you are treated and the results of these tests will not be given to you. Some of these tests are required but others are optional meaning you can decide whether you want to do them or not.

Pharmacokinetic Studies: Determining Blood Levels of Lorlatinib – Required

During this study blood samples will be collected to determine how much lorlatinib is in your blood (called pharmacokinetics). About 3mL (just over half a teaspoon) of blood will be drawn with each sample. A total of 9 blood samples will be obtained over 3 separate days during course 1 (Day 1, Day 2 and Day 15). The total amount of blood drawn for testing will be about 27 mL (almost 5 ½ teaspoons). If you have a central line (such as a port or a Broviac) these samples can be drawn through that line or through a small tube placed in a vein in your hand or arm. This amount of blood is considered safe to donate. Samples will be sent to a commercial laboratory contracted to perform these tests for the study. These samples will be the property of Pfizer and Pfizer may also use the PK Biological Samples for evaluation of the bioanalytical method.

Other Biology Research Tests in this Study - Optional

You will be asked if you want to participate in 3 optional research tests. You can decide not to let the doctors do these tests and still be able to be treated as part of this study. There are checkboxes at end of this form to mark whether you are willing to participate in these voluntary studies. The results of these research tests will not be shared with you or become part of your medical record. These results would also not be used to make decisions about your care while enrolled on this study.

- **Using extra blood to look for genetic changes seen in tumor cells.**
  Tumor cells often release small pieces of DNA into the blood stream where it can be detected by sensitive tests. For this study, researchers would like to take almost 4 additional teaspoons of blood (17mL) at study entry and at each time a disease evaluation is done (after cycle 2, 4, 6 and then every 4th cycle after that) to look at what genetic changes in your tumor can be seen in your blood over time. The blood will be sent to a commercial laboratory for genetic testing.

- **Comparing genetic changes between leftover tumor from a surgical procedure prior to tumor relapse (at diagnosis or when you had surgery done after diagnosis) to relapsed neuroblastoma tumor tissue and bone marrow aspirates and whether these changes affect how the tumor will respond to treatment with Lorlatinib.**
  Researchers would like to look at tumor tissue to determine if there are certain gene changes present that might make your neuroblastoma more or less likely to respond to the drug lorlatinib. These tests would be done on tumor tissue remaining from diagnosis, or any previous surgery where tumor tissue was removed (removal of primary tumor or removal of tumor at a relapse) in the past. The tissue and bone marrow aspirates will be sent to a research laboratory at Children's Hospital of Philadelphia for testing.

When You Have Finished Treatment with Lorlatinib

After you stop treatment on this study, you will continue to have tests and scans done (listed below) to measure how much tumor is left. If test results show you have abnormal organ function, tests are recommended by the study to be repeated monthly until test results are stable or normal. You doctor will tell you how often these tests and evaluations will be done.

Medical Tests after the Study:

Physical exam	Neuropsychological testing[1]
Blood tests	Bone marrow tests & various scans to check your tumor[2]
Electrocardiogram (EKG) to check the heart rhythm[3]	

[1]The same neuropsychological testing and evaluation done before starting study treatment will be done at the end of treatment with lorlatinib. The need for any further testing after this will be up to your doctor.

[2]Bone marrow tests and various scans (CT/MRI, MIBG or PET) are done for checking the response of your tumor to treatment. These tests will be done at the end of a course and at certain times following treatment to monitor your tumor status.

[3] Electrocardiogram (EKG) done at the end of the study to document if lorlatinib treatment has any effect on heart rhythm.

A table detailing the tests and procedures required before, during and after the study has been attached to the end of this consent (Consent Addendum 1).

HOW LONG WILL I BE ON THIS STUDY?

You can get an unlimited number of treatment cycles with lorlatinib as long as you are not having bad side effects and as long as your tumor is not getting worse.

After you stop treatment, you will continue to have tests and scans done to measure how much tumor is left. Your doctor will tell you how often these tests will be done. Researchers will continue to collect information about you for a lifetime. Information will be collected about whether you are still alive; whether your tumor has grown back and at what sites in the body; whether you have developed any side effects from the treatment;

or whether you have developed any additional cancer. Your doctor will give the researchers this information at regular intervals.

CAN I STOP BEING IN THE STUDY?
Yes. If you are thinking about stopping your participation on this study, you should talk to your doctor before making a final decision so he/she can tell you how to do this safely.

Your doctor may also stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow study rules; or if the study is stopped.

WHAT ARE THE RISKS OF THE STUDY?
This is a Phase 1 study. A Phase 1 study looks at how common and serious side effects can be for each patient at a specific dose of a drug. In a Phase 1 study, some patients may have very serious side effects and could die as a result of these side effects. You may be one of those patients who have serious side effects as a result of participating in this Phase 1 study.

In this study, researchers will be looking at side effects seen in patients taking different doses of lorlatinib. Since subjects will be assigned to different dose levels of lorlatinib, some subjects may receive doses that are too small to be effective while others may receive higher doses that may cause increased side effects.

Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Other drugs may be given to make side effects less serious and more comfortable (such as for nausea, headache or reaction to lorlatinib). Many side effects go away soon after you stop taking the study medications but it is always possible that side effects can be serious, long lasting or may never go away. There is also a risk of death. Patients are watched carefully and treatment will be stopped if bad side effects develop. There may also be risks we do not know about. You should talk to your doctor about any side effects that you have while taking part in this study.

While on the study, you are at risk for the side effects listed below:

Possible Risks of Lorlatinib

The following side effects are considered to be related to lorlatinib have been reported:

Very Common (may affect 10 or more in 100 people)	**Common** (may affect from 1 up to less than 10 in 100 people)
• Increase in cholesterol and triglycerides (fats in your blood) • Effects on mood (for example, irritability and mood swings) • Effects on memory (for example, confusion, memory loss and disturbance of attention) • Effects on the peripheral nerves which are those outside of the brain and spinal cord, including tingling, numbness or pain in hands and feet) • Changes in vision (including double vision, perceived flashes or floaters of light, light intolerance, vision blurred, vision sharpness reduced and visual impairment) • Hypertension • Diarrhea • Constipation • Joint pain • Build-up of fluid in the body or extremities causing swelling (edema) • Fatigue (feeling tired and exhausted) • Increase in body weight • Increase in blood sugar levels	• Hallucination and loss of contact with reality • Changes in mental status • Changes in speech (for example, slow speech or slurred speech) • Inflammation of the lungs (pneumonitis) which can cause shortness of breath and difficulty breathing. If severe, this can be life threatening.

The following events have also been reported in patients while they were taking lorlatinib, although the relationship to lorlatinib is uncertain:

Very common (may affect 10 or more in 100 people)

- Abnormalities in blood tests that may indicate liver damage
- Abnormal pancreas tests
- Decrease in hemoglobin in the blood that can cause weakness
- Headache
- Muscle pain
- Difficulty sleeping
- Rash

Common (may affect from 1 up to less than 10 in 100 people)

- Decrease of ejection fraction of the heart which may indicate severe heart problem
- A sudden and temporary loss of consciousness (syncope)
- Changes in the electrical activity of your heart that might lead to a heart rhythm problem and/or irregular heartbeat

Uncommon (may affect less than 1 in 100 people)

- Inflammation of the pancreas causing pain in the upper abdomen. This could become severe and may cause nausea and vomiting, fever and rapid heart rate. This could require hospitalization and may be life threatening
- Suicidal thoughts
- Psychosis

Lorlatinib has moderate influence on the ability to drive and use machines. Caution should be exercised when driving or operating machines as patients may experience CNS effects.

Possible Risks to Unborn Child

Patients who agree to participate in this study should not become pregnant while on this study. Lorlatinib may cause fetal harm when administered to a pregnant woman and is not recommended during pregnancy or for women of childbearing potential not using contraception. Women of childbearing potential should use nonhormonal methods of birth control. If a hormonal method of birth control is unavoidable, then a condom must be used in combination with the hormonal method. Female patients must continue to follow these birth control guidelines for 21 days after finishing the study. Male patients must wear condoms as one of their forms of birth control for the duration of the study and for 97 days after finishing the study. Further contraception use should be discussed with your personal physician. If you or your partner becomes pregnant while you are participating in this study, please notify your doctor immediately. For more information about risks and side effects, ask your doctor.

Possible Long Term Side Effects of Treatment with Lorlatinib
Side effects in adults treated with lorlatinib have occurred while patients have been receiving the drug or shortly after finishing the drug. It is not known if some side effects may be seen only after a long time after finishing treatment with lorlatinib.

Possible Risks from Having Blood Drawn
The risks from having your blood taken are minimal, but can include an infection or a blood clot. Experienced doctors or nurses will perform these blood draws to minimize this risk.

Unknown Risks
The treatment may have side effects that no one knows about yet. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?
There may or may not be direct medical benefit to you. The information learned from this study may or may not benefit other children or young people with solid cancers in the future.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THIS STUDY?
There are other options for you instead of this treatment. Instead of being in this study, you have these options:

- Treatment with other chemotherapy medicines
- Treatment with other experimental agents that may be available
- No neuroblastoma therapy at this time, with care to help you feel more comfortable

Please talk about these options with your doctor.

WILL MY MEDICAL INFORMATION BE KEPT PRIVATE?
We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance and data analysis include:

- New Approaches to Neuroblastoma Therapy (NANT) Consortium at Children's Hospital Los Angeles in Los Angeles, CA. The NANT Consortium identifies you by a number.
- Independent auditor evaluating quality assurance for the NANT Consortium.
- The National Cancer Institute (NCI) and other governmental agencies, like the Food and Drug Administration (FDA), Health Canada, or European regulatory agency(ies) involved in keeping research safe for people.
- Foundation Medicine, Inc. who is a collaborator on this study.
- Pfizer Inc., the pharmaceutical company which makes lorlatinib.

NANT has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. Information about the certificate is included at the end of this consent.

Because this study involves the treatment of a medical condition, a copy of this consent form will be placed in your medical record. This will allow the doctors that are caring for you to obtain information about what medications or procedures you are receiving in the study and treat you appropriately.

WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?
Taking part in this study may lead to added costs to your insurance company. Your health insurance company will be billed for many expenses associated with the costs of this study. These expenses include medications, treatments, hospital charges, and doctors' fees related to your participation in this study.

Lorlatinib and the flavoring agent (Ora-Plus®) are being provided free of charge for use in this study, but the costs associated with administering the drug is normally covered by your insurance company. The cost of doing a heart test called an EKG and neuropsychological testing at several time points during your participation in the study with lorlatinib is being done as part of research and will be paid for by the study. The special research blood and tissue studies will be done at no cost to you. However, you or your health plan may need to pay for the costs of the supplies and personnel who draw the blood from you for these tests.

You may have to pay for other things during this study, such as but not limited to, your time, the cost of food you buy while you are being treated at the hospital, car fare, travel to and from the hospital for treatment, parking, and baby sitter fees.
Taking part in this study may lead to added costs that may not be covered by your insurance company. Please ask about any expected added costs or insurance problems.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's website at http://cancer.gov/clinicaltrials/understanding/insurance-coverage . You can print a copy of the "Clinical Trials and Insurance Coverage" information from this website.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?
It is important that you tell your study doctor, _____ *[investigator's name(s)]* if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number].*

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

WHAT ARE MY RIGHTS AS A STUDY PARTICIPANT?
Taking part in this study is your choice. You may choose not to take part or not take part in the study. If you decide to take part in this study, you may remove yourself from the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. If you remove yourself from the study, we will still take care of you. We will explain what stopping the treatment may do and we will offer other treatments if they are available.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In case of injury resulting from this study, you do not lose any of you legal rights to seek payment by signing this form.

A Data Safety and Monitoring Board, an independent group of experts, will be reviewing data from this research throughout the study. We will tell you about new information from this Board or other studies that may affect your health or willingness to stay in the study.

WHO CAN ANSWER MY QUESTIONS ABOUT THE STUDY?
You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number].*
For questions about your rights while taking part in this study, call the _____ *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ *(telephone number).*

WHO IS FUNDING THIS RESEARCH STUDY?
This study is supported by Pfizer, Inc. Pfizer is a drug company that makes the drug being studied in this research project. Pfizer is giving money to Children's Hospital for some of the costs of the study. The results of the study will be reported to Pfizer. If the study shows that lorlatinib may be useful for a new purpose, this could benefit Pfizer financially.

The Children's Hospital Los Angeles/NANT is also providing funding for this study.

Dr. Mossé at Children's Hospital of Philadelphia, one of the principal investigators of this study, has served as a paid consultant to Pfizer. Her participation in this research has been reviewed and approved, subject to management, according to CHOP's/NANT Conflict of Interest Policy.

WHERE CAN I GET MORE INFORMATION?

You may call the NCI's **Cancer Information Service** at

1–800–4–CANCER (1–800–422–6237) or **TTY: 1–800–332–8615**

You may visit the NCI Web sites at http://cancer.gov/
For NCI's clinical trials information, go to http://cancer.gov/clinicaltrials/
For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

You will get a copy of this consent form. If you want more information about this study, ask your doctor.

CONSENT FOR EXTRA STUDIES FOR RESEARCH

The following tests are optional for all patients in the study. You may still participate in the study even if you do not agree to these tests.

1. **Using extra blood to look for genetic changes seen in tumor cells**

   Initial next to YES if you agree to let researchers take almost 4 extra teaspoons (17mL) at study entry and each time a disease evaluation is done) to look at what genetic changes in your tumor can be seen in your blood over time before and after treatment with lorlatinib. This blood would be drawn at a time when blood was being drawn for clinical purposes. The blood will be sent to Foundation Medicine Inc. for analysis who is a collaborator on the study. The results of these tests will be confidential and not made available to you or your treating physician.

   Initial next to NO, if you do not want researchers to take extra blood above what is needed for clinical purposes.

   _____Yes _____No

2. **Comparing genetic changes between tumor leftover from a surgical procedure prior to relapse (diagnosis or second look) to relapsed neuroblastoma tumor tissue and bone marrow aspirates and whether these changes affect how the tumor will respond to treatment with lorlatinib.**

   Initial next to YES, if you agree (and if there is tumor remaining) to let this tumor be sent to a laboratory so researchers can compare these samples and determine if there are certain gene changes present that might make your neuroblastoma more or less likely to respond to the drug lorlatinib. The results of these tests will be confidential and not made available to you or your treating doctor.

   Initial next to NO if you do not want leftover tumor from an earlier procedure to be sent to a research laboratory to look for certain gene changes that might make your neuroblastoma more or less likely to respond to the drug lorlatinib.

   _____Yes _____No

   Initial next to YES, if you agree to let extra bone marrow aspirates be collected to be sent to a laboratory so researchers can compare these samples and determine if there are certain gene changes present that might make your neuroblastoma more or less likely to respond to the drug lorlatinib. The results of these tests will be confidential and not made available to you or your treating doctor.

   Initial next to NO if you do not want these bone marrow aspirates collected to be sent to a research laboratory to look for certain gene changes that might make your neuroblastoma more or less likely to respond to the drug lorlatinib.

   _____Yes _____No

STATEMENT OF CONSENT

I have already read the information in this informed consent document. I have read all the attachments that were included with this informed consent document. I have asked all of my questions and I have gotten answers. I agree to enroll myself (my child) in this study.

_____
Print Patient Name

_____ _____/_____/_____
Print Name of Parent or Guardian Date

_____ _____/_____/_____
Signature of Parent or Guardian Date

_____ _____/_____/_____
Signature of Patient (If > 7 years old) Date

_____ _____/_____/_____
Signature of Physician or Date
Responsible Investigator

_____ ____/_____/_____
Signature of Witness Date

_____ ____/_____/_____
Signature of Translator Date

Consent Addendum I: Tests That Will Be Done On This Study

Observation	Before Entry	Cycle 1	Cycle 2	Subsequent Cycles	End of Therapy
Physical exam including neurological exam	X	Weekly	Start of cycle	Start of each cycle	X
Routine Blood tests** (Blood counts, electrolytes, liver, kidney function, function of pancreas- amylase/lipase)	X	Weekly	Weekly for blood counts and twice during cycle for all other blood tests	Start of each cycle	X
Routine Blood tests** (Fasting cholesterol, triglycerides, glucose)	X	Every other week	Start of cycle	Start of each cycle	X
Hemoglobin A1c (HbA1c)	X		Start of cycle	With Disease Evaluations in Courses 4 and 6 and after every 4 courses thereafter	X
Pregnancy test (All females 10 years of age and older)	X		Start of cycle	Start of each cycle	
Heart rhythm test (EKG)	X	One hour after day 1 treatment is finished	End of cycle	End of cycle (4,6 and every 4th cycle thereafter)	X
Neuropsychological Testing	Within one week before starting treatment	End of cycle	End of cycle	End of cycle (4,6 and every 4th cycle thereafter)	X
Neuropsychological evaluation with licensed psychologist for patients less than 3 years of age	Within one week before and up to two weeks after starting treatment		End of cycle	End of cycle 6, 10 and then every 8 cycles thereafter	X
Submit Patient Treatment Diaries		X	X	X	X
Blood for Lorlatinib drug level tests (PK - Required)		Day 1: 3 times Day 2: 1 time Day 15: 5 times			
Blood for circulating tumor cells (Optional)	X		With disease evaluation	End of cycle (4,6, and every 4th cycle thereafter)	
Bone Marrow Aspirate (Optional)	X		With disease evaluation	End of cycle (4,6, and every 4th cycle thereafter)	
Sampling of leftover tumor tissue (Optional)	Leftover tumor tissue can be sent at any time during the study				

	Tests done during Disease Evaluation				
Bone marrow aspirate and biopsy	X		Week 4	End of cycle (4,6 and every 4th cycle thereafter)	X
CT/MRI scans and/or MIBG/PET scans					
Blood and bone marrow for NANT Biology study[#]					

[#] Patients enrolled in the companion biology study may have additional samples of blood and bone marrow collected at study entry and with each disease evaluation time point. Please look at the biology study N04-05 consent form for more information

**Blood draws can be done more often if needed at the discretion of your study doctor

Consent Addendum II
Certificate of Confidentiality Information

NANT has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. The Certificate protects against the involuntary release of information about subjects collected during the course of our covered studies. The researchers involved in the studies cannot be forced to disclose the identity or any information collected in the study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, the subject or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if the subject or his/her guardian requests the release of information in writing, the Certificate does not protect against that voluntary disclosure. Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act. The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

APPENDIX VII: LORLATINIB IN COMBINATION WITH CONVENTIONAL CHEMOTHERAPY (COHORT B2) SAMPLE CONSENT

NANT 2015-02: PHASE 1 STUDY OF LORLATINIB, AN ORAL SMALL MOLECULE INHIBITOR OF ALK/ROS1, FOR PATIENTS WITH ALK-DRIVEN RELAPSED OR REFRACTORY NEUROBLASTOMA

LORLATINIB IN COMBINATION WITH CONVENTIONAL CHEMOTHERAPY (COHORT B2): FOR PATIENTS ONE YEAR OF AGE THROUGH 30 YEARS OF AGE

A New Approaches to Neuroblastoma Therapy (NANT) treatment protocol.

The word "you" used throughout this document refers to you or your child.

WHAT IS THIS STUDY ABOUT?
This study is a clinical trial, a type of research study. Clinical trials include only patients who choose to take part. Please take your time to make your decision about participating. You may discuss your decision with your friends, family, and health care team. If you have any questions, you may ask your doctor.

You are being asked to participate in this study because you have a kind of cancer called neuroblastoma. It may be that your cancer went away for a while but has grown back (relapsed) or it may be that it has never gone away (persistent or resistant tumor) after standard treatment. Standard treatment may have included chemotherapy, surgery, radiation therapy, high-dose chemotherapy with a stem cell transplant and/or immunotherapy.

WHY IS THIS STUDY BEING DONE?

The purposes of this study are:

- To find the highest safe dose of lorlatinib that can be given to children, adolescents and adults with refractory or relapsed neuroblastoma without causing severe side effects.
- To learn about the side effects of the drug lorlatinib when given in combination with cyclophosphamide and topotecan) in children, adolescents and adults.
- To determine if your tumor gets smaller after treatment with lorlatinib when given in combination with cyclophosphamide and topotecan.
- To measure the levels of lorlatinib in the blood when given together with cyclophosphamide and topotecan in children and adolescents.
- To look at genetic changes in tumor DNA found in the blood during treatment.
- To look at genetic changes in tumor tissue to see if they affect response to lorlatinib.
- To describe the amount of neuroblastoma tumor found in the blood and bone marrow by testing samples with a new test (called NB5 assay).

The research is being done because:
Currently there is no known effective treatment for your type of cancer. We are testing new experimental drugs such as lorlatinib in the hopes of finding a drug that may be effective against neuroblastoma tumors that have come back (relapsed) or that have never gone away (persistent/refractory) after treatment with standard therapy. This part of the study will combine three drugs: lorlatinib, cyclophosphamide and topotecan. You may have taken cyclophosphamide and/or topotecan before (but not all three together) for treatment of your neuroblastoma.

This study involves the use of an experimental drug called lorlatinib. In laboratory testing, lorlatinib blocks the Anaplastic Lymphoma Kinase (ALK). ALK may be important in the growth of certain types of cancer cells such as neuroblastoma. Lorlatinib is considered experimental because it has not been proven to work in a situation like yours. Lorlatinib has been approved by the United States Food and Drug Administration (FDA) to treat adults with non-small cell lung cancer, a different cancer than yours. It is not approved for neuroblastoma. Lorlatinib has been used only in a small number of adults so there is a lot we do not know about it yet. Lorlatinib has not previously been used in children and adolescents not enrolled on this study.

Cyclophosphamide and topotecan are chemotherapy drugs that are FDA-approved for the treatment of certain adult cancers, but have not been approved to treat children with neuroblastoma. These drugs have been used in combination to treat many children with neuroblastoma and in some patients this combination has reduced the amount of neuroblastoma present. Even if you have previously received treatment with cyclophosphamide and topotecan, you can still participate in this study.

All patients enrolled on this study are known to have a defect in the ALK gene in their tumor before they start treatment. You or your doctor should have the results of this test before being able to enroll on this study.

A dose of lorlatinib that can be given safely to children and adolescents was chosenfrom the dose escalation part of the study. Lorlatinib has not been given in combination with chemotherapy in patients with childhood tumors. In this part of the study, we will test the dose of lorlatinib that can be given safely in combination with cyclophosphamide and topotecan to children, adolescents and adults up to age 30 with relapsed/refractory neuroblastoma. After 4 cycles of chemotherapy, you and your physician may decide to stop the chemotherapy and continue lorlatinib without the chemotherapy.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

There will be about 60-75 patients enrolling on the 4 study cohorts. Of this number, about 12-18 children and adolescents and adults up to age 30 will be enrolled on this part of the study where lorlatinib is given together with cyclophosphamide and topotecan).

WHAT WILL HAPPEN TO ME IF I TAKE PART IN THIS STUDY?

Before You Begin the Study

Your doctor will have previously sent your tumor for genetic testing and these results showed your tumor has a defect in the *ALK* gene which allows you to be considered for participation in this study (Cohort B2).

You will need to have the following exams, tests or procedures to find out if you can take part in the study. Most of these exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study.

These tests will also be done at various times throughout the study and at the end of the study. The purpose of these tests is to see how well the treatment works and to measure the status of your neuroblastoma. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

A medical history & physical exam	Bone marrow tests[3] to check your tumor
Blood tests[1]	Various scans[4] to check your tumor
Pregnancy test (urine or blood)[2]	Electrocardiogram (EKG) to check the heart rhythm[5]
	Neuropsychological testing[6]

[1]Some blood tests (cholesterol and fat digestion [triglycerides]) may need to be done on an empty stomach, so you cannot eat or drink anything other than water for 8 hours before these tests are done (called fasting). Your doctor or nurse will tell you if it is necessary for you to fast before these blood tests are done.

[2]If you are a female at least 10 years old or who could have children, you will have a pregnancy test done by the doctor the week before starting treatment and then before each cycle of treatment begins. Both you and your parent/legal guardian (if applicable) will be informed of a positive pregnancy test. All men and women who could have children must either agree to practice abstinence from heterosexual intercourse or use two effective methods of birth control for as long as they participate in this study.

[3]Bone marrow tests are done by inserting a needle into the hip bone to remove the marrow which is inside the bone.

[4]Various scans are done for diagnosis and checking the response of the tumor to treatment. These may include CT and /or MRI scans and MIBG or PET scans. We will recommend scans specific for your case and we will answer your questions about these scans.

[5]Electrocardiogram (EKG) to document your heart rhythm before beginning lorlatinib treatment.

[6]Central nervous system effects (speech, memory and mood changes) were seen in previous studies treating adults with Lorlatinib. Neuropsychological testing will be done at within one week of starting treatment and at different times during this study to monitor for any changes in thinking skills, behavior and mood. Please see the section on Neuropsychological testing below in "During the Study" for more details on what tests are done and when they are done during this study.

During the Study

If the exams, tests and procedures show that you can be in the study, and you choose to take part, lorlatinib will be given once a day for 28 days and will be given together with cyclophosphamide/topotecan on the first 5 days. This entire period is called a cycle with each treatment cycle being 28 days long. You may continue to receive treatment with lorlatinib and cyclophosphamide/topotecan for up to 24 cycles or indefinitely if you are no longer receiving chemotherapy unless you develop serious side effects or your tumor worsens.

One Treatment Cycle **Cohort B2: Lorlatinib with chemotherapy**									
Week 1							Week 2	Week 3	Week 4
Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Days 8-14	Days 15 -21	Days 22-28
***Lorlatinib once a day** →									
CPM	CPM	CPM	CPM	CPM					
TOPO	TOPO	TOPO	TOPO	TOPO	MGF				

CPM: Cyclophosphamide
TOPO: Topotecan
MGF: Myeloid growth factor
*Lorlatinib should be given at least one hour before chemotherapy on days 1-5 of each cycle.

Lorlatinib

Lorlatinib will be given by mouth once a day followed by a small glass of water. Lorlatinib should be given at least one hour before chemotherapy on days 1 – 5 of each cycle. If you vomit lorlatinib within 20 minutes of taking the dose for the day, that dose can be repeated. This is the only time a dose of lorlatinib can be repeated.

Lorlatinib will be available as a tablet. If you are unable to swallow the tablets whole, you will be instructed on how to make a liquid lorlatinib solution at home by mixing the lorlatinib tablets with water and a flavoring agent (Ora-Plus®). Your nurse or doctor will help you decide what is best for you and will make sure you have the proper directions for taking this medication.

You will be given a patient diary at the beginning of each cycle of lorlatinib. Use the diary to record the date and time you take the drug, all vomited and missed doses, side effects that you experience and any other medications and supplements you are taking. The diary should be returned to clinic along with the medication bottle (even if it is empty) weekly during cycle 1 and then at the end of each treatment cycle. This will help us to know how much of the drug you take and how it made you feel.

Cyclophosphamide & Topotecan

You will receive both cyclophosphamide and topotecan into the bloodstream (either through your central line or through a small tube placed in a vein in your hand or arm) on days 1 through 5 of each cycle. You will receive each medicine over 30 minutes and the cyclophosphamide will be given first. These medicines are typically given in the clinic. You may stop cyclophosphamide and topotecan after 4 courses after discussion with your physician if it is deemed to be in your interest.

Myeloid Growth Factor

In addition, you will be given a medicine to help boost your white blood cell count. White blood cells help fight infection and having low white blood cells can increase your risk of developing an infection. This drug will be started on day 6 of each treatment cycle if you receive chemotherapy. Filgrastim or G-CSF is a shot given into the skin each day until the white blood cell count increases. Pegfilgrastim is a long-acting version of Filgrastim that is given as shot into the skin just once on day 6 of the cycle. Your doctor will talk with you about which of these study drugs you will receive.

During the study you will have tests and procedures done to check for side effects from taking lorlatinib in combination with chemotherapy and to see how your tumor is doing. Many of these tests are part of regular cancer care but you may have them done more often because you are on the study:

Physical exam	Electrocardiogram (EKG) to test heart rhythm [3]
Blood tests [1]	Bone marrow tests & various scans (CT/MRI, MIBG or PET) to check your tumor [4]
Pregnancy test (urine or blood) [2]	Neuropsychological testing [5]

[1] Some blood tests (cholesterol and fat digestion) may be done on an empty stomach, so patients cannot eat or drink anything other than water for 8-10 hours before these tests are done.

[2] A urine or blood pregnancy test will be done before each treatment cycle begins if you are a female at least 10 years old or who could have children. Both you and your parent/legal guardian will be informed of a positive pregnancy test. All men and women who could have children must continue to practice abstinence from heterosexual intercourse or use two effective methods of birth control for as long as they participate in this study.

[3] Electrocardiogram (EKG) done before starting study treatment will be repeated at certain times during the study to document if lorlatinib treatment has any effect on heart rhythm.

[4] Bone marrow tests and various scans are done for checking the response of your tumor to treatment. These tests will be done at certain times during the study to look at response to lorlatinib and check that your tumor has not gotten worse.

[5]**Neuropsychological Testing**

Neuropsychological evaluations try to understand how changes in the health of the brain may affect behavior or mood and how well a person is able to pay attention, remember things or solve problems. Since effects on speech, memory and mood were seen in a small number of adults receiving lorlatinib, neuropsychological testing will be done to monitor for changes in thinking skills, behavior and mood at different times during this study. Testing methods are based on the age of the patient and include computerized tests using an iPad, written questionnaires and evaluations by a licensed psychologist. Parents or legal guardians of patients less than 18 years of age will also participate by completing written questionnaires at the same time their child is being tested.

The results of the neuropsychological testing will be told to your doctor and entered as part of your medical record. Neuropsychological results will be used to make decisions about your care while enrolled on this study. If the testing results show areas of concern, you may be given more frequent testing as well as referrals for other care if needed. During testing, patients may skip questions that are stressful and may stop taking the tests at any time. Testing can be done as part of the clinic visit. You will need to talk with your doctor and nurse about scheduling to do these tests at times that are workable for you and your child. Please see the table at the end of the consent form that tells how often these tests will be done during the study.

- All patients 3 years of age and older will do computerized tests using an iPad. While the patient is taking these tests, the patient's parent or legal guardian will complete written questionnaires about the patient's mood and emotions, behavior, daily living/functional skills and social skills with others. The parent/legal guardian can be in the same room during the testing but they cannot help their child with their tests.

- Patients 18 years of age will complete computerized tests using an iPad and their own written questionnaires. Parents/Legal guardians do not have testing to do with patients of this age.

- Patients under 3 years of age will have an evaluation of overall functioning including language, motor and cognitive development done by a licensed psychologist. Parents/legal guardians will also complete written questionnaires at the same time.

<table>
<tr><th>Patient age at testing in years</th><th>Testing being done</th><th>Length of testing time for Patients</th><th>Length of testing time for Parents/legal guardians</th></tr>
<tr><td>1</td><td rowspan="2">Patient: licensed psychologist
Parent/legal guardian: written questionnaires</td><td rowspan="2">~ 60 - 90 minutes</td><td>~ 20 minutes</td></tr>
<tr><td>2</td><td>~ 50 minutes</td></tr>
<tr><td>3 - 5</td><td rowspan="4">Patient: computerized tests using an iPad
Parent/legal guardian: written questionnaires</td><td>~ 10 minutes</td><td>~ 50 minutes</td></tr>
<tr><td>6</td><td>~ 30 – 40 minutes</td><td>~ 50 minutes</td></tr>
<tr><td>7 - 9</td><td>~ 30 – 40 minutes</td><td>~ 50 - 55 minutes</td></tr>
<tr><td>10 - 17</td><td>~ 35 – 45 minutes</td><td>~ 50 - 55 minutes</td></tr>
<tr><td>18</td><td>Patient: computerized tests using an iPad and written questionnaires</td><td>~ 80 – 90 minutes</td><td>NA</td></tr>
</table>

NANT Biology Study (NANT 2004-05)

If you choose to participate in this research, you will also be asked to join a companion NANT biology study to collect blood, bone marrow and tumor tissue (if available) and reports from radiology scans from patients with neuroblastoma. The biology study also provides a place (called NANT biorepository) where any leftover samples of tumor tissue or bone marrow and blood collected on this study could be transferred and stored. While you will be asked to join the Biology Study (NANT 2004-05), the decision to store/bank any leftover

samples is optional and will not affect your ability to participate in this treatment study with lorlatinib. Your doctor will talk with you in detail about the NANT biology study and have you sign a separate consent form.

Additional Tests in this Study

We would like to do some extra tests called pharmacokinetic studies and biologic studies. These tests will help us learn more about lorlatinib and may help children and adolescents who receive this drug in the future. The information learned would not change the way you are treated and the results of these tests will not be given to you. Some of these tests are required but others are optional meaning you can decide whether you want to do them or not.

Pharmacokinetic Studies: Determining Blood Levels of Lorlatinib – Required

During this study blood samples will be collected to determine how much lorlatinib is in your blood (called pharmacokinetics). About 3mL (just over half a teaspoon) of blood will be drawn with each sample. A total of 9 blood samples will be obtained over 3 separate days during course 1 (Day 1, Day 2 and Day 15). The total amount of blood drawn for testing will be about 27 mL (almost 5 ½ teaspoons). If you have a central line (such as a port or a Broviac) these samples can be drawn through that line or through a small tube placed in a vein in your hand or arm. This amount of blood is considered safe to donate. Samples will be sent to a commercial laboratory contracted to perform these tests for the study. These samples will be the property of Pfizer and Pfizer may also use the PK Biological Samples for evaluation of the bioanalytical method.

Other Biology Research Tests in this Study - Optional

You will be asked if you want to participate in 3 optional research tests. You can decide not to let the doctors do these tests and still be able to be treated as part of this study. There are checkboxes at end of this form to mark whether you are willing to participate in these voluntary studies. The results of these research tests will not be shared with you or become part of your medical record. These results would also not be used to make decisions about your care while enrolled on this study.

- **Using extra blood to look for genetic changes seen in tumor cells.**
  Tumor cells often release small pieces of DNA into the blood stream where it can be detected by sensitive tests. About 17mL (almost four teaspoons) of blood will be drawn at study entry and at each time disease evaluation testing is done (after cycles 2, 4, 6 and then every 4th cycle) to look at what genetic changes in your tumor may be seen over time from the small pieces of tumor DNA found in your blood. The blood will be sent to a commercial laboratory contracted to perform this testing for the study.

- **Comparing genetic changes between leftover tumor from a surgical procedure prior to tumor relapse (at diagnosis or when you had surgery done after diagnosis) to relapsed neuroblastoma tumor tissue and bone marrow aspirates and whether these changes affect how the tumor will respond to treatment with Lorlatinib.**
  Researchers would like to look at tumor tissue to determine if there are certain gene changes present that might make your neuroblastoma more or less likely to respond to the drug lorlatinib. These tests would be done on tumor tissue remaining from diagnosis, or any previous surgery where tumor tissue was removed (removal of primary tumor or removal of tumor at a relapse) in the past. The tissue and bone marrow aspirates will be sent to a research laboratory at Children's Hospital of Philadelphia for testing.

When You Have Finished Treatment with Lorlatinib

After you stop treatment on this study, you will continue to have tests and scans done (listed below) to measure how much tumor is left. If test results show you have abnormal organ functions, tests are recommended by the study to be repeated monthly until test results are stable or normal. You doctor will tell you how often these tests and evaluations will be done.

Medical Tests after the Study:

Physical exam	Neuropsychological testing[1]
Blood tests	Bone marrow tests & various scans (CT/MRI, MIBG or PET) to check your tumor[2]
Electrocardiogram (EKG) to check the heart rhythm[3]	

[1]The same neuropsychological testing and evaluation done before starting study treatment will be done at the end of treatment with lorlatinib. The need for any further testing after this will be up to your doctor.

[2]Bone marrow tests and various scans are done for checking the response of your tumor to treatment. These tests will be done at the end of a course and at certain times following treatment to monitor your tumor status.

[3]Electrocardiogram (EKG) done at the end of the study to document if lorlatinib treatment has any effect on heart rhythm.

A table detailing the tests and procedures required before, during and after the study has been attached to the end of this form (Consent Addendum 1).

HOW LONG WILL I BE ON THIS STUDY?
You can get up to 24 cycles with lorlatinib and chemotherapy or indefinitely if you are no longer receiving chemotherapy as long as you are not having bad side effects and as long as your tumor is not getting worse.

After you stop treatment, you will continue to have tests and scans done to measure how much tumor is left. Your doctor will tell you how often these tests will be done. Researchers will continue to collect information about you for a lifetime. Information will be collected about whether you are still alive; whether your tumor has grown back and at what sites in the body; whether you have developed any side effects from the treatment; or whether you have developed any additional cancer. Your oncologist or family doctor will give the researchers this information at regular intervals.

CAN I STOP BEING IN THE STUDY?
Yes. If you are thinking about stopping your participation on this study, you should talk to your doctor before making a final decision so he/she can tell you how to do this safely.

Your doctor may also stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow study rules; or if the study is stopped.

WHAT ARE THE RISKS OF THE STUDY?
This is a Phase 1 study. A Phase 1 study looks at how common and serious side effects can be for each patient at a specific dose of a drug. In a Phase 1 study, some patients may have very serious side effects and could die as a result of these side effects. You may be one of those patients who have serious side effects as a result of participating in this Phase 1 study.

In this study, researchers will be looking at side effects seen in patients taking different doses of lorlatinib as well as lorlatinib given together with chemotherapy.
Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Other drugs may be given to make side effects less serious and more comfortable. Many side effects go away soon after you stop taking the study medications but it is always possible that side effects can be serious, long lasting or may never go away. There is also a risk of death. Patients are watched carefully and treatment will be stopped

if bad side effects develop. There may also be risks we do not know about. You should talk to your doctor about any side effects that you have while taking part in this study.

While on the study, you are at risk for the side effects listed below:

Possible Risks of Lorlatinib:

The following side effects are considered to be related to lorlatinib have been reported:

Very Common (may affect 10 or more in 100 people)	**Common** (may affect from 1 up to less than 10 in 100 people)
• Increase in cholesterol and triglycerides (fats in your blood) • Effects on mood (for example, irritability and mood swings) • Effects on memory (for example, confusion, memory loss and disturbance of attention) • Effects on the peripheral nerves which are those outside of the brain and spinal cord, including tingling, numbness or pain in hands and feet) • Changes in vision (including double vision, perceived flashes or floaters of light, light intolerance, vision blurred, vision sharpness reduced and visual impairment) • Hypertension • Diarrhea • Constipation • Joint pain • Build-up of fluid in the body or extremities causing swelling (edema) • Fatigue (feeling tired and exhausted) • Increase in body weight • Increase in blood sugar levels	• Hallucination and loss of contact with reality • Changes in mental status • Changes in speech (for example, slow speech or slurred speech) • Inflammation of the lungs (pneumonitis) which can cause shortness of breath and difficulty breathing. If severe, this can be life threatening.

The following events have also been reported in patients while they were taking lorlatinib, although the relationship to lorlatinib is uncertain:

Very common (may affect 10 or more in 100 people)

- Abnormalities in blood tests that may indicate liver damage
- Abnormal pancreas tests
- Decrease in hemoglobin in the blood that can cause weakness
- Headache
- Muscle pain
- Difficulty sleeping
- Rash

Common (may affect from 1 up to less than 10 in 100 people)

- Decrease of ejection fraction of the heart which may indicate severe heart problem
- A sudden and temporary loss of consciousness (syncope)
- Changes in the electrical activity of your heart that might lead to a heart rhythm problem and/or irregular heartbeat

Uncommon (may affect less than 1 in 100 people)

- Inflammation of the pancreas causing pain in the upper abdomen. This could become severe and may cause nausea and vomiting, fever and rapid heart rate. This could require hospitalization and may be life threatening
- Suicidal thoughts
- Psychosis

Lorlatinib has moderate influence on the ability to drive and use machines. Caution should be exercised when driving or operating machines as patients may experience CNS effects.

Possible Side Effects of Cyclophosphamide:

Likely	Less Likely	Rare But Serious

• Loss of appetite
• Nausea
• Vomiting
• Fewer white blood cells in the blood.
  ○ A low number of white blood cells may make it easier to get infections.
• Hair loss
• Decreased ability of the body to fight infection
• Absence or decrease in the number of sperm which may be temporary or permanent which may decrease the ability to have children
	• Abdominal pain
	• Diarrhea
	• Fewer red blood cells and platelets in the blood
	  ○ A low number of red blood cells may make you feel tired and weak.
	  ○ A low number of platelets may cause you to bruise and bleed more easily.
	• Bleeding and inflammation of the urinary bladder
	• Absence or decrease monthly periods which may be temporary or permanent and which may decrease the ability to have children
		• Temporary blurred vision
		• Nasal stuffiness with fast IV infusions
		• Irregular heart rate with fast IV infusions
		• Skin rash
		• Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure, rapid heart rate chills and fever
		• Abnormal hormone function which may lower the level of salt in the blood
		• Heart muscle damage which may occur with very high doses and which may be fatal
		• Darkening of areas of the skin and finger nails
		• Fingernail changes
		• Slow healing of wounds
		• Infections
		• Infertility which is the inability to have children
		• Damage and scarring of lung tissue which may make you short of breath
		• A new cancer or leukemia resulting from this treatment.
		• Damage or scarring of urinary bladder tissue

Possible Side Effects of Topotecan:

Likely	Less Likely	Rare But Serious

• Diarrhea
• Nausea
• Vomiting
• Constipation
• Fewer white blood cells, red blood cells and platelets in the blood.
  ○ A low number of white blood cells can make it easier to get infections
  ○ A low number of red blood cells can make you feel tired and weak
  ○ A low number of platelets causes you to bruise and bleed more easily
• Fever including fever with a low white blood cell count which could indicate infection and may require hospitalization and treatment with antibiotics
• Pain which may be in your abdomen, back or bones
• A feeling of weakness and/or tiredness
• Temporary hair loss
	• Loss of appetite
	• Headache
	• Lack of muscle strength or weakness
	• Rash, hives, itching or a red bumpy rash
	• A mild lowering of the blood pressure which usually does not require treatment
	• Shortness of breath
	• Inflammation and/or sores in the mouth, throat and/or esophagus
	• Elevation in the blood of certain enzymes found in the liver which may indicate liver irritation or damage
	• An infection in the blood which will require admission to the hospital and treatment with antibiotics
		• Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure and a rapid heart rate
		• Severe allergic reaction which can be life threatening with rapid build-up of fluid under the skin, in the lining of the intestine and possibly in the throat or swelling of the tongue which could make it difficult to breath.
		• Chest pain
		• Shaking chills
		• Elevation in the blood of certain enzymes or bilirubin found in the liver which could indicate liver irritation or damage
		• Numbness and tingling in the fingers and toes
		• Muscle or joint aches and pains
		• Bleeding into the tumor which may cause damage depending on the location of the tumor
		• Small amount of blood and/or protein in the urine or an elevation in blood creatinine which may indicate mild kidney damage

Growth Factors are not anti-cancer medicines. It helps the growth of white blood cells that fight infection (filgrastim/pegfilgrastim).

Possible Side Effects of Neupogen (Filgrastim):

Likely (happens to 21-100 children out every 100 children)	**Less Likely** (happens to 5-20 children out every 100 children)	**Rare** (happens to < 5 children out every 100 children)
• Aching or pain in bones.	• Local irritation/pain at the site of the injection. • Higher than normal levels in the blood of uric acid and of liver enzymes which may indicate liver irritation or damage. • Fever • A low number of platelets in the blood which may cause you to bruise and bleed more easily.	• Allergic reactions which can be life threatening with shortness of breath, low blood pressure, rapid heart rate, hives, facial swelling. This reaction is very rare and has been associated mainly with intravenous administration. • If you are known to have sickle cell disease , this drug may cause sickle cell crises • Severe damage to the spleen (an organ in the abdomen which stores blood cells) which could lead to pain and loss of blood into the abdomen or rupture of the spleen. • Difficulty breathing and lung damage that may be due to the white blood cells, stimulated by Pegfilgrastim , travelling to the lungs when they are inflamed or infected (Adult Respiratory Distress Syndrome) • Bone marrow dysfunction (MDS) or secondary leukemia in patients with very bad ongoing low white cell counts that require prolonged administration of this drug. • Worsening of skin rashes • Low Fever • Inflammation of blood vessels leading to a raised purple rash and bruising • Higher than normal white blood count. • Low blood pressure and/or increased heart rate • Wheezing or shortness of breath • Skin rash, hives or facial swelling

Possible Side Effects of Neulasta (Pegfilgrastim):

Likely (happens to 21-100 children out every 100 children)	**Less Likely** (happens to 5-20 children out every 100 children)	**Rare** (happens to < 5 children out every 100 children)
• Aching or pain in bones.	• Local irritation at the site of the injection. • Headache • Higher than normal levels in the blood of uric acid and of liver enzymes which may indicate liver irritation or damage. • A low number of platelets in the blood which may cause you to bruise and bleed more easily.	• Low grade fever • Allergic reactions which can be life threatening with shortness of breath, low blood pressure, rapid heart rate, hives, facial swelling. This reaction is very rare and has been associated mainly with intravenous administration. • Redness and flushing of the face and body. • Enlarged spleen • Severe damage to the spleen (an organ in the abdomen which stores blood cells) which could lead to pain and loss of blood into the abdomen. • If you are known to have sickle cell disease , this drug may cause sickle cell crises • Markedly higher than normal white blood cell count which may be associated with fever and red, often painful patches on the skin (Sweet's syndrome). • Difficulty breathing and lung damage that may be due to the white blood cells, stimulated by Pegfilgrastim, travelling to the lungs when they are inflamed or infected (Adult Respiratory Distress Syndrome)

Possible Risks to Unborn Child

Patients who agree to participate in this study should not become pregnant while on this study. Lorlatinib may cause fetal harm when administered to a pregnant woman and is not recommended during pregnancy or for women of childbearing potential not using contraception. Women of childbearing potential should use nonhormonal methods of birth control. If a hormonal method of birth control is unavoidable, then a condom must be used in combination with the hormonal method. Female patients must continue to follow these birth control guidelines for 21 days after finishing the study. Male patients must wear condoms as one of their forms of birth control for the duration of the study and for 97 days after finishing the study. Further contraception use should be discussed with your personal physician. If you or your partner becomes pregnant while you are participating in this study, please notify your doctor immediately. For more information about risks and side effects, ask your doctor.

Possible Long Term Side Effects of This Treatment

Side effects in adults treated with lorlatinib have occurred while patients have been receiving the drug or shortly after finishing the drug. It is not known if some side effects may be seen only after a long time after finishing treatment with lorlatinib.

Possible Risks from Having Blood Drawn

The risks from having your blood taken are minimal, but can include an infection or a blood clot. Experienced doctors or nurses will perform these blood draws to minimize this risk.

Unknown Risks

The treatment may have side effects that no one knows about yet. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

There may or may not be direct medical benefit to you. The information learned from this study may or may not benefit other children or young people with solid cancers in the future.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THIS STUDY?
There are other options for you instead of this treatment. Instead of being in this study, you have these options:

- Treatment with other chemotherapy medicines
- Treatment with other experimental agents that may be available.
- No neuroblastoma therapy at this time, with care to help you feel more comfortable.

Please talk about these options with your doctor.

WILL MY MEDICAL INFORMATION BE KEPT PRIVATE?
We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance and data analysis include:

- New Approaches to Neuroblastoma Therapy (NANT) Consortium at Children's Hospital Los Angeles in Los Angeles, CA. The NANT Consortium identifies you by a number.
- Independent auditor evaluating quality assurance for the NANT Consortium.
- The National Cancer Institute (NCI) and other governmental agencies, like the Food and Drug Administration (FDA) or Health Canada, involved in keeping research safe for people.
- Foundation Medicine, Inc. who is a collaborator on this study.
- Pfizer Inc., the pharmaceutical company which makes lorlatinib.

NANT has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. Information about the certificate is included at the end of this consent.

Because this study involves the treatment of a medical condition, a copy of this consent form will be placed in your medical record. This will allow the doctors that are caring for you to obtain information about what medications or procedures you are receiving in the study and treat you appropriately.

WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?
Taking part in this study may lead to added costs to your insurance company. Your health insurance company will be billed for many expenses associated with the costs of this study. These expenses include medications, treatments, hospital charges, and doctors' fees related to your participation in this study.

Lorlatinib and the flavoring agent (Ora-Plus®) are being provided free of charge for use in this study, but the costs associated with administering the drug is normally covered by your insurance company. Cyclophosphamide and topotecan is normally covered by your insurance company. The cost of doing a heart test called an EKG and neuropsychological testing at several time points during your participation in the study with Lorlatinib is being done as part of research and will be paid for by the study.
The special research blood and tissue studies will be done at no cost to you. However, you or your health plan may need to pay for the costs of the supplies and personnel who draw the blood from you for these tests.

You may have to pay for other things during this study, such as but not limited to, your time, the cost of food you buy while you are being treated at the hospital, car fare, travel to and from the hospital for treatment, parking, and baby sitter fees.

Taking part in this study may lead to added costs that may not be covered by your insurance company. Please ask about any expected added costs or insurance problems.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage . You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?
It is important that you tell your study doctor, _____ *[investigator's name(s)],* if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number].*

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

WHAT ARE MY RIGHTS AS A STUDY PARTICIPANT?
Taking part in this study is your choice. You may choose not to take part or not take part in the study. If you decide to take part in this study, you may remove yourself from the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. If you remove yourself from the study, we will still take care of you. We will explain what stopping the treatment may do and we will offer other treatments if they are available.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In case of injury resulting from this study, you do not lose any of you legal rights to seek payment by signing this form.

A Data Safety and Monitoring Board, an independent group of experts, will be reviewing data from this research throughout the study. We will tell you about new information from this Board or other studies that may affect your health or willingness to stay in the study.

WHO CAN ANSWER MY QUESTIONS ABOUT THE STUDY?
You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number].*

For questions about your rights while taking part in this study, call the _____ *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ *(telephone number).*

WHO IS FUNDING THIS RESEARCH STUDY?
This study is supported by Pfizer, Inc. Pfizer is a drug company that makes the drug being studied in this research project. Pfizer is giving money to Children's Hospital for some of the costs of the study. The results of the study will be reported to Pfizer. If the study shows that lorlatinib may be useful for a new purpose, this could benefit Pfizer financially.

The Children's Hospital Los Angeles/NANT is also providing funding for this study.

Dr. Mossé at Children's Hospital of Philadelphia, one of the principal investigators of this study, has served as a paid consultant to Pfizer. Her participation in this research has been reviewed and approved, subject to management, according to CHOP's/NANT Conflict of Interest Policy.

WHERE CAN I GET MORE INFORMATION?

You may call the NCI's **Cancer Information Service** at

1–800–4–CANCER (1–800–422–6237) or **TTY: 1–800–332–8615**

You may visit the NCI Web sites at http://cancer.gov/
For NCI's clinical trials information, go to http://cancer.gov/clinicaltrials/
For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

You will get a copy of this consent form. If you want more information about this study, ask your doctor.

CONSENT FOR EXTRA STUDIES FOR RESEARCH

The following tests are optional for all patients in the study. You may still participate in the study even if you do not agree to these tests.

1. **Using extra blood to look for genetic changes seen in tumor cells**
   Initial next to YES if you agree to let researchers take almost 4 extra teaspoons (17mL) at study entry and each time a disease evaluation is done) to look at what genetic changes in your tumor can be seen in your blood over time before and after treatment with lorlatinib. This blood would be drawn at a time when blood was being drawn for clinical purposes. The blood will be sent to Foundation Medicine Inc. for analysis who is a collaborator on this study. The results of these tests will be confidential and not made available to you or your treating physician.

   Initial next to NO, if you do not want researchers to take extra blood above what is needed for clinical purposes.

   _____Yes _____No

2. **Comparing genetic changes between tumor leftover from a surgical procedure prior to relapse (diagnosis or second look) to relapsed neuroblastoma tumor tissue and bone marrow aspirates and whether these changes affect how the tumor will respond to treatment with Lorlatinib.**

   Initial next to YES, if you agree (and if there is tumor remaining) to let this tumor be sent to a laboratory so researchers can compare these samples and determine if there are certain gene changes present that might make your neuroblastoma more or less likely to respond to the drug lorlatinib. The results of these tests will be confidential and not made available to you or your treating doctor.

   Initial next to NO if you do not want leftover tumor from an earlier procedure to be sent to a research laboratory to look for certain gene changes that might make your neuroblastoma more or less likely to respond to the drug lorlatinib.

   _____Yes _____No

   Initial next to YES, if you agree to let extra bone marrow aspirates be collected to be sent to a laboratory so researchers can compare these samples and determine if there are certain gene changes present that might make your neuroblastoma more or less likely to respond to the drug lorlatinib. The results of these tests will be confidential and not made available to you or your treating doctor.

   Initial next to NO if you do not want these bone marrow aspirates collected to be sent to a research laboratory to look for certain gene changes that might make your neuroblastoma more or less likely to respond to the drug lorlatinib.

   _____Yes _____No

STATEMENT OF CONSENT

I have already read the information in this informed consent document. I have read all the attachments that were included with this informed consent document. I have asked all of my questions and I have gotten answers. I agree to enroll myself (my child) in this study.

_____
Patient Name

_____ _____/_____/_____
Print Name of Parent or Guardian Date

_____ _____/_____/_____
Signature of Parent or Guardian Date

_____ _____/_____/_____
Signature of Patient (If > 7 years old) Date

_____ _____/_____/_____
Signature of Physician or Date
Responsible Investigator

_____ ____/_____/_____
Signature of Witness Date

_____ ____/_____/_____
Signature of Translator Date

Consent Addendum I: Tests That Will Be Done On This Study

Observation	Before Entry	Cycle 1	Cycle 2	Subsequent Cycles	End of Therapy
Physical exam including neurological exam	X	Weekly	Start of cycle	Start of each cycle	X
Routine blood tests** (Blood counts, electrolytes, liver, kidney function, function of pancreas-amylase/lipase)	X	Weekly for other tests and twice weekly for blood counts	Weekly for blood counts and twice during cycle for all other blood tests	Start of each cycle and weekly for blood counts	X
Routine Blood tests** (Fasting cholesterol, triglycerides, glucose)	X	Every other week	Start of cycle	Start of each cycle	X
Hemoglobin A1c (HbA1c)	X		Start of cycle	With Disease Evaluations in Courses 4 and 6 and after every 4 courses thereafter	X
Blood tests for cholesterol, triglycerides and function of the pancreas (amylase/lipase)	X	Weekly	Start of cycle	Start of each cycle	X
Pregnancy test (All females10 years of age and older)	X		Start of cycle	Start of each cycle	
Heart rhythm test (EKG)	X	One hour after day 1 treatment is finished	End of cycle	End of cycle (4,6 and every 4th cycle thereafter)	X
Neuropsychological Testing	Within one week before starting treatment	End of cycle	End of cycle	End of cycle (4,6 and every 4th cycle thereafter)	X
Neuropsychological evaluation with licensed psychologist for patients less than 3 years of age	Within one week before and up to two weeks after starting treatment		End of cycle	End of cycle 6, 10 and then every 8 cycles thereafter	X
Submit Patient Treatment Diaries		X	X	X	X
Blood for Lorlatinib drug level tests (PK - Required)		Day 1: 3 times Day 2: 1 time Day 15: 5 times			
Blood for circulating tumor cells (Optional)	X		With disease evaluation	End of cycle (4,6 and every 4th cycle thereafter)	

Bone Marrow Aspirate (Optional)	X		With disease evaluation	End of cycle (4,6, and every 4th cycle thereafter)	
Sampling of leftover tumor tissue (Optional)	Leftover tumor tissue can be sent at any time during the study				
	Tests done at Disease Evaluation				
Bone marrow aspirate and biopsy	X		Week 4	End of cycle (4,6 and every 4th cycle thereafter)	X
CT/MRI scans and/or MIBG/PET scans					
Blood and bone marrow for NANT Biology study[#]					

[#] Patients enrolled in the companion biology study may have additional samples of blood and bone marrow collected at study entry and with each disease evaluation time point. Please look at the biology study (NANT 2004-05) consent form for more information.

**Blood draws can be done more often if needed at the discretion of your study doctor

Consent Addendum II

Certificate of Confidentiality Information

NANT has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. The Certificate protects against the involuntary release of information about subjects collected during the course of our covered studies. The researchers involved in the studies cannot be forced to disclose the identity or any information collected in the study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, the subject or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if the subject or his/her guardian requests the release of information in writing, the Certificate does not protect against that voluntary disclosure. Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act. The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

APPENDIX VIII: DOSE EXPANSION COHORT A2: PATIENTS ≥ 18 YEARS OF AGE SAMPLE CONSENT

NANT 2015-02: PHASE 1 STUDY OF LORLATINIB, AN ORAL SMALL MOLECULE INHIBITOR OF ALK/ROS1, FOR PATIENTS WITH ALK-DRIVEN RELAPSED OR REFRACTORY NEUROBLASTOMA

COHORT A2: PATIENTS 18 YEARS OF AGE AND OLDER

A New Approaches to Neuroblastoma Therapy (NANT) treatment protocol.

WHAT IS THIS STUDY ABOUT?
This study is a clinical trial, a type of research study. Clinical trials include only patients who choose to take part. Please take your time to make your decision about participating. You may discuss your decision with your friends, family, and health care team. If you have any questions, you may ask your doctor.

You are being asked to participate in this study because you have a kind of cancer called neuroblastoma. It may be that your cancer went away for a while but has grown back (relapsed) or it may be that it has never gone away (persistent or resistant tumor) after standard treatment. Standard treatment may have included chemotherapy, surgery, radiation therapy, high-dose chemotherapy with a stem cell transplant and/or immunotherapy.

WHY IS THIS STUDY BEING DONE?

The Purposes Of This Study Are:

- To find the highest dose of lorlatinib that can be given to adults with refractory or relapsed neuroblastoma without causing severe side effects.
- To learn about the side effects of the drug lorlatinib when given to adults.
- To determine if your tumor gets smaller after treatment with lorlatinib.
- To measure the levels of lorlatinib in the blood
- To look at genetic changes in tumor DNA found in the blood during treatment.
- To look at genetic changes in tumor tissue to see if they affect response to lorlatinib.
- To describe the amount of neuroblastoma tumor found in the blood and bone marrow by testing samples with a new test (called NB5 assay).

The Research Is Being Done Because:
Currently there is no known effective treatment for your type of cancer. We are testing new experimental drugs such as lorlatinib in the hopes of finding a drug that may be effective against neuroblastoma tumors that have come back (relapsed) or that have never gone away (persistent/refractory) after treatment with standard therapy.

This study involves the use of an experimental drug called lorlatinib. In laboratory testing, lorlatinib blocks the Anaplastic Lymphoma Kinase (ALK) gene. ALK may be important in the growth of certain types of cancer cells such as neuroblastoma. Lorlatinib is considered experimental because it has not been proven to work in a situation like yours. Lorlatinib has been approved by the United States Food and Drug Administration (FDA) to treat adults with non-small cell lung cancer, a different cancer than yours.It is not approved for neuroblastoma. Lorlatinib has been used only in a small number of adults so there is a lot we do not know about it yet. In these previous studies, the recommended dose of lorlatinib that can be given safely was

determined for adults. In this study, we are also studying higher dose levels. Adults will receive 2 dose levels of lorlatinib on this cohort. All patients enrolled on this study are known to have a defect in the ALK gene in their tumor before they start treatment.

In this study, the lorlatinib dose you will be given is higher than the recommended dose given to adults with other cancers who have been treated with lorlatinib. This is because based on laboratory studies, it is thought that higher levels of lorlatinib might be needed to have an effect on neuroblastoma. Other adults have been treated at similar higher dose levels in the past and side effects experienced were temporary and resolved after stopping or decreasing the dose of lorlatinib. You will be closely monitored for any side effects with this treatment.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

There will be about 60-75 patients enrolling on the 4 study cohorts. You have been given this consent because the planned enrollment is on cohort A2. When you join the study, you will be assigned a certain lorlatinib dose. Cohort A2 will test up to 2 lorlatinib doses. There will be a a minimum of 20 patients enrolling on these two doses. Investigators are trying to decide the highest dose of lorlatinib that can be given without bad side effects.

WHAT WILL HAPPEN TO ME IF I TAKE PART IN THIS STUDY?

Before You Begin the Study

Your doctor will have previously sent your tumor for genetic testing and these results showed your tumor has a defect in the ALK gene which allows you to be considered for participation in this study.

You will need to have the following exams, tests or procedures to find out if you can take part in the study. Most of these exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. These tests will also be done at various times throughout the study and at the end of the study. The purpose of these tests is to see how well the treatment works and to measure the status of your neuroblastoma. If you have had some of them recently, they may not need to be repeated. This will be up to your doctor.

A medical history & physical exam	Bone marrow tests[3] to check your tumor
Blood tests[1]	Various scans[4] to check your tumor
Pregnancy test (urine or blood)[2]	Electrocardiogram (EKG) to check the heart rhythm[5]
	Neuropsychological testing[6]

[1]Some blood tests (cholesterol and fat digestion [triglycerides]) may need to be done on an empty stomach, so you cannot eat or drink anything other than water for 8-10 hours before these tests are done (called fasting). Your doctor or nurse will tell you if it is necessary for you to fast before these blood tests are done.

[2]If you are a female at least 10 years old or who could have children, you will have a pregnancy test done by the doctor the week before starting treatment and then before each cycle of treatment begins. Both you and your parent/legal guardian (if applicable) will be informed of a positive pregnancy test. All men and women who could have children must either agree to practice abstinence from heterosexual intercourse or use two effective methods of birth control for as long as they participate in this study.

[3]Bone marrow tests are done by inserting a needle into the hip bone to remove the marrow which is inside the bone.

[4]Various scans are done for diagnosis and checking the response of the tumor to treatment. These may include CT and /or MRI scans and MIBG or PET scans. We will recommend scans specific for your case and we will answer your questions about these scans.

[5]Electrocardiogram (EKG) to document your heart rhythm before beginning lorlatinib treatment.

[6]Central nervous system effects (speech, memory and mood changes) were seen in previous studies treating adults with Lorlatinib. Neuropsychological testing will be done at within one week of starting treatment and at different times during this study to monitor for any changes in thinking skills, behavior and mood. Please see the section on Neuropsychological testing below in "During this Study" for more details on what tests are done and when they are done during this study.

During the Study

If the exams, tests and procedures show that you can be in the study, and you choose to take part, lorlatinib will be given for 28 days. This entire period is called a cycle with each treatment cycle being 28 days long. You may continue to take lorlatinib for an unlimited number of cycles unless you develop serious side effects or your tumor worsens.

One Treatment Cycle (Cohort A2: adults and children/adolescents higher BSA group meeting adult dosing criteria)			
Week 1	Week 2	Week 3	Week 4
Days 1 - 7	Days 8 – 14	Days 15 - 21	Days 22 - 28
Lorlatinib once a day →			

Lorlatinib will be given by mouth once a day followed by a small glass of water. If you vomit lorlatinib within 20 minutes of taking the dose for the day, that dose can be repeated. This is the only time a dose of lorlatinib can be repeated.

Lorlatinib will be available as a tablet. If you are unable to swallow the tablets whole, you will be instructed on how to make a liquid lorlatinib solution at home by mixing the lorlatinib tablets with water and a flavoring agent (Ora-Plus®). Your nurse or doctor will help you decide what is best for you and will make sure you have the proper directions for taking this medication.

You will be given a patient diary at the beginning of each cycle of lorlatinib. Use the diary to record the date and time you take the drug, all vomited and missed doses, side affects you experience and any other medications and supplements you are taking. The diary should be returned to clinic along with the medication bottle (even if it is empty) weekly during cycle 1 and then after each treatment cycle of lorlatinib. This will help us to know how much of the drug you take and how it made you feel.

During the study you will have tests and procedures done to check for side effects from taking lorlatinib and to see how your tumor is doing. Many of these tests are part of regular cancer care but you may have them done more often because you are on the study:

Physical exam	Electrocardiogram (EKG) to test heart rhythm[3]
Blood tests[1]	Bone marrow tests & various scans (CT/MRI, MIBG or PET) to check your tumor[4]
Pregnancy test (urine or blood)[2]	Neuropsychological testing[5]

[1]Some blood tests (cholesterol and fat digestion) can only be done on an empty stomach, so patients cannot eat or drink anything other than water for 8-10 hours before these tests are done.

[2]A urine or blood pregnancy test will be done before each treatment cycle begins if you are a female who could have children. Both you and your parent/legal guardian will be informed of a positive pregnancy test.

All men and women who could have children must continue to practice abstinence from heterosexual intercourse or use two effective methods of birth control for as long as they participate in this study.

[3]Electrocardiogram (EKG) done before starting study treatment will be repeated at certain times during the study to document if lorlatinib treatment has any effect on heart rhythm.

[4]Bone marrow tests and various scans are done for checking the response of your tumor to treatment. These tests will be done at certain times during the study to look at response to lorlatinib and check that your tumor has not gotten worse.

[5]**Neuropsychological Testing**

Neuropsychological evaluations try to understand how changes in the health of the brain may affect behavior or mood and how well a person is able to pay attention, remember things or solve problems. Since effects on speech, memory and mood were seen in a small number of adults receiving lorlatinib, neuropsychological testing will be done to monitor for changes in thinking skills, behavior and mood at different times during this study. A table at the end of the consent lists how often neuropsychological testing will be done during the study. Testing methods are based on the age of the patient and include computerized tests using an iPad, written questionnaires and evaluations by a licensed psychologist. Parents or legal guardians of patients less than 18 years of age will also participate by completing written questionnaires at the same time their child is being tested.

The results of the neuropsychological testing will be told to your doctor and entered as part of your medical record. Neuropsychological results will be used to make decisions about your care while enrolled on this study. If the testing results show areas of concern, you may be given more frequent testing as well as referrals for other care if needed. During testing, patients may skip questions that are stressful and may stop taking the tests at any time. Testing can be done as part of the clinic visit. You will need to talk with your doctor and nurse about scheduling to do these tests at times that are workable for you and your child.

- Patients 18 years of age and older will complete computerized tests using an iPad and their own written questionnaires. Parents/Legal guardians do not have testing to do with patients of this age.

<table>
<tr><th>Patient age at testing in years</th><th>Testing being done</th><th>Length of testing time for Patients</th><th>Length of testing time for Parents/legal guardians</th></tr>
<tr><td>1</td><td rowspan="2">Patient: licensed psychologist
Parent/legal guardian: written questionnaires</td><td rowspan="2">~ 60 - 90 minutes</td><td>~ 20 minutes</td></tr>
<tr><td>2</td><td>~ 50 minutes</td></tr>
<tr><td>3 - 5</td><td rowspan="4">Patient: computerized tests using an iPad
Parent/legal guardian: written questionnaires</td><td>~ 10 minutes</td><td>~ 50 minutes</td></tr>
<tr><td>6</td><td>~ 30 – 40 minutes</td><td>~ 50 minutes</td></tr>
<tr><td>7 - 9</td><td>~ 30 – 40 minutes</td><td>~ 50 - 55 minutes</td></tr>
<tr><td>10 - 17</td><td>~ 35 – 45 minutes</td><td>~ 50 - 55 minutes</td></tr>
<tr><td>18 – 25</td><td rowspan="2">Patient: computerized tests using an iPad and written questionnaires</td><td rowspan="2">~ 80 - 90 minutes</td><td rowspan="2">NA</td></tr>
<tr><td>26+</td></tr>
</table>

NANT Biology Study (NANT 2004-05)

You will also be expected to join a companion NANT biology study to collect blood, bone marrow and tumor tissue (if available) and reports from radiology scans from patients with neuroblastoma. The biology study also provides a place (called NANT biorepository) where any leftover samples of tumor tissue or bone marrow and blood collected on this study could be transferred and stored. While you will be asked to join the Biology Study (NANT 2004-05), the decision to store/bank any leftover samples is optional and will not affect your ability to participate in this treatment study with Lorlatinib. Your doctor will talk with you in detail about the NANT biology study and have you sign a separate consent form.

Additional Tests in this Study

We would like to do some extra tests called pharmacokinetic studies and biologic studies. These tests will help us learn more about lorlatinib and may help children and adolescents who receive this drug in the future. The information learned would not change the way you are treated and the results of these tests will not be given to you. Some of these tests are required but others are optional meaning you can decide whether you want to do them or not.

Pharmacokinetic Studies: Determining Blood Levels of Lorlatinib – Required

During this study blood samples will be collected to determine how much lorlatinib is in your blood (called pharmacokinetics). About 3mL (just over half a teaspoon) of blood will be drawn with each sample. A total of 9 blood samples will be obtained over 3 separate days during course 1 (Day 1, Day 2 and Day 15). The total amount of blood drawn for testing will be about 27 mL (almost 5 ½ teaspoons). If you have a central line (such as a port or a Broviac) these samples can be drawn through that line or through a small tube placed in a vein in your hand or arm. This amount of blood is considered safe to donate. Samples will be sent to a commercial laboratory contracted to perform these tests for the study. These samples will be the property of Pfizer and Pfizer may also use the PK Biological Samples for evaluation of the bioanalytical method.

Other Biology Research Tests in this Study – Optional

You will be asked if you want to participate in 3 optional research tests. You can decide not to let the doctors do these tests and still be able to be treated as part of this study. There are checkboxes at end of this form to mark whether you are willing to participate in these voluntary studies. The results of these research tests will not be shared with you or become part of your medical record. These results would also not be used to make decisions about your care while enrolled on this study.

- **Using extra blood to look for genetic changes seen in tumor cells.**
  Tumor cells often release small pieces of DNA into the blood stream where it can be detected by sensitive tests. About 17mL (almost four teaspoons) of blood will be drawn at study entry and at each time disease evaluation testing is done (after cycles 2, 4, 6 and then every 4th cycle) to look at what genetic changes in your tumor may be seen over time from the small pieces of tumor DNA found in your blood. The blood will be sent to a commercial laboratory contracted to perform this testing for the study.

- **Comparing genetic changes between leftover tumor from an earlier procedure (diagnosis or second look) to relapsed neuroblastoma tumor tissue and bone marrow aspirates and whether these changes affect how the tumor will respond to treatment with Lorlatinib.**
  Researchers would like to look at tumor tissue to determine if there are certain gene changes present that might make your neuroblastoma more or less likely to respond to the drug lorlatinib. These tests would be done on tumor tissue remaining from diagnosis, or any previous surgery where tumor tissue was removed (removal of primary tumor or removal of tumor at a relapse) in the past. The tissue and bone marrow aspirates will be sent to a research laboratory at Children's Hospital of Philadelphia for testing.

When you have finished treatment with Lorlatinib

After you stop treatment on this study, you will continue to have tests and scans done (listed below) to measure how much tumor is left. If test results show you have abnormal organ functions, tests are recommended by the study to be repeated monthly until test results are stable or normal. You doctor will tell you how often these tests and evaluations will be done.

Medical Tests after the Study:

Physical exam	Neuropsychological testing[1]
Blood tests	Bone marrow tests and Various scans (CT/MRI, MIBG or PET) to check your tumor[2]
Electrocardiogram (EKG) to check the heart rhythm[3]	

[1]The same neuropsychological testing and evaluation done before starting study treatment will be done at the end of treatment with lorlatinib. The need for any further testing after this will be up to your doctor.

[2]Bone marrow tests and various scans are done for checking the response of your tumor to treatment. These tests will be done at the end of a course and at certain times following treatment to monitor your tumor status.

[3] Electrocardiogram (EKG) done at the end of the study to document if lorlatinib treatment has any effect on heart rhythm.

A table detailing the tests and procedures required before, during and after the study has been attached to the end of this form (Consent Addendum 1).

HOW LONG WILL I BE ON THIS STUDY?

You can get an unlimited number of treatment cycles with lorlatinib as long as you are not having bad side effects and as long as your tumor is not getting worse.

After you stop treatment, you will continue to have tests and scans done to measure how much tumor is left. Your doctor will tell you how often these tests will be done. Researchers will continue to collect information about you for a lifetime. Information will be collected about whether you are still alive; whether your tumor has grown back and at what sites in the body; whether you have developed any side effects from the treatment;

or whether you have developed any additional cancer. Your oncologist or family doctor will give the researchers this information at regular intervals.

CAN I STOP BEING IN THE STUDY?
Yes. If you are thinking about stopping your participation on this study, you should talk to your doctor before making a final decision so he/she can tell you how to do this safely.

Your doctor may also stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow study rules; or if the study is stopped.

WHAT ARE THE RISKS OF THE STUDY?
This is a Phase 1 study. A Phase 1 study looks at how common and serious side effects can be for each patient at a specific dose of a drug. In a Phase 1 study, some patients may have very serious side effects and could die as a result of these side effects. You may be one of those patients who have serious side effects as a result of participating in this Phase 1 study.

In this study, researchers will be looking at side effects seen in patients taking different doses of lorlatinib. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Other drugs may be given to make side effects less serious and more comfortable (such as for nausea, headache or reaction to lorlatinib). Many side effects go away soon after you stop taking the study medications but it is always possible that side effects can be serious, long lasting or may never go away. There is also a risk of death. Patients are watched carefully and treatment will be stopped if bad side effects develop. There may also be risks we do not know about. You should talk to your doctor about any side effects that you have while taking part in this study.

While on the study, you are at risk for the side effects listed below:

<u>Possible Risks of Lorlatinib</u>

The following side effects are considered to be related to lorlatinib have been reported:

Very Common (may affect 10 or more in 100 people)	**Common** (may affect from 1 up to less than 10 in 100 people)
• Increase in cholesterol and triglycerides (fats in your blood) • Effects on mood (for example, irritability and mood swings) • Effects on memory (for example, confusion, memory loss and disturbance of attention) • Effects on the peripheral nerves which are those outside of the brain and spinal cord, including tingling, numbness or pain in hands and feet) • Changes in vision (including double vision, perceived flashes or floaters of light, light intolerance, vision blurred,	• Hallucination and loss of contact with reality • Changes in mental status • Changes in speech (for example, slow speech or slurred speech) • Inflammation of the lungs (pneumonitis) which can cause shortness of breath and difficulty breathing. If severe, this can be life threatening.

vision sharpness reduced and visual impairment) • Hypertension • Diarrhea • Constipation • Joint pain • Build-up of fluid in the body or extremities causing swelling (edema) • Fatigue (feeling tired and exhausted) • Increase in body weight • Increase in blood sugar levels	

The following events have also been reported in patients while they were taking lorlatinib, although the relationship to lorlatinib is uncertain:

Very common (may affect 10 or more in 100 people)

- Abnormalities in blood tests that may indicate liver damage
- Abnormal pancreas tests
- Decrease in hemoglobin in the blood that can cause weakness
- Headache
- Muscle pain
- Difficulty sleeping
- Rash

Common (may affect from 1 up to less than 10 in 100 people)

- Decrease of ejection fraction of the heart which may indicate severe heart problem
- A sudden and temporary loss of consciousness (syncope)
- Changes in the electrical activity of your heart that might lead to a heart rhythm problem and/or irregular heartbeat

Uncommon (may affect less than 1 in 100 people)

- Inflammation of the pancreas causing pain in the upper abdomen. This could become severe and may cause nausea and vomiting, fever and rapid heart rate. This could require hospitalization and may be life threatening
- Suicidal thoughts
- Psychosis

Lorlatinib has moderate influence on the ability to drive and use machines. Caution should be exercised when driving or operating machines as patients may experience CNS effects.

Possible Risks to Unborn Child
Patients who agree to participate in this study should not become pregnant while on this study. Lorlatinib may cause fetal harm when administered to a pregnant woman and is not recommended during pregnancy or for women of childbearing potential not using contraception. Women of childbearing potential should use nonhormonal methods of birth control. If a hormonal method of birth control is unavoidable, then a condom must be used in combination with the hormonal method. Female patients must continue to follow these birth control guidelines for 21 days after finishing the study. Male patients must wear condoms as one of their forms of birth control for the duration of the study and for 97 days after finishing the study. Further contraception use should be discussed with your personal physician. If you or your partner becomes pregnant while you are participating in this study, please notify your doctor immediately. For more information about risks and side effects, ask your doctor.

Possible Long Term Side Effects of Treatment with Lorlatinib
Side effects in adults treated with lorlatinib have occurred while patients have been receiving the drug or shortly after finishing the drug. It is not known if some side effects may be seen only after a long time after finishing treatment with lorlatinib.

Possible Risks from Having Blood Drawn
The risks from having your blood taken are minimal, but can include an infection or a blood clot. Experienced doctors or nurses will perform these blood draws to minimize this risk.

Unknown Risks
The treatment may have side effects that no one knows about yet. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?
There may or may not be direct medical benefit to you. The information learned from this study may or may not benefit other children, young people and adults with solid cancers in the future.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THIS STUDY?
There are other options for you instead of this treatment. Instead of being in this study, you have these options:

- Treatment with other chemotherapy medicines
- Treatment with other experimental agents that may be available.
- No neuroblastoma therapy at this time, with care to help you feel more comfortable.

Please talk about these options with your doctor.

WILL MY MEDICAL INFORMATION BE KEPT PRIVATE?
We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance and data analysis include:

- New Approaches to Neuroblastoma Therapy (NANT) Consortium at Children's Hospital Los Angeles in Los Angeles, CA. The NANT Consortium identifies you by a number.
- Independent auditor evaluating quality assurance for the NANT Consortium.
- The National Cancer Institute (NCI) and other governmental agencies, like the Food and Drug Administration (FDA) or Health Canada, involved in keeping research safe for people.
- Foundation Medicine, Inc. who is a collaborator on this study.
- Pfizer Inc., the pharmaceutical company which makes lorlatinib.

NANT has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. Information about the certificate is included at the end of this consent.

Because this study involves the treatment of a medical condition, a copy of this consent form will be placed in your medical record. This will allow the doctors that are caring for you to obtain information about what medications or procedures you are receiving in the study and treat you appropriately.

WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?
Taking part in this study may lead to added costs to your insurance company. Your health insurance company will be billed for many expenses associated with the costs of this study. These expenses include medications, treatments, hospital charges, and doctors' fees related to your participation in this study.

Lorlatinib and the flavoring agent (Ora-Plus®) are being provided free of charge for use in this study, but the costs associated with administering the drug is normally covered by your insurance company. The cost of doing a heart test called an EKG and neuropsychological testing at several time points during your participation in the study with lorlatinib is being done solely as part of research and will be paid for by the study.

The special research blood and tissue studies will be done at no cost to you. However, you or your health plan may need to pay for the costs of the supplies and personnel who draw the blood from you for these tests.

You may have to pay for other things during this study, such as but not limited to, your time, the cost of food you buy while you are being treated at the hospital, car fare, travel to and from the hospital for treatment, parking, and baby sitter fees.

Taking part in this study may lead to added costs that may not be covered by your insurance company. Please ask about any expected added costs or insurance problems.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's website at http://cancer.gov/clinicaltrials/understanding/insurance-coverage . You can print a copy of the "Clinical Trials and Insurance Coverage" information from this website.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?
It is important that you tell your study doctor, _____ *[investigator's name(s)],* if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number].*

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

WHAT ARE MY RIGHTS AS A STUDY PARTICIPANT?
Taking part in this study is your choice. You may choose not to take part or not take part in the study. If you decide to take part in this study, you may remove yourself from the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. If you remove yourself from the study, we will still take care of you. We will explain what stopping the treatment may do and we will offer other treatments if they are available.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In case of injury resulting from this study, you do not lose any of you legal rights to seek payment by signing this form.

A Data Safety and Monitoring Board, an independent group of experts, will be reviewing data from this research throughout the study. We will tell you about new information from this Board or other studies that may affect your health or willingness to stay in the study.

WHO IS FUNDING THIS RESEARCH STUDY?

This study is supported by Pfizer, Inc. Pfizer is a drug company that makes the drug being studied in this research project. Pfizer is giving money to Children's Hospital for some of the costs of the study. The results of the study will be reported to Pfizer. If the study shows that lorlatinib may be useful for a new purpose, this could benefit Pfizer financially.

The Children's Hospital Los Angeles/NANT is also providing funding for this study.

Dr. Mossé at Children's Hospital of Philadelphia, one of the principal investigators of this study, has served as a paid consultant to Pfizer. Her participation in this research has been reviewed and approved, subject to management, according to CHOP's/NANT Conflict of Interest Policy.

WHO CAN ANSWER MY QUESTIONS ABOUT THE STUDY?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number].*

For questions about your rights while taking part in this study, call the _____ *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ *(telephone number).*

WHERE CAN I GET MORE INFORMATION?

You may call the NCI's **Cancer Information Service** at

1–800–4–CANCER (1–800–422–6237) or **TTY: 1–800–332–8615**

You may visit the NCI Web sites at http://cancer.gov/
For NCI's clinical trials information, go to http://cancer.gov/clinicaltrials/
For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

You will get a copy of this consent form. If you want more information about this study, ask your doctor.

CONSENT FOR EXTRA STUDIES FOR RESEARCH

The following tests are optional for all patients in the study. You may still participate in the study even if you do not agree to these tests.

1. <u>Using extra blood to look for genetic changes seen in tumor cells</u>

Initial next to YES if you agree to let researchers take almost 4 extra teaspoons (17 mL) at study entry and each time a disease evaluation is done) to look at what genetic changes in your tumor can be seen in your blood over time before and after treatment with lorlatinib. This blood would be drawn at a time when blood was being drawn for clinical purposes. The blood will be sent to Foundation Medicine Inc. for analysis who is a collaborator on this study. The results of these tests will be confidential and not made available to you or your treating physician.

Initial next to NO, if you do not want researchers to take extra blood above what is needed for clinical purposes.

_____Yes _____No

2. <u>Comparing genetic changes between tumor leftover from an earlier procedure (diagnosis or second look) to relapsed neuroblastoma tumor tissue and bone marrow aspirates and whether these changes affect how the tumor will respond to treatment with Lorlatinib.</u>

Initial next to YES, if you agree (and if there is tumor remaining) to let this tumor be sent to a laboratory so researchers can compare these samples and determine if there are certain gene changes present that might make your neuroblastoma more or less likely to respond to the drug lorlatinib. The results of these tests will be confidential and not made available to you or your treating doctor.

Initial next to NO if you do not want left over tumor from an earlier procedure to be sent to a research laboratory to look for certain gene changes that might make your neuroblastoma more or less likely to respond to the drug lorlatinib.

_____Yes _____No

Initial next to YES, if you agree to let extra bone marrow aspirates be collected to be sent to a laboratory so researchers can compare these samples and determine if there are certain gene changes present that might make your neuroblastoma more or less likely to respond to the drug lorlatinib. The results of these tests will be confidential and not made available to you or your treating doctor.

Initial next to NO if you do not want these bone marrow aspirates collected to be sent to a research laboratory to look for certain gene changes that might make your neuroblastoma more or less likely to respond to the drug lorlatinib.

_____Yes _____No

STATEMENT OF CONSENT

I have already read the information in this informed consent document. I have read all the attachments that were included with this informed consent document. I have asked all of my questions and I have gotten answers. I agree to enroll myself (my child) in this study.

_____
Print Patient Name

_____ _____/_____/_____
Signature of Patient Date

_____ _____/_____/_____
Signature of Physician or Responsible Investigator Date

_____ ____/_____/_____
Signature of Witness Date

_____ ____/_____/_____
Signature of Translator Date

Consent Addendum I: Tests that will be done on this study.

Observation	Before Entry	Cycle 1	Cycle 2	Subsequent Cycles	End of Therapy
Physical exam including neurological exam	X	Weekly	Start of cycle	Start of each cycle	X
Routine blood tests** (Blood counts, electrolytes, liver, kidney function, , function of pancreas-amylase/lipase)	X	Weekly	Weekly for blood counts and twice during cycle for all other blood tests	Start of each cycle	X
Routine Blood tests** (Fasting cholesterol, triglycerides, glucose)	X	Every other week	Start of cycle	Start of each cycle	X
Hemoglobin A1c (HbA1c)	X		Start of cycle	With Disease Evaluations in Courses 4 and 6 and after every 4 cycles thereafter	X
Pregnancy test (All females 10 years of age and older)	X		Start of cycle	Start of each cycle	
Heart rhythm test (EKG)	X	One hour after day 1 treatment is finished	End of cycle	End of cycle (4,6 and every 4th cycle thereafter)	X
Neuropsychological Testing	Within one week before starting treatment	End of cycle	End of cycle	End of cycle (4, 6 and every 4th cycle thereafter)	X
Neuropsychological evaluation with licensed psychologist for patients less than 3 years of age	Within one week before and up to one week after starting treatment		End of cycle	End of cycle 6, 10 and then every 8 cycles thereafter	X
Submit Patient Treatment Diaries		X	X	X	X
Blood for Lorlatinib drug level tests (PK - Required)		Day 1: 3 times Day 2: 1 time Day 15: 5 times			
Bone Marrow Aspirate (Optional)	X		With disease evaluation	End of cycle (4,6, and every 4th cycle thereafter)	
Blood for circulating tumor cells (Optional)	X		With disease evaluation	End of cycle (4,6 and every 4th cycle thereafter)	
Sampling of leftover tumor tissue (Optional)	Leftover tumor tissue can be sent at any time during the study				
	Tests done at Disease Evaluation				
Bone marrow aspirate and biopsy	X		Week 4	End of cycle (4,6 and every 4th cycle thereafter)	X
CT/MRI scans and/or MIBG/PET scans					
Blood and bone marrow for NANT Biology study[#]					

[#] Patients enrolled in the companion biology study may have additional samples of blood and bone marrow collected at study entry and with each disease evaluation time point. Please look at the biology study N04-05 consent form for more information.

**Blood draws can be done more often if needed at the discretion of your study doctor

Consent Addendum 2

Certificate of Confidentiality Information

NANT has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. The Certificate protects against the involuntary release of information about subjects collected during the course of our covered studies. The researchers involved in the studies cannot be forced to disclose the identity or any information collected in the study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, the subject or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if the subject or his/her guardian requests the release of information in writing, the Certificate does not protect against that voluntary disclosure. Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act. The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

APPENDIX IX: SAMPLE ASSENT FORM COHORTS A1 AND B1

NANT 2015-02: PHASE 1 STUDY OF PF-06463922 (LORLATINIB), AN ORAL SMALL MOLECULE INHIBITOR OF ALK/ROS1, FOR PATIENTS WITH ALK-DRIVEN RELAPSED OR REFRACTORY NEUROBLASTOMA

Cohorts A1 and B1: Taking Lorlatinib only

A New Approaches to Neuroblastoma Therapy (NANT) treatment protocol

INVESTIGATOR [Insert Name of Investigator]
[Insert Name of Institution]

[Insert Address (include City, State and Zip Code)]
[Insert Telephone/Fax Numbers]
[Insert Email]

1. Dr. _____ is doing a research study about using other medicines to get rid of Neuroblastoma.

2. You have a kind of cancer called **neuroblastoma.** We are doing a study about this kind of cancer. It may be that your cancer went away for a while but has come back. Or it may be that it has never gone away. We are asking you to take part in a research study because doctors want to learn more about treating neuroblastoma using a medicine called **lorlatinib** to see what effects (both good and bad) this medicine has on patients and their cancer. Lorlatinib is a medicine that is given by mouth either as a pill (tablet) or a liquid. The doctors think that giving this drug may help get rid of neuroblastoma cancer cells.

3. **If you agree to be in this study this is what will happen:**
You will take lorlatinib by mouth every day followed by a small glass of water. Lorlatinib is given in cycles that last about one month (28 days). You can continue taking lorlatinib for as many cycles as you can unless there are side effects or your tumor gets worse. Lorlatinib works differently than some of the other medicines you have gotten before to treat your neuroblastoma. Before this study started, the doctors sent a sample of your tumor to a laboratory for testing and found out there is a change in the ALK gene. The ALK gene is a gene that when it has been changed, can help your neuroblastoma tumor to grow. Lorlatinib works on the ALK gene. Researchers hope it will stop your neuroblastoma tumor from growing.

Coming to See the Doctors:
During and after you have finished the treatment, you will have appointments with the doctors who are taking care of you. This is called "**Follow-Up**". This is to see how well the treatment has worked so far. The doctors will want to do some special tests to find this information out. They will include;

- Blood tests (we will do this twice each week to start with, and then less often). You may need to fast (not eat anything and not drink anything other than water) for 8 hours before certain blood tests. This will happen once per week in the first month of treatment and then just once per month during the rest of treatment.
- A heart test called an EKG that shows the doctors your heart beat. This is done by attaching wires from an EKG machine to your chest with sticky pads. It takes less than 5 minutes to do this test once all the wires are attached.
- MRI, CT, and MIBG Scans (special pictures of your tumor)
- Bone marrow test (to look for tumor in your bone marrow)
- Feel your belly, look into your eyes and ears, and listen to your heart and lungs.
- Ask you and your parents a lot of questions about how you are feeling, how you are doing in school, and any problems you might be having.

    - The doctors will have you answer questions about how you are doing using an iPad. This should take about 30 minutes to do. At the same time you are using your iPad; your parents will also answer questions about how you are doing using pen and paper. This testing will be done at the beginning then monthly to every other month for a year then less often after that. Your doctor will let you know if any of these testing needs to be done more often.
- You will come to visit your doctor every week or so to start with, then less often if everything is going well.
- To measure the amount of medicine in your blood, we will draw 9 blood samples (about 5 teaspoons total) over the first 2 days of treatment with lorlatinib. We can use your central line to draw these blood samples. If you don't have a central line, you will need to have a needle poke or a small plastic tube placed in a vein of your hand or arm to collect these samples.

4. **When you are in a research study, sometimes good things and bad things can happen.**
   Sometimes things happen to kids in research studies that may make them feel bad. These are called "risks". Some of the risks of this study are:
   - You may feel lightheaded, jittery, irritable or hungry while you are fasting before certain tests
   - You may have swelling in your arms and legs
   - You may have tingling, or prickly feeling or numbness in your hands and feet
   - You may have a hard time concentrating, remembering things or talking to others.
   - You may feel tired
   - You may feel sick to your stomach and you may throw up
   - You may not feel like eating
   - You may get diarrhea or constipation
   - You may feel difficulty breathing
   - You may gain weight
   - The treatments may not work and your tumor may grow, or it might come back again after the treatment has finished. If this happens, we will try other ways to stop the tumor from growing.
   - You could get a different kind of cancer, this doesn't happen often, but can happen years later.
   - It is possible you could die from the treatment or cancer.

Not all of these things may happen to you. It's possible that none of them will happen. Or bad things may happen that we don't know about yet.

- Things that happen to children in research studies that are good are called "benefits". Some of the good things for this research study could be:
    - This treatment might make your neuroblastoma tumor stay the same size or get smaller for some time.
    - We hope to learn more about this new treatment which could help other children with neuroblastoma

5. We will do everything possible to keep your information private and prevent people outside of the study from seeing information about you.

6. Please talk this over with your parents before you decide whether or not to be in this study. We will also ask your parents to give their permission for you to take part in this study. But even if your parents say "yes" <u>you</u> can still decide not to do this.

7. You do not have to be in this study if you don't want to. You may stop being in this study at any time. Remember, being in this study is up to <u>you</u>.

8. You can ask any questions that you have about the study. If you have a question later that you didn't think of now, you can call me or ask me next time you see me.

- Study doctor's phone number: _____

9. **Special Study Tests:**

   You will have blood tests done to measure the amount of lorlatinib in your blood. This blood test will be done 9 times over 3 days in the first course. A central line can be used to draw these blood samples. Otherwise you may need to have a needle poke or a small plastic tube placed in a vein of your hand or arm for these samples.

   There are extra tests on this study that are optional meaning that you can say no to doing these tests and still be part of the main study. Please discuss this with your family. These extra tests are done for research only so the results won't be told to your doctor or to you.

   #1: Almost 4 teaspoons of extra blood will be taken at the same time blood will be drawn as part of your normal neuroblastoma care. This would be done when you start the study and then every time after when you have tests and scans to look at how your tumor is doing (called a disease evaluation).

   #2: The doctors will compare old and new tumor samples and bone marrow aspirates collected from you as part of your normal neuroblastoma care. They will be looking at changes in the ALK gene in these tumor samples.

Signing your name at the bottom means that you agree to be in this study. You and your parents will be given a copy of this form after you have signed it.

Name of Patient: _____

_____ Yes, I want to be in the study.

_____ No, I do not want to be in the study.

_____ _____
Signature of Patient **Date**

_____ _____
Name of Physician or Responsible Investigator **Date**

_____ _____
Signature of Physician or Responsible Investigator **Date**

APPENDIX X: SAMPLE ASSENT FORM COHORT A2

NANT 2015-02: PHASE 1 STUDY OF PF-06463922 (LORLATINIB), AN ORAL SMALL MOLECULE INHIBITOR OF ALK/ROS1, FOR PATIENTS WITH ALK-DRIVEN RELAPSED OR REFRACTORY NEUROBLASTOMA

Cohort A2: Taking Lorlatinib only

A New Approaches to Neuroblastoma Therapy (NANT) treatment protocol

INVESTIGATOR [Insert Name of Investigator]
[Insert Name of Institution]

[Insert Address (include City, State and Zip Code)]
[Insert Telephone/Fax Numbers]
[Insert Email]

1. Dr. _____ is doing a research study about using other medicines to get rid of Neuroblastoma.

2. You have a kind of cancer called **neuroblastoma.** We are doing a study about this kind of cancer. It may be that your cancer went away for a while but has come back. Or it may be that it has never gone away. We are asking you to take part in a research study because doctors want to learn more about treating neuroblastoma using a medicine called **lorlatinib** to see what effects (both good and bad) this medicine has on patients and their cancer. Lorlatinib is a medicine that is given by mouth either as a pill (tablet) or a liquid. The doctors think that giving this drug may help get rid of neuroblastoma cancer cells.

2. **If you agree to be in this study this is what will happen:**
You will take lorlatinib by mouth every day followed by a small glass of water. Lorlatinib is given in cycles that last about one month (28 days). You can continue taking lorlatinib for as many cycles as you can unless there are side effects or your tumor gets worse. Lorlatinib works differently than some of the other medicines you have gotten before to treat your neuroblastoma. Before this study started, the doctors sent a sample of your tumor to a laboratory for testing and found out there is a change in the ALK gene. The ALK gene is a gene that when it has been changed, can help your neuroblastoma tumor to grow. Lorlatinib works on the ALK gene. Researchers hope it will stop your neuroblastoma tumor from growing.

Coming to See the Doctors:
During and after you have finished the treatment, you will have appointments with the doctors who are taking care of you. This is called "**Follow-Up**". This is to see how well the treatment has worked so far. The doctors will want to do some special tests to find this information out. They will include;

- Blood tests (we will do this twice each week to start with, and then less often). You may need to fast (not eat anything and not drink anything other than water) for 8 hours before certain blood tests. This will happen once per week in the first month of treatment and then just once per month during the rest of treatment.
- A heart test called an EKG that shows the doctors your heart beat. This is done by attaching wires from an EKG machine to your chest with sticky pads. It takes less than 5 minutes to do this test once all the wires are attached.
- MRI, CT, and MIBG Scans (special pictures of your tumor)
- Bone marrow test (to look for tumor in your bone marrow)
- Feel your belly, look into your eyes and ears, and listen to your heart and lungs.

- Ask you and your parents a lot of questions about how you are feeling, how you are doing in school, and any problems you might be having.
    - The doctors will have you answer questions about how you are doing using an iPad. This should take about 30 minutes to do. At the same time you are using your iPad; your parents will also answer questions about how you are doing using pen and paper. This testing will be done at the beginning then monthly to every other month for a year then less often after that. Your doctor will let you know if any of these testing needs to be done more often.
- You will come to visit your doctor every week or so to start with, then less often if everything is going well.
- To measure the amount of medicine in your blood, we will draw 9 blood samples (about 5 teaspoons total) over the first 2 days of treatment with lorlatinib. We can use your central line to draw these blood samples. If you don't have a central line, you will need to have a needle poke or a small plastic tube placed in a vein of your hand or arm to collect these samples.

3. **When you are in a research study, sometimes good things and bad things can happen.**
Sometimes things happen to kids in research studies that may make them feel bad. These are called "risks". Some of the risks of this study are:
    a. You may feel lightheaded, jittery, irritable or hungry while you are fasting before certain tests
    b. You may have swelling in your arms and legs
    c. You may have tingling, or prickly feeling or numbness in your hands and feet
    d. You may have a hard time concentrating, remembering things or talking to others.
    e. You may feel tired
    f. You may feel sick to your stomach and you may throw up
    g. You may not feel like eating
    h. You may get diarrhea or constipation
    i. You may feel difficulty breathing
    j. You may gain weight
    k. The treatments may not work and your tumor may grow, or it might come back again after the treatment has finished. If this happens, we will try other ways to stop the tumor from growing.
    l. You could get a different kind of cancer, this doesn't happen often, but can happen years later.
    m. It is possible you could die from the treatment or cancer.

    Not all of these things may happen to you. It's possible that none of them will happen. Or bad things may happen that we don't know about yet.
    - Things that happen to children in research studies that are good are called "benefits". Some of the good things for this research study could be:
        - This treatment might make your neuroblastoma tumor stay the same size or get smaller for some time.
        - We hope to learn more about this new treatment which could help other children with neuroblastoma

4. We will do everything possible to keep your information private and prevent people outside of the study from seeing information about you.

5. Please talk this over with your parents before you decide whether or not to be in this study. We will also ask your parents to give their permission for you to take part in this study. But even if your parents say "yes" <u>you</u> can still decide not to do this.

6. You do not have to be in this study if you don't want to. You may stop being in this study at any time. Remember, being in this study is up to <u>you</u>.

7. You can ask any questions that you have about the study. If you have a question later that you didn't think of now, you can call me or ask me next time you see me.
    - Study doctor's phone number: _____

8. **Special Study Tests:**

You will have blood tests done to measure the amount of lorlatinib in your blood. This blood test will be done 9 times over the 3 days in the first course. A central line can be used to draw these blood samples. Otherwise you may need to have a needle poke or a small plastic tube placed in a vein of your hand or arm for these samples.

There are extra tests on this study that are optional meaning that you can say no to doing these tests and still be part of the main study. These extra tests are done for research only so the results won't be told to your doctor or to you.

#1: Almost 4 teaspoons of extra blood will be taken at the same time blood will be drawn as part of your normal neuroblastoma care. Please discuss this with your family. This would be done when you start the study and then every time after when you have tests and scans to look at how your tumor is doing (called a disease evaluation).

#2: The doctors will compare old and new tumor samples and bone marrow aspirates collected from you as part of your normal neuroblastoma care. They will be looking at changes in the ALK gene in these tumor samples.

Signing your name at the bottom means that you agree to be in this study. You and your parents will be given a copy of this form after you have signed it.

Name of Patient: _____

_____ Yes, I want to be in the study.
_____ No, I do not want to be in the study.

_____ _____
Signature of Patient **Date**

_____ _____
Name of Physician or Responsible Investigator **Date**

_____ _____
Signature of Physician or Responsible Investigator **Date**

APPENDIX XI: SAMPLE ASSENT FORM COHORT B2

NANT 2015-02: PHASE 1 STUDY OF PF-06463922 (LORLATINIB), AN ORAL SMALL MOLECULE INHIBITOR OF ALK/ROS1, FOR PATIENTS WITH ALK-DRIVEN RELAPSED OR REFRACTORY NEUROBLASTOMA

Cohort B2: Taking Lorlatinib combined with chemotherapy (cyclophosphamide/topotecan)

A New Approaches to Neuroblastoma Therapy (NANT) treatment protocol

INVESTIGATOR [Insert Name of Investigator]
[Insert Name of Institution]

[Insert Address (include City, State and Zip Code)]
[Insert Telephone/Fax Numbers]
[Insert Email]

1. Dr. _____ is doing a research study about using other medicines to get rid of Neuroblastoma.

2. You have a kind of cancer called **neuroblastoma.** We are doing a study about this kind of cancer. It may be that your cancer went away for a while but has come back. Or it may be that it has never gone away. We are asking you to take part in a research study because doctors want to learn more about treating neuroblastoma using three experimental medicines called **lorlatinib, cyclophosphamide and topotecan** and to see what effects (both good and bad) these medicines has on patients and their cancer. Lorlatinib is a medicine that is given by mouth either as a pill (tablet) or a liquid. Cyclophosphamide and topotecan are medicines that are given into the bloodstream either through your central line or a small tube placed in a vein in your hand or arm. The doctors think that giving these three drugs together may help get rid of neuroblastoma cancer cells.

3. **If you agree to be in this study this is what will happen:**

   The medicines will be given in cycles that each last about one month (28 days). Your doctor will explain the schedule for each cycle to you and your parents. You can continue to get this treatment unless you have bad side effects or your tumor gets worse. These medicines work differently than some of the other medicines you have gotten before to treat your neuroblastoma.

   Before this study started, the doctors sent a sample of your tumor to a laboratory for testing and found out there is a change in the ALK gene. The ALK gene is a gene that when it has been changed, can help your neuroblastoma tumor to grow. Lorlatinib works on the ALK gene. Researchers hope it will stop your neuroblastoma tumor from growing when used together the chemotherapy medinces cyclophosphamide and topotecan.

   Lorlatinib:
   You will take lorlatinib by mouth every day followed by a small glass of water.

   Cyclophosphamide and topotecan:
   You will take cyclophosphamide and topotecan by I.V. once a day for the first 5 days of every cycle. You will be in the clinic on those days. You do not need to be in the hospital to get these chemotherapy medicines.

Other medicines (not chemotherapy):

You will need to take Neupogen (given once a day as an injection) or Neulasta (given once each cycle as an injection). These medicines are given to help your normal blood cells get better after getting chemotherapy medicines like cyclophosphamide and topotecan.

Coming to See the Doctors:

During and after you have finished the treatment, you will have appointments with the doctors who are taking care of you. This is called "**Follow-Up**". This is to see how well the treatment has worked so far. The doctors will want to do some special tests to find this information out. They will include;

- Blood tests (we will do this twice each week to start with, and then less often). You may need to fast (not eat anything and not drink anything other than water) for 8 hours before certain blood tests. This will happen once per week in the first month of treatment and then just once per month during the rest of treatment.
- A heart test called an EKG that shows the doctors your heart beat. This is done by attaching wires from an EKG machine to your chest with sticky pads. It takes less than 5 minutes to do this test once all the wires are attached.
- MRI, CT, and MIBG Scans (special pictures of your tumor)
- Bone marrow test (to look for tumor in your bone marrow)
- Feel your belly, look into your eyes and ears, and listen to your heart and lungs.
- Ask you and your parents a lot of questions about how you are feeling, how you are doing in school, and any problems you might be having.
    - The doctors will have you answer questions about how you are doing using an iPad. This should take about 30 minutes to do. At the same time you are using your iPad; your parents will also answer questions about how you are doing using pen and paper. This testing will be done at the beginning then monthly to every other month for a year then less often after that. Your doctor will let you know if any of these testing needs to be done more often.
- You will come to visit your doctor every week or so to start with, then less often if everything is going well.
- To measure the amount of medicine in your blood, we will draw 9 blood samples (about 5 teaspoons total) over the first 2 days of treatment with lorlatinib. We can use your central line to draw these blood samples. If you don't have a central line, you will need to have a needle poke or a small plastic tube placed in a vein of your hand or arm to collect these samples.

4. **When you are in a research study, sometimes good things and bad things can happen.**

Sometimes things happened to children in research studies that may make them feel bad. These are called "risks". Some of the risks of this study are:

- You may feel lightheaded, jittery, irritable or hungry while you are fasting before certain tests
- You may have swelling in your arms and legs
- You may have tingling, or prickly feeling or numbness in your hands and feet
- You may have a hard time concentrating, remembering things or talking to others.
- You may feel tired
- You may feel sick to your stomach and you may throw up
- You may not feel like eating
- You might have a fever and maybe an infection where you will need to be in the hospital to get medicines to treat the infection. You may feel tired and weak and need a blood transfusion or you may get bruises or have bleeding (most often a nosebleed) and need a platelet transfusion.
- You may get sores in your mouth that makes it difficult to eat and drink. If this happens, you may need some pain medicines and you may need to stay in the hospital.
- You may get diarrhea or constipation.

- You may feel difficulty breathing
- You may gain weight
- The treatments may not work, and your tumor may grow, or it might come back again after the treatment has finished. If this happens we will try other ways to stop the tumor from growing
- You could get a different kind of cancer, this doesn't happen often, but can happen years later
- It is possible that you could die from the treatment or cancer

Not all of these things may happen to you. It's possible that none of them will happen. Or bad things may happen that we don't know about yet.

Things that happen to children in research studies that are good are called "benefits". Some of the good things for this research study could be:

- This treatment might make your neuroblastoma tumor stay the same size or get smaller for some time.
- We hope to learn more about this new treatment which could help other children with neuroblastoma

5. We will do everything possible to keep your information private and prevent people outside of the study from seeing information about you.

6. Please talk this over with your parents before you decide whether or not to be in this study. We will also ask your parents to give their permission for you to take part in this study. But even if your parents say "yes" you can still decide not to do this.

7. You do not have to be in this study if you don't want to. You may stop being in this study at any time. Remember, being in this study is up to you.

8. You can ask any questions that you have about the study. If you have a question later that you didn't think of now, you can call me or ask me next time you see me.

    - Study doctor's phone number: _____

9. **Special Study Tests:**

You will have blood tests done to measure the amount of lorlatinib in your blood. This blood test will be done 9 times over 3 days in the first course. A central line can be used to draw these blood samples. Otherwise you may need to have a needle poke or a small plastic tube placed in a vein of your hand or arm for these samples.

There are extra tests on this study that are optional meaning that you can say no to doing these tests and still be part of the main study. Please discuss this with your family. These extra tests are done for research only so the results won't be told to your doctor or to you.

#1: Almost 4 teaspoons of extra blood will be taken at the same time blood will be drawn as part of your normal neuroblastoma care. This would be done when you start the study and then every time after when you have tests and scans to look at how your tumor is doing (called a disease evaluation).

#2: The doctors will compare old and new tumor samples and bone marrow aspirates collected from you as part of your normal neuroblastoma care. They will be looking at changes in the ALK gene in these tumor samples.

Signing your name at the bottom means that you agree to be in this study. You and your parents will be given a copy of this form after you have signed it.

Name of Patient: _____

_____ Yes, I want to be in the study.

_____ No, I do not want to be in the study.

_____ _____
Signature of Patient **Date**

_____ _____
Name of Physician or Responsible Investigator **Date**

_____ _____
Signature of Physician or Responsible Investigator **Date**