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**TITLE: Phase II Study of Clofarabine in Patients with Recurrent or Refractory Langerhans Cell Histiocytosis and LCH-related Disorders**

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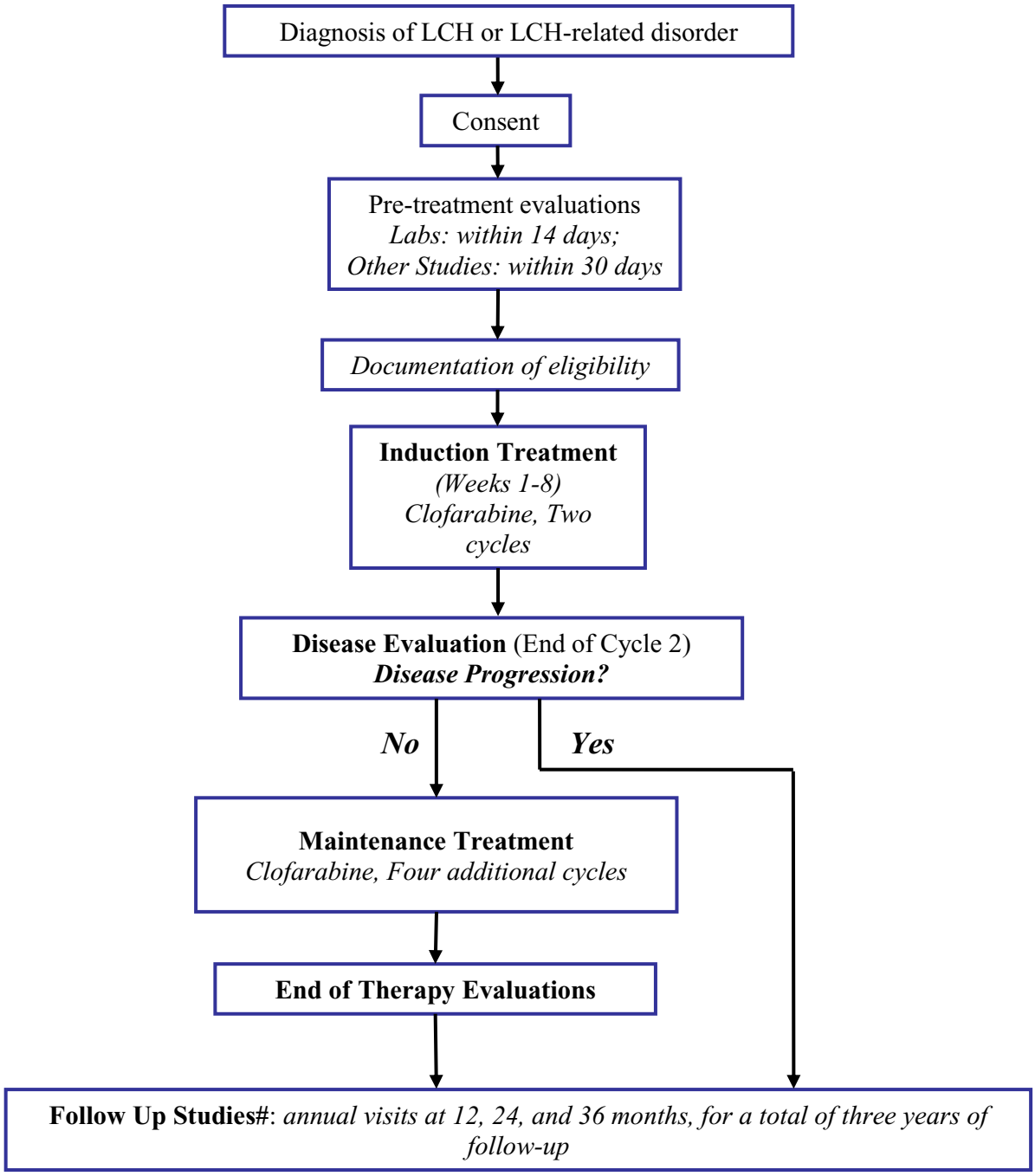
**Agent:** Clofarabine (IND#114482) – Sanofi-Aventis

**SCHEMA**




***** See Section 3 for stratification factors.
# Participants removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse events.

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# 1. OBJECTIVES

## 1.1 Overview

The Histiocytoses are a group of rare neoplastic diseases involving histiocytes. Langerhans Cell Histiocytosis (LCH), the most common of the group, is a disease caused by clonal proliferation of Langerhans cells that is characterized by a spectrum of varying degrees of organ involvement and dysfunction. Treatment of LCH is risk-adapted; patients with single lesions may respond well to local treatment, whereas patients with multi-system disease and risk-organ involvement (hematopoietic, liver, spleen) require more intensive therapy. While survival for patients without organ dysfunction is excellent, mortality rates for patients with organ dysfunction may reach 30 to 40%. For patients with low-risk disease, while cure is almost universal, disease reactivation rates are in excess of 30%. Related disorders, including Juvenile Xanthogranuloma (JXG), Rosai Dorfman Disease (RDD), Erdheim Chester Disease (ECD), Histiocytic Sarcoma (HS), and Interdigitating Dendritic cell Sarcoma/Histiocytosis (IDCMH) share some histopathologic and clinical features with LCH. There is currently no established therapy for any of these entities. Thus, new treatments are needed. Nucleoside analogues such as cladribine and cytarabine have proven to be effective in the management of Histiocytoses. More recently, clofarabine has proven to be effective in patients with refractory LCH and LCH-related disorders, thus suggesting that this newer nucleoside analogue should be investigated. In this Phase II study we are proposing to evaluate the efficacy of clofarabine in participants with recurrent or refractory LCH. In a separate stratum, we aim to register participants with histiocytic diseases other than LCH who require systemic therapy to accumulate experience with clofarabine in this rare patient population.

## 1.2 Study Design

This is a phase II efficacy study of clofarabine in patients with recurrent or refractory Langerhans Cell Histiocytosis (LCH) and LCH-related disorders that require chemotherapy.

## 1.3 Primary Objective

To estimate the response rate of participants with recurrent or refractory LCH to clofarabine.

## 1.4 Secondary Objectives

a) To estimate the progression-free survival and overall survival of participants with recurrent or refractory LCH to clofarabine.

b) To determine if clofarabine therapy can be delivered as planned (‘chemotherapy feasibility’), and to describe toxicities of clofarabine in participants with LCH.

c) To describe the toxicities and responses to clofarabine treatment in participants with LCH-related disorders.

# 2. BACKGROUND

## 2.1 Study Disease

Langerhans Cell Histiocytosis (LCH) is a proliferative disorder of activated Langerhans cells (LC) with highly variable biological behavior and clinical severity.[1] The histopathology of the lesion is uniform regardless of the clinical severity of the disease, and consists of collections of LC, interdigitating cells and macrophages, accompanied by T lymphocytes with variable numbers of multinucleated giant histiocytes and eosinophils.[2] The pathogenesis of LCH is poorly understood. Because LCH has been demonstrated to be a monoclonal disease it may be considered a neoplastic disorder.[3] However, different patterns of clinical involvement indicate other pathogenetic mechanisms. The occurrence of spontaneous remission [4] and the benign histopathological appearance of the lesions in LCH suggest a reactive clonal disorder rather than a malignant process, at least in some cases. Langerhans cells, like other dendritic cells, have a critical role in the immune system, and it has been suggested that LCH could be the result of immune dysregulation. Although no consistent immunologic abnormalities have been described, there is increasing evidence that LCH may be the result of an uncontrolled and abnormal proliferation of Langerhans cells secondary to either immune dysregulation or following exposure to a yet undetermined stimulus.[5] In order to reconcile the clonal origin of the pathologic Langerhans cells with the evidences for immune dysregulation, a hypothesis has emerged that proposes that the monoclonal expansion seen in LCH could represent a host response to chronic antigenic stimulation. Under conditions of chronic stimulation, dominant clones of dendritic cells might emerge. These clones might still retain some ability to respond to normal immune regulatory loops, as exemplified by the therapeutic effect of cyclosporine.

### Treatment of LCH

The treatment of LCH over the years has reflected the changing concepts of the disease process. Indeed, the difficulties in developing more effective therapies are linked to the deficiencies in the understanding of the pathogenesis of LCH. Retrospective studies of Lahey [6] and Komp et al [7] showed that, although many organs can harbor proliferating Langerhans cells, only if organ function were disrupted was such involvement of prognostic significance. Patients could then be stratified into different risk categories based on the extent of their disease and the degree of organ dysfunction. Two large cooperative trials [8,9] later confirmed those findings, and also identified a subgroup of patients (defined by age > 2 years and absence of organ dysfunction) with an excellent prognosis despite multi-system involvement. Treatment for patients with LCH is currently risk-adapted. Patients with single-system disease confined to a single site usually require only local therapy or observation. Patients with more extensive disease (multiple bone lesions or multiple lymph nodes) usually require systemic therapy. The best therapeutic option in these cases has not been defined, and responses have been observed with short courses of steroids with or without the addition of chemotherapeutic agents.[10] The treatment recommended by the Histiocyte Society for this group of patients includes a 6-week induction with prednisone and vinblastine, followed by continuation treatment with pulses of the same agents every 3 weeks. The prognosis for this group of patients is usually excellent, although approximately 30% of the patients will experience disease reactivations that continue to respond to treatment.

Five major cooperative trials have addressed treatment for patients with multi-system disease: the Italian AIEOP-CNR-HX 83 protocol,[8] the Austrian/German DAL-HX 83/90 protocol,[9] and the three trials of the Histiocyte Society (LCH-I,[11] LCH-II,[12] and LCH-III protocols). All these protocols were risk-adapted, and were based in different combinations of prednisone, vinblastine, etoposide, methotrexate and 6-mercaptopurine. In all those studies, survival rates are in excess of 90% for patients with multi-system disease without involvement of risk organs. For this group of patients, the treatment currently recommended by the Histiocyte Society is a 12-month regimen with prednisone and vinblastine. Involvement of the risk organs carries the worse prognosis. This high-risk group of patients is characterized by early age at presentation (usually < 2 years), and different degrees of liver, spleen, hematopoietic, and lung involvement. Patients respond poorly to treatment, and mortality rate is approximately 40%.

**Treatment of Recurrent LCH**

Disease reactivation is common in patients with LCH, and two groups of patients are identified:

a) Patients with "low-risk" disease. Includes patients with reactivation of multifocal bone disease or low-risk multisystem disease (without risk organ involvement); disease reactivations occur in approximately one-third of patients, and they usually respond well to second-line therapy. Many regimens have been described, including oral 6-mercaptopurine and methotrexate,[13] indomethacin,[14] bisphosphonates,[15] and cladribine.[16]

b) Patients with "high-risk" disease. This high-risk group is characterized by the presence of risk organ involvement, and poor response to standard treatment. Mortality is high, and recent data suggest that an intense regimen with cladribine and high-dose cytarabine may be effective.[17,18] Allogeneic hematopoietic stem cell transplantation has also been proposed for those cases. [19]

**Treatment of Recurrent or Refractory LCH with Nucleoside Analogues**

Treatment of LCH with 2-CdA

The enzyme adenosine deaminase (ADA) has an essential role in the intracellular degradation of purine nucleosides derived from DNA breakdown. In ADA deficient cells, deoxyadenosine is metabolized by deoxycytidine kinase (dCk), resulting in increased cellular concentrations of deoxyadenosine mono-, di-, and tri-phosphates (dAMP, dADP, and dATP), that are toxic to the cells.[20] 2-chlorodeoxyadenosine (2-CdA, cladribine) is a purine analog resistant to ADA but not to dCk. This results in accumulation of chlorinated deoxyadenosine nucleotides that may be eventually incorporated into the DNA of dividing cells, which results in induction of arrest in the S phase of the cell cycle,[21] and activation of the apoptotic pathway. However, in contrast with conventional antimetabolites, 2-CdA is extremely toxic to mature, non-dividing lymphocytes. High concentrations of deoxynucleotides might interfere with the repair of DNA breaks, thus initiating the process of programmed cell death. [22]In children, 2-CdA has mainly been used in the treatment of AML, where responses of up to 59% are obtained as a single agent. [23]Normal mature lymphocytes and monocytes express high levels of dCk.[24] In vitro studies have shown that 2-CdA is a highly selective anti-monocyte agent, which causes decreased monocyte function and viability and decreased IL-6 secretion.[25] Because tissue histiocytes are derived from the same stem cells as circulating monocytes, 2-CdA has been investigated for the treatment of patients with histiocytic disorders. Excellent clinical responses, with an overall response rate of 82% have been reported in adults with recurrent LCH.[26] In children, the role of 2-CdA has been explored in two scenarios.

a) For patients with low-risk disease reactivation, cladribine has shown to induce responses in > 90% of the patients, although further reactivations still occur.[16,27-29] One additional benefit of cladribine is its effect on CNS disease (a common complication of LCH).[30,31]A major limitation with the use of cladribine is its limitation to a short treatment course; more than 4 or 6 courses of treatment are associated with prolonged myelosuppression, causing a clinical picture similar to myelodysplasia.

b) For patients with high-risk disease, cladribine as a single agent has little effect, [28] and a more intensive regimen is needed. The combination of high-doses of cladribine (9 mg/m$^2$/day x 5 days) with cytarabine (1 gr/m$^2$/day x 5 days) has induced complete responses in patients with refractory disease.[17,32] While this treatment seems to be effective, it is associated with high morbidity, with treatment-related mortality in excess of 20%.

**Treatment of LCH-related Disorders**

Several rare entities that occur in children and adults are defined by the proliferation and/or accumulation of cells of the histiocyte lineage but differ from LCH in histology, immunohistochemistry and clinical behavior.

Rosai-Dorfman Disease (RDD), also known as Sinus Histiocytosis with Massive Lymphadeopathy, is a disease of children and young adults that is characterized by proliferation of S100 positive, CD1a negative histiocytes. RDD most often presents as massive bilateral cervical lymphadenopathy, sometimes associated with symptoms of systemic inflammation. Many RDD patients experience a relapsing/remitting course but one that is ultimately benign and self-resolving. For the subset of RDD patients who have extranodal involvement or nodal disease with risk for life threatening complications, systemic treatment is indicated. A variety of chemotherapy and immunomodulatory agents have been tried with variable success. There is currently no standard treatment approach. Cladribine[33] and clofarabine[34] have shown encouraging activity in limited published experience in RDD.

Juvenile Xanthogranuloma (JXG) is a rare, benign histiocytic disorder that most often presents in infancy as single or multiple skin nodules. Biopsy shows Touton giant cells that are negative for CD1a and langerin (and usually S100 as well), but positive for Factor XIIIa, fascin, CD14, CD68, and CD163. Ocular, CNS, liver/spleen and lung involvement occurs in a small minority of JXG cases. Treatment of extra-cutaneous JXG with LCH- based regimens,[35]cladribine[36] and clofarabine[34] has met with some success.

Erdheim-Chester disease (ECD) is a rare non-Langerhans histiocytic disorder most commonly characterized by multifocal osteosclerotic lesions of the long bones demonstrating sheets of foamy histiocytes on biopsy with or without histiocytic infiltration of extraskeletal tissues. The pathogenesis of Erdheim-Chester disease (ECD) is poorly understood. Attempts to establish clonality have produced varied results, and although occasional clonal cytogenetic aberrations have been identified, none are characteristic or diagnostic.[37] An activating point mutation of the BRAF isoform of RAF (BRAF V600E) is identified in approximately 50 percent of cases of ECD and several case series have reported clinical responses to the BRAF inhibitor vemurafenib.[38-40] There is no standard treatment regimen for patients with symptomatic ECD, and patients should be encouraged to enroll in a clinical trial. Most patients are treated with conventional or pegylated interferon-alpha rather than systemic chemotherapy.[41]. The BRAF inhibitors vemurafenib or dabrafenib are reasonable options for patients with a BRAF V600E mutation who fail to respond to or cannot tolerate interferon-alpha. Systemic chemotherapy agents such as cladribine,

methothrexate and cyclophosphamide may be effective but are poorly studied.[42,43] The optimal treatment of patients who fail interferon and who are not candidates for or do not respond to BRAF inhibitors remains unclear. Given the activity of clofarabine in other histiocyte disorders additional study in ECD is warranted.

Histiocytic sarcoma (HS) is an extremely rare and generally aggressive malignancy typically comprised of non-cohesive, large cells that are polygonal or ovoid with spindling and abundant eosinophilic cytoplasm. Occasionally, the neoplastic cells can have a foamy appearance, but this is not nearly as pronounced as in Erdheim-Chester disease. There is typically a prominent inflammatory infiltrate, but necrosis is minimal. Hemophagocytosis may occasionally be present. The malignant cells usually expressed CD68, lysozyme, CD4, and CD 163. CD1a, S100, T and B-cell markers aside from CD4, and epithelial markers are usually absent. Birbeck granules are lacking.[44] HS can occur as a de novo disease or concomitant with or subsequent to other hematologic neoplasms including follicular lymphoma, myeloid leukemias, and germ cell tumors. Patients with localized disease have a favorable prognosis after surgical resection, radiation, or both.[45] Unfortunately, patients with disseminated disease have a very poor prognosis. Patients are often treated with regimens used in aggressive lyphomas such as CHOP and ICE but response rates are poor.[46] There are anecdotal reports of responses to agents such as cladribine[47] and alemtuzumab[48] but new therapeutic options are desperately needed. There are reports of responses with clofarabine in HS[34] and given the general lack of other effective options further study is warranted.

Interdigitating dendritic cell sarcoma (Interdigitating cell malignant histiocytosis or IDCMH) is an extremely rare neoplasm of unknown cause. The neoplastic cells are usually found in the paracortical region of lymph nodes and are consistently positive for S 100 and vimentin. Fascin is also often positive. Expression of CD68, lysozyme and CD45 is variable. CD1a and CD207 are negative and the Ki67 proliferative index is low. The majority of patients have localised disease at diagnosis. Isolated nodal disease makes up 47% of reported cases, isolated extranodal disease 25% and combined nodal and extranodal 28%.[49] Extranodal sites include the liver, spleen, tonsils, bone marrow, lungs, skin, soft tissue, bowel, and bladder. Patients with metastatic disease have a poor outcome (38% survival at 1 year) though patients with localized disease can do well (85% survival at 1 year). The median survival for patients with metastatic disease is 9 months (0.25 – 72 months).[49] Patients with metastatic disease are usually treated with chemotherapy. A range of chemotherapy treatments have been reported but responses are often absent/short-lived, and outcomes remain poor. Chemotherapy regimens reported include ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine); CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone); docetaxel + gemcitabine; IE (ifosfamide and eoposide).[49] Given the poor outcome of patients with metastic diseases inclusion in a clinical trial with a new therapeutic agent known to have activity in histiocyte disorders is appropriate.

## 2.2 IND Agent

Clofarabine (2-chloro-9-[2'-deoxy-2'-fluoro-β-D-arabinofuranosyl] adenine; Cl-F-ara A; CAFdA) is a rationally designed, second generation purine nucleoside analogue. Clofarabine was designed as a hybrid molecule to overcome the limitations and incorporate the best qualities of both fludarabine (F-ara-A) and cladribine (2-CdA, CdA) both of which are currently approved by various regulatory authorities for treatment of hematologic malignancies. Because clofarabine has a chloro- group at the 2-position of adenine, its chemical structure is more closely related to 2-CdA than to F-ara-A. Halogenation at the 2-position of adenine renders this class of compounds resistant to intracellular degradation by the enzyme

adenosine deaminase. Substitution of a fluorine at the C-2'-position of the arabinofuranosyl moiety of clofarabine increases its stability in gastric acid[50,51] and decreases its susceptibility to phosphorolytic cleavage by the bacterial enzyme *Escherichia coli* purine nucleoside phosphorylase in the gastrointestinal tract,[51] both of which may lead to enhanced oral bioavailability. Clofarabine was approved in December 2004 by the United States Food and Drug Administration (US FDA) for the treatment of pediatric patients with relapsed or refractory acute lymphoblastic leukemia (ALL) after at least 2 prior regimens based on the induction of complete responses.

### 2.2.1 Mechanism of Action

The precise mechanism of action of clofarabine on dividing and non-dividing cells is unknown. Like other nucleoside analogues (cytarabine, cladribine, and fludarabine), clofarabine must be converted within cells to the 5'-triphosphate form by deoxycytidine kinase (dCK) and mono- and di-phosphokinases to be active. Clofarabine is more efficient as a substrate for purified recombinant dCK, exceeding cladribine and the natural substrate, deoxycytidine.[52] Evidence suggests that the primary cytotoxic effect of clofarabine is due to its inhibition of DNA synthesis and repair. The triphosphate form of clofarabine is an inhibitor of both DNA polymerase α and ε and ribonucleotide reductase.[53] These inhibitory effects lead to depletion of intracellular deoxynucleotide triphosphate pools and inhibition of elongation of DNA strands during synthesis and DNA repair.[54] With respect to inhibition of ribonucleotide reductase, clofarabine and cladribine are superior to fludarabine.[52] With respect to inhibition of DNA polymerase α, clofarabine and fludarabine are similar and both are superior to cladribine.[52] Thus, in comparison to cladribine and fludarabine, clofarabine more completely inhibits both ribonucleotide reductase and DNA polymerase α, versus one or the other.

Unlike fludarabine, clofarabine is active in vitro in non-dividing cells and in cells with a low proliferation rate. Clofarabine can induce the apoptotic pathway as part of its cytotoxic effect on cells.[51] Clofarabine has been shown to disrupt the integrity of mitochondria in primary chronic lymphocytic leukemia (CLL) cells. The damage leads to release of pro-apoptotic mitochondrial factors.[55] These effects are postulated to induce apoptosis in indolent, non-dividing CLL cells. This result was not seen with fludarabine and may explain, at least in part, the enhanced cytotoxicity of clofarabine,[55] although the physiologic and clinical implications of these observations remain uncertain and under continued investigation.

### 2.2.2 Pharmacokinetics and Pharmacology

#### Pharmacokinetics of Clofarabine in Adult Patients with Acute Myeloid Leukemia (AML)

Pharmacokinetic data were collected from 13 adult patients with refractory or relapsed AML in an open-label study in which they were treated with clofarabine 40 mg/m$^2$/day IV infusion over 1 hour for 5 consecutive days.[56] Stationary pharmacokinetics were observed between Days 1 and 5, and plasma concentrations declined rapidly thereafter and exhibited biphasic kinetics. The estimated terminal half-life was approximately 6 hours and ranged from 4.1 to 8.6 hours. Consistent with this short half-life, pre-dose concentrations on Day 2 were about 10% or less of maximal concentrations at the end of infusion. After 4 days of dosing, pre-dose concentrations

averaged 13.8 ng/mL and ranged from 4.0 to 23.1 ng/mL. Because of the short half-life of clofarabine, there was little-to-negligible accumulation with once daily dosing of clofarabine at 40 mg/m$^2$ by 1-hour IV infusion.

**Pharmacokinetics of Clofarabine in Pediatric Patients with Acute Lymphoblastic Leukemia (ALL)**

The population pharmacokinetics of clofarabine was studied in 40 pediatric patients aged 2 to 19 years (21 males/19 females) with relapsed or refractory ALL or AML. At the given 52 mg/m$^2$ dose, similar concentrations were obtained over a wide range of body surface areas (BSAs). Clofarabine was 47% bound to plasma proteins, predominantly to albumin. Based on non-compartmental analysis, systemic clearance and volume of distribution at steady-state were estimated to be 28.8 L/h/m$^2$ and 172 L/m$^2$, respectively. The terminal half-life was estimated to be 5.2 hours. No apparent difference in pharmacokinetics was observed between patients with ALL and AML or between males and females. No relationship between clofarabine or clofarabine triphosphate exposure and toxicity or response was found in this population. Based on 24-hour urine collections in the pediatric studies, 49-60% of the dose is excreted in the urine unchanged. In vitro studies using isolated human hepatocytes indicate very limited metabolism (0.2%), therefore the pathways of non-renal elimination remain unknown.

Although no clinical drug-drug interaction studies have been conducted to date, on the basis of the in vitro studies, cytochrome p450 inhibitors and inducers are unlikely to affect the metabolism of clofarabine. The effect of clofarabine on the metabolism of cytochrome p450 substrates has not been studied. The pharmacokinetics of clofarabine have not been evaluated in patients with renal or hepatic dysfunction.[57]

Peripheral blood mononuclear cell (PBMC) clofarabine triphosphate concentrations were assessed in selected pediatric patients with relapsed or refractory ALL or AML in the pivotal Phase 2 studies of clofarabine (Genzyme Corp. Data on file).[58] Triphosphate concentrations were similar in magnitude to adults given the same or similar dose. The half-life of the triphosphate could not be adequately characterized but was estimated to be greater than 24 hours. No correlation between triphosphate concentrations and either dose or parent clofarabine concentration was found.

## 2.3 Rationale for the use of clofarabine in recurrent or refractory LCH

Clofarabine is a second-generation deoxyadenosine analog, designed to improve the efficacy and minimize the toxicity of its congeners cladribine and fludarabine. Whereas fludarabine triphosphate primarily inhibits DNA polymerases and cladribine triphosphate particularly inhibits ribonucleotide reductase, clofarabine triphosphate inhibits both DNA polymerases and ribonucleotidase reductase in addition to inducing apoptosis through release of mitochondrial cytochrome C. The cellular retention of phosphorylated clofarabine metabolites is longer than that of other purine nucleoside analogues. Clofarabine has demonstrated significant activity in ALL, AML, and MDS including patients refractory to other deoxyadenosine analogs.[59-63] In a Phase I trial of clofarabine in children with refractory hematologic malignancies, DLT at 70 mg/m2/day x 5 days was hyperbilirubinemia and skin rash, and MTD was 52 mg/m2/day for 5 consecutive days. [62] In a subsequent Phase II study using the MTD in children with

recurrent or refractory ALL response rate was 30%. [61] At this dose, toxicity was characterized by electrolyte abnormalities (hypokalemia, hypophosphatemia) and mild elevation of liver enzymes and bilirubin. Two-thirds of the patients developed severe (≥ grade 3) infectious complications, including sepsis and septic shock (20% of patients). [61]

Given the good results obtained with cladribine in children with recurrent LCH, there could be a role for the use of clofarabine in this population. We recently treated a 2-year-old girl with low-risk multi-system LCH with clofarabine. This child was diagnosed at 7 months of age and treated with standard vinblastine/prednisone for 12 months. End of therapy evaluation showed residual FDG avid bone lesions on PET, and three months after completing therapy the patient had frank clinical and radiological disease progression. Treatment with cladribine was started, with symptomatic improvement but lack of complete response by PET-CT. Progressive disease was noted after the fourth course of cladribine. Treatment with clofarabine was then started at 30 mg/m2/day for 5 days. The patient had marked symptomatic improvement, and PET-CT after one course showed complete response, with no areas of abnormal FDG uptake for the first time since diagnosis. The patient developed grade 4 neutropenia after the second course, and the treatment was subsequently modified to 25 mg/m2/day for 3 days, given in monthly courses for a total of 6 courses. The patient remains in remission six months after completing treatment. A similar approach was used to treat a 5-year-old girl with high-risk multi-system LCH that had failed treatment with vinblastine/prednisone. This patient subsequently received salvage treatment with methotexate, mercaptopurine, etoposide, cladribine (as single agent and in combination with cytarabine), and a combination of cyclophosphamide, prednisone, vincristine, and daunomycin. Treatment with clofarabine 25 mg/m2/day x 5 days was started, and the patient achieved a complete response after 2 courses. These two cases demonstrate that clofarabine has activity in refractory LCH and may be a better alternative to cladribine for patients with refractory or recurrent disease. [64] Following this initial experience, two other small series by investigators associated with this study have confirmed the early findings and suggesting that this agent is among the most effective drugs tested against high-risk LCH. [65,66] Additional information available through personal experience of the study investigators supports this observation. However, prospective studies are needed to define the role of clofarabine.

**Rationale for use of Clofarabine in LCH-related disorders**

The optimal treatment for patients with RDD, JXG, ECD, HS, and IDCMH is not established. In particular, the prognosis of HS and IDCMH remains poor. Although there is a reasonable amount of data in the literature to support the use of interferon and BRAF inhibitors in ECD, the optimal treatment of ECD refractory to these agents and the optimal treatment of HS, JXG, and IDCMH remain to be defined. Therefore, given the paucity of data and the activity of clofarabine in LCH, inclusion of these histologies in the present trial is justified.

**Study and Dose Rationale**

The safety profile of clofarabine appears acceptable within the target populations studied to date in the clinical studies summarized above, and clofarabine has demonstrated anti-cancer activity through inhibition of DNA synthesis and repair, induction of apoptosis, and possibly through other mechanisms. Numerous responses have been observed after treatment with clofarabine in heavily pre-treated relapsed/refractory patients with ALL or AML. As documented above, there is also a strong rationale for

the study of clofarabine in refractory LCH, although a less intensive regimen may be effective. In this study, a dose of 25 mg/m$^2$/day will be administered for 5 days. Evaluation of response will be performed after 2 cycles, and participants showing response will receive four additional cycles of clofarabine at the same dose for the first 5 days in each cycle. The selected dose is significantly lower than the maximum tolerated dose of 52 mg/m$^2$/d defined in pediatric phase I trials; this lower dose has been selected based on the excellent response rates noted in patients with recurrent or refractory LCH using doses of 25-30 mg/m$^2$/d. [64,65]

## 3 PARTICIPANT SELECTION

Patients will undergo baseline/screening procedures as defined in Table 2 within 14 days prior to starting protocol therapy.

### Stratum 1: Recurrent or Refractory LCH

Participants with multi-focal or multi-system disease who have recurred after at least one prior systemic chemotherapy regimen.

### Stratum 2: LCH-Related Disorders Requiring Systemic Therapy

Participants with LCH-related disorders who require systemic chemotherapy including: Participants with RDD who have not responded to or recurred after treatment with corticosteroids. ECD subjects who have confirmed presence of BRAF V600E mutation must have not responded to, have recurred after, or be unable to receive treatment with a BRAF inhibitor.

Laboratory tests required for eligibility must be completed within 14 days prior to study entry. Baseline tumor measurements and other studies must be performed within 30 days of study entry.

### 3.1 Inclusion Criteria

Participants must meet the following criteria on screening examination to be eligible to participate in the study:

1. Prior diagnosis of Langerhans Cell Histiocytosis (stratum 1) or LCH-related disorder (stratum 2) established by standard diagnostic criteria and confirmed histologically.
2. Evidence of active disease (histological confirmation of reactivation or progression is not required).
3. Performance Score > 70% (use Lansky score for age <16 and Karnofsky score for age = >16, see Appendix I).
4. Patients of all ages will be eligible.
5. Provide signed written informed consent.

6. In stratum 1, patients must have failed one prior systemic chemotherapy regimen. In stratum 2, RDD patients must have failed treatment with corticosteroid. EDC patients who have confirmed BRAF V600E mutations must have failed treatment with BRAF inhibitor or are not considered to be eligible for such treatment.
7. There is no limitation of amount or the type of prior therapy or drugs.
8. Female patents of childbearing potential must have a negative serum pregnancy test within 14 days prior to enrollment. Male and female patients must use an effective contraceptive method during the study and for a minimum of 6 months after study treatment.
9. Capable of understanding the investigational nature, potential risks and benefits of the study, and able to provide valid informed consent.
10. Participants must have adequate marrow functions as defined below, except those who involvement of hematopoietic system for whom these criteria can be waived:
    - Absolute neutrophil count ≥ 750 cells/μL
    - Platelets ≥ 750 cells/μL
11. Participants must have adequate organ function as defined below:
    - Total bilirubin ≤ 2.5 x institutional upper limit of normal.
    - AST (SGOT)/ALT (SGPT) < 2.5 x institutional upper limit of normal unless it is related to involvement by LCH.
    - Pediatric Population (patients < 18 years): Creatinine within normal limits or calculated creatine clearance ≥ 90 mL/min/1.73 $m^2$ as calculated by the Schwartz formula for estimated glomerular filtration rate (GFR) where GFR (mL/min/1.73 $m^2$) = k x Hight (cm)/serum creatinine (mg/dL). k is proportionally constant which varies with age and is a function of urinary creatine excretion per unit of body size; 0.45 up to 12 months of age; 0.55 children and adolescent girls; and 0.70 adolescent boys.
    - Adult Population (patients >= 18 years): Serum creatinine ≤ 1.0 mg/dL; if serum creatinine >1.0 mg/dL, then the estimated glomerular filtration rate (GFR) must be > 60 mL/min/1.73 $m^2$ as calculated by the Modification of Diet in Renal Disease equation where Pediatric GFR (mL/min/1.73 $m^2$) = 186 x (Serum Creatinine)$^{-1.154}$ x (age in years)$^{-0.203}$ x (0.74 if patient is female) x (1.212 if patient is black), where serum creatinine is measured in mg/dL.
    - Alkaline phosphatase ≤ 2.5 x institutional upper limit of normal.

### 3.2 Exclusion Criteria

Participants who exhibit any of the following conditions at screening will not be eligible for admission into the study.

1. Participants who have had chemotherapy or radiotherapy within 2 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 2 weeks earlier. Corticosteroid treatment is allowed.
2. Participants may not be receiving any other investigational agents targeting Histiocytosis.
3. Clofarabine is excreted primarily by the kidneys. Therefore, drugs with known renal toxicity (e.g. vancomycin, amphotericin B, acyclovir, cyclosporin, methotrexate, tacrolimus) should be avoided to the extent possible during the 5 days of clofarabine treatment in each cycle or, if required, administered cautiously and with close monitoring.
4. Use of alternative medications (e.g., herbal or botanical that could interfere with clofarabine) is not permitted during the entire study period.
5. Uncontrolled intercurrent illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
6. Pregnant women are excluded from this study because clofarabine is a nucleoside analog with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk of adverse events in nursing infants secondary to treatment of the mother with clofarabine, breastfeeding should be discontinued if the mother is treated with clofarabine. These potential risks may also apply to other agents used in this study.
7. Individuals with a history of a different malignancy are ineligible except for the following circumstances. Individuals with a history of other malignancies are eligible if they have been disease-free for at least 5 years and are deemed by the investigator to be at low risk for recurrence of that malignancy. Individuals with the following cancers are eligible if diagnosed and treated within the past 5 years: cervical cancer in situ, and basal cell or squamous cell carcinoma of the skin.
8. Patients with a history of prior hematopoietic stem cell transplantation (HSCT), elevated conjugated serum bilirubin at study entry, uncontrolled systemic fungal, bacterial, or other infection, a history of hepatitis B or C infection or a history of cirrhosis.
9. Individuals who are known to be HIV-positive on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with clofarabine. In addition, these individuals are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in participants receiving combination antiretroviral therapy when indicated.

### 3.3 Inclusion of Women, Minorities and Other Underrepresented Populations

Individuals of both genders and all ethnic backgrounds are eligible for this study.

# 4 REGISTRATION PROCEDURES

## 4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of protocol therapy.

An investigator will confirm eligibility criteria and will complete and sign the protocol-specific eligibility checklist.

Following registration, participants may begin protocol therapy and should begin protocol therapy within 7 days. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

## 4.2 Registration Process for DF/HCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research titled *Subject Registration* (SOP #: REGIST-101) must be followed.

## 4.3 General Guidelines for Other Investigative Sites

Eligible participants will be enrolled on study centrally at the Dana-Farber Cancer Institute by the Study Coordinator (or designee). All sites should follow the procedure specified in section 4.4 to register participants prior to the initiation of protocol treatment.

Following registration, participants should begin protocol treatment within 7 days. Issues that would cause treatment delays should be discussed with the Overall PI. If a participant does not receive protocol therapy following registration, the participant's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

## 4.4 Registration Process for Other Investigative Sites

To register a participant, the following forms and source documents should be completed by the participating institution, signed, and e-mailed or faxed to the Lead Institution clinical research coordinator listed on the first page of this protocol, or faxed to 617-632-3977 (Attention: Victoria Koch):

- Signed informed consent document with patient initials and date of birth on every page of the consent
- HIPAA authorization form (if separate from the informed consent document)
- Completed Eligibility Checklist signed by the site investigator or an attending physician whose name is listed in the delegation of responsibility log sheet
- Documentation of consent and eligibility note

- Copy of a pathology report confirming diagnosis of LCH
- All required eligibility source documents (as specified in Table 2)

The Lead Institution (DFCI) will review the submitted documents in order to verify eligibility. To complete the registration process, the Lead Institution will:

- Follow DF/HCC Standard Operating Procedure for Human Subject Research titled *Subject Registration* (SOP #: REGIST–101) and register the participant on the protocol.
- Upon receiving confirmation of registration, the Lead Institution will inform the Participating Institution and provide the study specific participant case number, and, if applicable, assigned treatment and/or dose level within 2 business days.

**Treatment may not begin without confirmation from the Coordinating Center that the participant has been registered.**

**NOTE: Registration can only be conducted during the business hours of 8:00 AM and 5:00 PM Eastern Standard Time Monday through Friday.** Same day treatment registrations will only be accepted with prior notice and discussion with the DF/HCC Lead Institution.

## 5 TREATMENT PLAN

Each patient can receive a maximum of 6 cycles of study treatment. Each treatment cycle will last 4 weeks (28 days) and a delay up to day 42 is allowed if necessary to meet eligibility criteria for starting subsequent cycles. Patients will be stratified into two groups for response analysis purposes:

**Table 1: Treatment Plan for all Patients**

| INDUCTION | | | MAINTENANCE | | | |
|---|---|---|---|---|---|---|
| **Cycle** | | | | | | |
| **1** | **2** | | **3** | **4** | **5** | **6** |
| Clofarabine<br>25 mg/m$^2$/day<br>Days 1-5<br>I.V. 2 hrs +/- 30 min | | Disease Evaluation | Clofarabine<br>25 mg/m$^2$/day<br>Days 1-5<br>I.V. 2 hrs +/- 30 min | | | |

**Induction:** Clofarabine on Days 1-5 of each cycle, administered as I.V. infusion at 25 mg/m$^2$/day. No drug treatment from Day 6 to Day 28. This cycle will be repeated once.

Evaluation of disease response (see Section 9) will be performed after 2 cycles of Induction Therapy. In the absence of disease progression, participants will be eligible to receive up to 4 cycles of Maintenance Therapy, which is identical to the Induction Therapy.

**Maintenance:** Clofarabine on Days 1-5 of each cycle, administered as I.V. infusion at 25 mg/m$^2$/day. No drug treatment from Day 6 to Day 28. Cycle will be repeated for up to three more times every 28 days.

Treatment may be administered on an outpatient basis. Expected toxicities and potential risks as well as dose modifications for clofarabine is described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

### 5.1 Criteria to Proceed with Cycle 1

The following assessment must be completed within 3 days prior to starting Cycle 1. **Patients need to re-meet lab eligibility criteria as described in section 3.1.**

1. Complete physical examination including height, weight and BSA.
2. Performance status ≥70% (use Lansky score for age < 16 and Karnofsky score for age = >16, see Appendix I).
3. Concurrent medical conditions.
4. Hematology: CBC with differential and platelet count and peripheral blood smear.
5. Serum chemistries: Electrolytes (calcium, magnesium, phosphorus, sodium, potassium, chloride, and bicarbonate), blood urea nitrogen (BUN), creatinine, and serum glucose. Liver function tests (total protein/albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin).
6. Uric Acid as clinically indicated.
7. Urinalysis.
8. Baseline adverse event assessment from time of signing informed consent.

### 5.2 Criteria to Proceed with Subsequent Cycles

A treatment cycle will be repeated every 28 days (or no more than 42 days) if the participant does not have disease progression and any non-hematologic toxicities have recovered to grade 1 or become a tolerable grade 2, except those grade 3 toxicities specified in section 6.3.2.

The following assessment must be completed within 3 days prior to starting all subsequent cycles. **Patients need to re-meet lab eligibility criteria as described in section 3.1.**

1. Complete physical examination including height, weight and BSA.
2. Performance status ≥70% (use Lansky score for age < 16 and Karnofsky score for age = >16, see Appendix I).
3. Hematology: CBC with differential and platelet count and peripheral blood smear.
4. Serum chemistries: Electrolytes (calcium, magnesium, phosphorus, sodium, potassium, chloride, and bicarbonate), blood urea nitrogen (BUN), creatinine, and serum glucose. Liver function tests (total protein/albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin).

5. Uric Acid as clinically indicated.
6. Urinalysis.
7. Concomitant Medications/Transfusions.
8. Adverse event assessment.

### 5.3 Drug Administration

Clofarabine should be diluted with NS or D5W prior to administering by IV infusion over 2 hours (+/- 30 minutes). The dosage is based on the participant's body surface area (BSA), calculated using the actual height and weight obtained on the day of treatment or at least within three days before the start of each cycle. To prevent drug incompatibilities, no other medications should be administered through the same IV line.

Participants may receive hydration per institutional standards during clofarabine treatment, giving careful consideration to the cardiac and renal function of the participant. Hyperhydration is not required.

### 5.4 General Concomitant Medication and Supportive Care Guidelines

#### 5.4.1 Prophylactic Steroid Administration

Prophylactic steroid (i.e. hydrocortisone or dexamethasone) has been administered by some investigators in investigator sponsored clinical studies with clofarabine and has been reported to minimize the occurrence and/or severity of the following potential clofarabine-related toxicities: nausea, vomiting, skin rash/desquamation, and capillary leak syndrome.

#### 5.4.2 Management of Capillary Leak Syndrome

In previous studies, during or shortly after IV clofarabine administration a few participants developed signs and symptoms consistent with capillary leak syndrome. In these heavily pretreated participants, it has been difficult to separate potential drug-related cases of capillary leak syndrome from concurrent medical conditions such as infection/sepsis, progressive disease, or other underlying problems resulting from prior antileukemic therapies.

For these reasons, during and after each dose of clofarabine, the onset of the following signs or symptoms ≥ grade 2 will be assessed:

- Tachypnea or other evidence of respiratory distress;
- Unexplained hypotension; and/or
- Unexplained tachycardia.

If one or more of these signs or symptoms occur during study drug infusion, clofarabine administration will be interrupted or held as clinically indicated. It is recognized that the total infusion time for this clofarabine dose in this circumstance may exceed 2 hours. Thus, if the

participant's condition stabilizes or improves, clofarabine administration may resume. Pretreatment (30-60 minutes prior to clofarabine administration) with steroids (e.g. hydrocortisone 50-100 mg/m$^2$/day for up to 3 days or its equivalent, or dexamethasone 5-10 mg/m$^2$/day) is recommended for all subsequent doses during the remainder of that treatment cycle and for all subsequent treatment cycles.

### 5.4.3 Anti-Emetics

Clofarabine is moderately emetogenic. Therefore, standard anti-emetic therapy (such as prochlorperazine or a 5HT3 antagonist, or/and dexamethasone) should be administered prior to therapy.

### 5.4.4 Blood Products

All blood products are to be irradiated and leukocyte-reduced according to each institution's guidelines. Also, CMV-negative participants should receive CMV-negative blood products according to each institution's guidelines.

### 5.4.5 Infection Prophylaxis

The use of prophylactic antibacterial, antifungals, and antiviral agents is recommended according to each institution's guidelines.

### 5.4.6 Treatment of Fever and Neutropenia

Treatment of fever and neutropenia should follow institutional guidelines.

### 5.4.7 Colony Stimulating Factors

Participants experiencing prolonged neutropenia (ANC < 500/mm$^3$ for > 7 days) may receive myeloid growth factor support (filgrastim or peg-filgrastim). For subsequent cycles, growth factor support should be administered starting at least 24 hours after the last dose of clofarabine, and if administered daily, until ANC > 1,500/mm$^3$ after expected decrease in neutrophil counts.

### 5.4.8 Concomitant Therapy

No concomitant cytotoxic therapy or investigational therapy is allowed during the study.

Clofarabine is excreted primarily by the kidneys. Therefore, drugs with known renal toxicity (e.g. vancomycin, amphotericin B, acyclovir, cyclosporin, methotrexate, tacrolimus) should be avoided to the extent possible during the 5 days of clofarabine treatment in each cycle or, if required, administered cautiously and with close monitoring. Additionally, the liver is a known target organ for clofarabine toxicity. Therefore, concomitant use of medications known to induce hepatic toxicity (e.g., voriconazole, cyclosporine, methotrexate, tacrolimus) should be avoided to the extent possible or, if required, administered cautiously and with close monitoring. Hepatic and renal

function should be assessed prior to and during treatment with clofarabine and it is recommended that the participant's fluid status and hepatic and renal function be carefully monitored during the drug administration period. Use of alternative medications (e.g., herbal or botanical for anticancer purposes) is not permitted during the entire study period.

### 5.5 Duration of Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse events, treatment may continue for a maximum of 6 cycles of study treatment or until one of the criteria for removal from protocol therapy (section 5.7) applies.

### 5.6 Duration of Follow Up

After completion of protocol therapy or removal from protocol therapy, participants will be followed for 3 years, or until death, whichever occurs first. Follow-up studies should be done annually at 12, 24, and 36 months after therapy (see Table 2 for scheduled tests).

### 5.7 Criteria for Removal from Protocol Therapy

Participants will be removed from protocol therapy when they have not met eligibility criteria for starting subsequent cycles as defined in section 5.2 by end of cycle 2, or if they have met any of the criteria listed below:

- Disease progression or death
    - Participants who experience disease progression that requires systemic therapy will be followed for survival, disease status and subsequent treatment for 3 years, but will not be required to complete any other protocol-defined follow-up assessments.
- Intercurrent illness that prevents further administration of treatment
- Second malignancy
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the medication regimen and/or documentation requirements
- Participant decides to withdraw from the study
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the opinion of the treating investigator.
- The participant becomes pregnant or fails to use adequate birth control if able to conceive

The reason for removal from protocol therapy and the date the participant is removed must be documented in the study-specific case report form (CRF). Alternative care options will be discussed with the participant.

Documentation of why the patient was removed from treatment and if the patient wishes to continue to be followed is required. This documentation needs to be sent to the DFCI Study team within 7 days of the patient being removed from treatment, if they are coming off treatment early.

For Decentralized Subject Registrations, the research team updates the relevant Off Treatment/Off Study information in OnCore.

In the event of unusual or life-threatening complications, or any change of on study status, participating investigators must immediately notify the Principal Investigator (or Protocol Chair), Barbara Degar, MD at (617) 632-5186 and e-mail the Lead Institution clinical research coordinator listed on the first page of this protocol.

### 5.8 Criteria for Removal from Study

Participants will be removed from the study for the following reasons:

a) Completion of 3-year follow-up period
b) Death
c) Lost to follow-up
d) Withdrawal of consent for data submission
e) Study completion

## 6 DOSE DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made using the following recommendations. Toxicity assessments will be done using the CTEP Version 4.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) which is identified and located on the CTEP website at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

If possible, symptoms should be managed symptomatically. In the case of toxicity, appropriate medical treatment should be used (including anti-emetics, anti-diarrheas, etc.).

All adverse events experienced by participants will be collected from the time of the first dose of study treatment, through the study and up to 30 days from the last dose of treatment. Participants experiencing toxicities that are possibly related to the study treatment at the off-study visit will be followed up until the conditions resolved or clinically stabilized.

### 6.1 Anticipated Toxicities

For detailed information on clofarabine toxicology refer to the Investigator's Brochure for clofarabine.[67]

### 6.1.1 Toxicity

Adult Patients
Drug-related AEs observed in at least 10% of adult participants treated with clofarabine in previous clinical trials include myelosuppression, nausea, vomiting, infections, fatigue, headache, diarrhea, rigors, dermatitis, anorexia, febrile neutropenia, myalgia, asthenia, petechiae, transient elevated liver enzymes, stomatitis, mucositis, pyrexia, flushing, constipation, edema, dehydration, nervousness, stomach pain, insomnia, depression, dry skin, back pain, and decreased weight.[8]

Adverse events reported in <10% of adult participants include tumor lysis syndrome, capillary leak syndrome, palmar plantar erythrodysesthesia, pancreatitis, seizures, irregular heartbeat, edema, pericardial effusion, multi-organ failure, and death.[8]

Pediatric Patients
The most common side effects observed in previous clinical studies of pediatric patients treated with clofarabine 52 mg/m$^2$ include vomiting NOS, nausea, febrile neutropenia, diarrhea NOS, headache NOS, pruritus NOS, pyrexia, dermatitis NOS, fatigue, rigors, abdominal pain NOS, tachycardia NOS, anorexia, petechiae, epistaxis, pain in limb, hypotension NOS, anxiety NEC, cough, constipation, erythema NEC, mucosal inflammation NOS, pain NOS, flushing, edema NOS, and hematuria.[8]

Pediatric patients have also experienced increased liver enzymes and increased creatinine. Moderate neurological changes have been reported in some patients. Infections were reported in almost half of the patients treated with clofarabine.

Other potential SAEs include pericardial effusion, LVSD, tumor lysis syndrome, SIRS, and capillary leak syndrome.[8]

Sanofi US Services Inc., on behalf of itself, and its affiliate, Genzyme Corporation is conducting a Phase I/II study to assess concomitant use of clofarabine, etoposide and cyclophosphamide in pediatric patients with acute leukemias. In the Phase I portion of the study, febrile neutropenia, pyrexia and neutropenia were the most commonly reported serious adverse events and were reported in 64%, 20%, and 16% of patients, respectively. There were 10 patient deaths in the trial (malignant disease, n=5; adverse events, n=2: infection/micrococcus meningitis, CNS hemorrhage; and other causes, n=3: intracranial hemorrhage, multi-organ failure, unknown etiology). Dose-limiting toxicities included a grade 3 elevation of lipase, abdominal pain and possible veno-occlusive disease (VOD) that resolved (cohort 3) and 1 case of prolonged bone marrow aplasia (cohort 5). In the Phase II portion 3 of the 4 first patients treated reported veno-occlusive disease (VOD) symptoms including hyperbilirubinemia, hepatomegaly, right upper quadrant pain, ascites and/or weight gain. VOD-like signs and symptoms initially presented within 5 to 12 days of the first dose of clofarabine in these patients. Two of the patients with VOD symptomatology had a history of HSCT and total body irradiation (TBI) within the previous 4 to 7 months.[3] All 3 patients with VOD-like symptoms had ongoing severe infections and/or capillary leak syndrome preceding the occurrence of hepatotoxicity. The fourth patient reported grade 4 hyperbilirubinemia and had a history of HSCT and TBI greater than 1 year prior to study entry. As a result of these safety

findings, the updated protocol now states that patients with a history of prior HSCT, elevated conjugated serum bilirubin at study entry, uncontrolled systemic fungal, bacterial, or other infection, a history of hepatitis B or C infection or a history of cirrhosis are to be excluded from study participation. The warnings and precautions section of the Clofarabine (Clolar) package insert has also been revised to reflect the recent safety findings.[8]

### 6.2 Toxicity Management

Please refer to section 5.4 (General Concomitant Medication and Supportive Care Guidelines) for management of toxicity.

### 6.3 Dose Modifications/Delays

#### 6.3.1 Hematologic Toxicity

- Participants who experience prolonged neutropenia (ANC < 500/ $\mu$ L for > 7 days) may receive growth factor support (see 5.3.7). If neutropenia persists (ANC < 500/ $\mu$ L) despite the addition of growth factor support and in the absence of hematopoietic involvement by Histiocytosis, but recovered by day 42 of the cycle, the subsequent cycle may start at a reduced dose of clofarabine by 25%. If prolonged neutropenia (ANC < 500/ $\mu$ L for > 7 days) recurs in subsequent cycles after dose reduction, the participant should come off protocol treatment.
- Participants who experience prolonged thrombocytopenia (platelets < 75,000/μL for > 7 days) in the absence of hematopoietic involvement by Histiocytosis should have their dose of clofarabine reduced by 25% in subsequent cycles. If prolonged thrombocytopenia (platelets < 75,000/μL for > 7 days) recurs in subsequent cycles, the participant should come off protocol treatment.
- If ANC or platelets counts are not recovered by day 42 in the absence of hematopoietic involvement by Histiocytosis, the participant should be taken off study.

#### 6.3.2 Non-Hematologic Toxicity

- Participants who experience ≥ grade 3 drug-related non-hematologic toxicity or asymptomatic grade 2 serum creatinine or serum total bilirubin during any clofarabine administration period should have clofarabine held until recovery to baseline or grade < 2 before resuming treatment at the same dose. Excluded from this rule are grade 3 skin rash, ≥ grade 3 anorexia, transient isolated elevations in hepatic transaminases or alkaline phosphatase, and nausea/vomiting, diarrhea, or ≥ grade 3 mucositis that resolves (with or without supportive care) to < grade 3 within 48 hours of onset.

# 7 DRUG FORMULATION AND ADMINISTRATION

## Clofarabine Drug Information

### 7.1 Nomenclature

Chemical Name: 2-chloro-9-(2′-deoxy-2′-fluoro-β-D-arabinofuranosyl)-9H-purine-6-amine

Other names: CLOLAR, clofarabine; CAFdA; Cl-F-ara-A;
2-chloro-2′-fluoro-deoxy-9-β arabinofuranosyladenine

2-chloro-9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)adenine (Cl-F-ara-A)

2-chloro-2′-arabino-fluoro-2′-deoxyadenosine

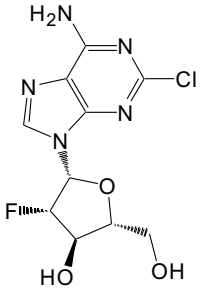
2-chloro-2′-ara-fluorodeoxyadenosine (CAFdA)

2-chloro-2′-fluorodeoxyadenosine (CAFdA)

### 7.2 Molecular Structure

**Figure 4-1: Molecular Structure**

$C_{10}H_{11}ClFN_5O_3$




### 7.3 Description

Clofarabine is a white to off-white solid with a melting point of 228°C to 230°C and a molecular weight of 303.5. The drug substance is very stable in the dry state, and aqueous solutions are stable to heat treatment. Clofarabine is freely soluble in water (1.5 mg/mL) or buffered solutions at room temperature. Clofarabine is not less than 97% pure on a dried basis by high performance liquid chromatography (HPLC) analysis.

### 7.4 Form

Clofarabine is formulated at a concentration of 1 mg/mL. Clofarabine is supplied in 1 vial size: a 20-mL clear, glass vial with gray stopper and blue flip off seal. The 20-mL vials contain 20 mL (20 mg) of sterile solution. The pH range of the solution is 4.5 to 7.5. The solution is clear and practically colorless, preservative free, and free from foreign matter.

### 7.5 Storage and Handling

Vials containing undiluted clofarabine for injection should be stored at controlled room temperature. The current commercial expiry period for Clolar (clofarabine) is 24 months at room temperature. Ongoing stability studies will continue to confirm the appropriate quality of drug product used for clinical trials beyond 24 months.

### 7.6 Preparation

Clofarabine should be filtered through a sterile 0.2 micron syringe filter and then diluted with 5% Dextrose or 0.9% Sodium Chloride prior to intravenous infusion to a final concentration between 0.15mg/ml and 0.4mg/ml. Clofarabine for injection should be diluted with 0.9% sodium chloride injection USP or European Pharmacopeia (EP) normal saline (NS) or 5% dextrose injection (D5W) USP or EP prior to IV infusion. The resulting admixture may be stored at room temperature but must be used within 24 hours of preparation. The dosage is based on the participant's body surface area (BSA), calculated using the actual height and weight before the start of each cycle and should not be adjusted downward to "ideal" weight. To prevent drug incompatibilities, no other medications should be infused concurrently through the same IV lines as clofarabine. Also, no blood products should be administered at the same time as clofarabine.

### 7.7 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

### 7.8 Availability

Clofarabine is an investigational agent in this study and will be supplied free-of-charge from Sanofi US Services Inc., on behalf of itself, and its affiliate, Genzyme Corporation

### 7.9 Administration

Clofarabine should be administered as I.V. infusion via peripheral or central access over 2-hours in a window of 1.5 to 2.5 hours.

### 7.10 Ordering

Clofarabine will be supplied by Sanofi US Services Inc., on behalf of itself, and its affiliate, Genzyme Corporation free of charge. The Coordinating Center will order the drug directly from Sanofi US Services Inc., on behalf of itself, and its affiliate, Genzyme Corporation. Each participating site will submit drug order requests using a specific drug order form supplied by the Coordinating Center. The completed form should be sent to: Victoria_koch@dfci.harvard.edu.

For US sites, allow 5-7 business days for initial drug orders and 3-5 business days for drug re-orders from the acknowledgement of order receipt to the date of delivery. For Canadian sites, allow 7-10 business days for initial and re-orders from the acknowledgement of order receipt to the date of delivery. There are no weekend, Monday, or Holiday deliveries. For questions regarding shipments, please contact Jigisha Patel via email at Jigisha.patel@sanofi.com.

### 7.11 Accountability

Participating pharmacies will be required to submit Drug Accountability Logs at the time of monitoring documenting receipt and shipment of drug supply, dispensing/ordering of supply, and destruction of unused study medication and/or damaged or expired drug.

### 7.12 Destruction and Return

At the end of the study, unused supplies of clofarabine should be destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record Form.

## 8 STUDY CALENDAR

Baseline laboratory tests are to be conducted within 14 days prior to start of protocol therapy. Other evaluations (scans, pathology, EKG, etc.) must be done within 30 days of study entry. In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

All assessments must be performed prior to administration of any study medication. All study assessments and medications should be administered within ± 3 days of the protocol-specified date, unless otherwise noted.

All follow-up assessments must be performed 12, 24, and 36 months from the off-treatment date (i.e. Day 28 of last administered cycle) +/- 31 days.

A calendar for the time points when the required study data should be obtained is provided below.

**Table 2: Required Data / Study Calendar**

| Assessments | Baseline/ Screening (within 14 days) | Before Starting Each Cycle (within 3 days) | During Each Cycle | End of Cycle 2[5] | End of Treatment (+/- 7 days from day 28 of Cycle 6) | Follow-up[7] (+/- 31 days) |
|---|---|---|---|---|---|---|
| Informed Consent | X[1] | | | | | |
| Medical History<br>Concurrent Condition<br>Concomitant Medications/ Transfusions | X | | | | | |
| Height | | X | | | X | |
| Weight | | X | | | X | |
| BSA | | X | | | X | |
| Physical exam/Vital Signs | X | X | | | X | |
| Performance Status | X[1] | X | | | X | |
| Hematology (CBC/Diff/Plts) | X[1] | X | Weekly[4] | | X | X[2] |
| Electrolytes including Ca++, PO4, Mg++ | X | X | Weekly[4] | | X | X[2] |
| Creatinine, BUN, Serum glucose | X[1] | X | Weekly[4] | | X | X[2] |
| LFTs (Total Protein/Alb., ALT, AST, ALP, Billi.) | X[1] | X | Weekly[4] | | X | X[2] |
| Uric acid | X | X[2] | | | X[2] | |
| Serum β-HCG[3] | X[1] | | | | X | |
| EKG | X | | | | X[2] | |
| Urinalysis | X | X | | | X | |
| Bone Marrow Biopsy, Aspirate and Smear | X[2] (within 30 days) | | | X[2] | X[2] | X[2] |
| Disease Assessment/ Response Documentation (CT/MRI/ Bone Scan/ PET, as clinically indicated) | X[1] (within 30 days) | | | X | X[6] | X[8] |
| Chest X-Ray PA and L | X | | | | X | |
| Skeletal survey (stratum 1 only) | X | | | X | X[6] | X[8] |
| Clofarabine Administration | | | Days 1-5 | | | |
| Adverse Event Assessment | X | X | Weekly[4] | | X | |

[1] **Source documents are required for eligibility review before registration**.
[2] As clinically indicated.
[3] For females of childbearing potential.
[4] Weekly assessments are recommended as clinically indicated, to be completed every 7 days, +/- 3 days.
[5] End of Cycle 2 assessments must be completed on Day 28 of Cycle 2 +/- 7 days, and prior to starting Cycle 3.
[6] End of treatment disease assessment imaging window +/- 14 days from day 28 of Cycle 6.
[7] All Follow-Up Assessments to be performed 12, 24, and 36 months from the off-treatment date (i.e. Day 28 of last administered cycle) +/- 31 days.
[8] 12, 24, and 36 months after completion of therapy (i.e. Day 28 of last administered cycle)

# 9 CRITERIA FOR RESPONSE – STRATUM 1

In contrast to leukemia or other malignancies the terms "remission" or "relapse" should be avoided. In accordance with the nature of Histiocytosis the following definitions should be applied to judge the effect of treatment. The response criteria stated below has been designed by the Histiocyte Society to be applied in therapeutic studies of LCH and should be used for therapeutic decisions.[68]

**Table 3: Definition of Disease State**

| Main Category | Sub-categories | Definition |
|---|---|---|
| Non-active Disease (NAD) | | Resolution of all signs/symptoms (no evidence of disease) |
| Active Disease (AD) | Regressive Disease (Better) | Regression of signs/symptoms, and no new lesions. |
| | Stable Disease (Stable) | Persistence of signs or symptoms, and no new lesions. |
| | Progressive Disease* (Worse) | Progression of signs/symptoms and/or appearance of new lesions. |

* Progression of skeletal lesions is defined as unequivocal enlargement of the size of existing lesions and/or appearance of new lesions.

## 9.1 Definition of Response Criteria

**Table 4: Three Categories of Response**

| Response Category | Definition |
|---|---|
| Better | • Complete disease resolution (NAD)<br>• Regression (AD better) |
| Intermediate | • Stable (unchanged) |
| Worse | • Progression* |

* Progression of skeletal lesions is defined as unequivocal enlargement of the size of existing lesions and/or appearance of new lesions. In patients with risk organ involvement the overall response (and hence therapeutic decision) depends on response in risk organs.

## 9.2 CRITERIA FOR RESPONSE – STRATUM 2

For PET-based assessments, a clinical response of progressive metabolic disease (PMD), no metabolic response (NMR), partial metabolic response (PMR), or complete metabolic response (CMR) will be determined. PMD/PD includes radiological evidence of progression per Lugano Classification Revised Staging System for malignant lymphoma[69]. The PET scan metabolic uptake will be graded using the Deauville 5-point scale, with a score of ≤ 3 considered to represent a CMR.

Deauville 5-point scale: 1 = no uptake above background; 2 = uptake ≤ mediastinum; 3 = uptake > mediastinum but ≤ liver; 4 = uptake moderately > liver; 5 = uptake markedly higher than liver and/or new lesions; X = new areas of uptake unlikely to be related to lymphoma.

**Table 5: CMR / CR**

| Response/Site | FDG PET-CT-Based (Complete Metabolic Response) | CT-Based (CR)[a] All of the following: |
|---|---|---|
| Lymph nodes and extralymphatic sites | Score 1, 2 or 3 with or without a residual mass on 5-Point-Scale. It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake. | Target nodes/nodal masses must regress to ≤ 1.5cm in LDi<br><br>No extra lymphatic sites of disease |
| Non-measured lesion | Not applicable | Absent |
| Organ enlargement | Not applicable | Regress to normal |
| New lesions | None | None |
| Bone marrow[b] | No evidence of FDG-avid disease in marrow | Normal by morphology; if indeterminate, IHC negative |

[a] CT-Based could also apply to MRI-based
[b] Only if bone marrow involvement at diagnosis

**Table 6: PMR / PR**

| Response/Site | FDG PET-CT-Based (Complete Metabolic Response) | CT-Based (CR)[a] All of the following: |
|---|---|---|
| Target nodes/nodal masses, extranodal lesions | Score 4 or 5 with reduced uptake compared with baseline and residual mass(es) of any size<br><br>At interim, these findings suggest responding disease<br><br>At end of treatment, these findings suggest residual disease | ≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites<br><br>When a lesion is too small to measure on CT, assign 5mm X 5mm as the default value; when no longer visible, 0 X 0mm; for a node > 5mm X 5mm, but smaller than normal, use actual measurement for calculation |
| Non-measured lesion | Not applicable | Absent/normal, regressed, but no increase |
| Organ enlargement | Not applicable | Spleen must have regressed by >50% in length beyond normal |
| New lesions | None | None |
| Bone marrow[b] | Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan. | Not applicable |

[a] CT-Based could also apply to MRI-based
[b] Only if bone marrow involvement at diagnosis

**Table 7: NMR/ SD**

| Response/Site | FDG PET-CT-Based (Complete Metabolic Response) | CT-Based (CR)[a] All of the following: |
|---|---|---|
| Lymph nodes and extralymphatic sites | Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment | < 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites; no criteria for Progressive Disease met |
| Non-measured lesion | Not applicable | No increase consistent with Progression |
| Organ enlargement | Not applicable | No increase consistent with Progression |
| New lesions | None | None |
| Bone marrow[b] | No change from baseline | Not applicable |

[a] CT-Based could also apply to MRI-based
[b] Only if bone marrow involvement at diagnosis

**Table 8: PMD / PD**

| Response/Site | FDG PET-CT-Based (Complete Metabolic Response) | CT-Based (CR)[a] All of the following: |
|---|---|---|
| Individual target nodes/nodal masses<br><br>Extranodal lesions | Score 4 or 5 with an increase in intensity of uptake from baseline and/or new FDG-avid foci consistent with lymphoma at interim or end-of-treatment assesssment | An individual node/lesion must be abnormal with:<br><br>LDi > 1.5 cm &<br>Increase by ≥ 50% from PPD nadir &<br>An increase in LDi or SDi from nadir<br>0.5 cm for lesions ≤ 2cm<br>1.0 cm for lesions > 2cm<br><br>In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15cm spleen must increase to 16cm). If no prior splenomegaly, must increase by at least 2cm from baseline.<br><br>New or recurrent splenomegaly |
| Non-measured lesion | None | New or clear progression of preexisting nonmeasured lesions |
| New lesions | New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation).<br><br>If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered. | Regrowth of previously resolved lesions<br><br>A new node > 1.5cm in any axis<br><br>A new extranodal site > 1.0cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma. Assessable disease of any size unequivocally attributable to lymphoma. |
| Bone marrow[b] | New or recurrent FDG-avid foci | New or recurrent involvement |

[a] CT-Based could also apply to MRI-based
[b] Only if bone marrow involvement at diagnosis

### 9.3 Other Response Parameters

Response should be maintained for 8 weeks.

## 10 ADVERSE EVENT REPORTING REQUIREMENTS

All adverse events that occur after the initial dose of study treatment, during treatment, or within 30 days of the last study intervention need to be captured. Adverse events will be followed for 30 days after the last study intervention if a participant discontinues protocol treatment early. All AEs need to be followed until resolution.

### 10.1 Adverse Event (AE) Characteristics, Collection and Routine Reporting

An adverse event (AE) is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.

**All AEs (grades 1-5)** whether reported by the participant, discovered during questioning, directly observed, or detected by physical examination, laboratory test or other means, will be recorded in the participant's medical record and on the appropriate study-specific case report forms.

- **NOTE:** Abnormal laboratory values or diagnostic test results constitute adverse events only if they are clinically significant (i.e. cause a cycle to be delayed, induce clinical signs or symptoms or require treatment or further diagnostic tests).

**CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

**Attribution** is the relationship between an adverse event and the study treatment. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment.
- Possible – The AE may be related to the study treatment.
- Unlikely - The AE is doubtfully related to the study treatment.
- Unrelated - The AE is clearly NOT related to the study treatment.

Adverse events can be **'Expected' or 'Unexpected**.'

- **Expected adverse events** are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list (see Section 6.1), the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.
- **Unexpected adverse events** are an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational medicinal product or package insert/summary of product characteristics for an

approved product). An expected ADR with a fatal outcome should be considered unexpected unless the local/regional product labeling specifically states that the Adverse Drug Reaction (ADR) might be associated with a fatal outcome.

Reportable Adverse Events **must** be reported in routine study data submissions to the Overall PI on the adverse events case report forms (i.e. in InForm).

### 10.2 Serious Adverse Events (SAE) and Expedited Reporting

A serious adverse event (SAE) is any adverse event, occurring at any dose and regardless of causality that:

- Results in death (Grade 5)
- Is life-threatening. Life-threatening means that the person was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Requires intensive inpatient medical interventions, including mechanical ventilation, pressor support, and/or fluid resuscitation, or emergent surgical operations. Unplanned hospital admission for febrile neutropenia, bacteremia or other documented infections, seizure, pancreatitis, thrombosis, nausea/vomiting, diarrhea, and other expected toxicities from the study treatment will not be considered a serious adverse event unless the severity of the condition is considered life-threatening and/or lead to intensive medical interventions or surgical procedure.
- Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered SAEs if the illness or disease existed before the person was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly or birth defect; or
- Is an important medical event when, based upon appropriate medical judgment, it may jeopardize the participant and require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical 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.
- Per DFCI's Expedited Reporting requirements, the following events also require expedited (SAE) reporting:
    - Unexpected Grade 2 (moderate) and Grade 3 (severe) events that are possibly, probably or definitely related/associated with the intervention.
    - Unexpected Grade 4 (life-threatening or disabling) events regardless of attribution.
    - All Grade 5 (fatal) Events – When the participant is enrolled and actively participating in the trial OR when the event occurs within 30 days of the last study intervention.
        - Note: If the participant is in long term follow up, report the death at the time of continuing review.

**Events not considered to be serious adverse events are hospitalizations for:**

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- Elective or pre-planned treatment for a pre-existing condition that did not worsen
- Emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- Respite care

The Overall Principal Investigator/Sponsor (Dr. Barbara Degar) and the study team at the lead institution should be informed within **1 business day**, by email or phone of all SAEs that occur after the initial dose of study treatment, during treatment, or within 30 days after the last study intervention. In the event that the participating investigator does not become aware of the SAE immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event **within 24 business hours after learning of it** and document the time of his or her first awareness of the event. Report serious adverse events by telephone, email or facsimile:

Barbara Degar, MD
Pediatric Oncology
Dana-Farber Cancer Institute
450 Brookline Ave
Boston, MA 02215
Phone: 617-632-5186
Email: Barbara_Degar@dfci.harvard.edu
Fax: 617-632-4811

At the same time, an e-mail should also be sent to the Lead Site clinical research coordinator listed on page one of this protocol.

Within the following 24-48 business hours, the participating investigator should relay follow-up information to the PI and study team as necessary.

### 10.3 AESI: An adverse event of special interest:

AESI is an adverse event (serious or non-serious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them. AESIs may be added or removed during a study by protocol amendment.

### 10.4 New safety finding:

Any (other than reportable individual case safety report (ICSR)) safety issue that may require expedited reporting because providing information that may lead to a change in the known risk-benefit balance for the product and as mentioned, but not limited to, in the following regulatory texts: Europe: Volume 9A of the Rules Governing Medicinal products in the European Union (September 2008) Section 4.1; and US: FDA: 21 CFR Parts 312 Investigational New Drug Application- Section 312.32, (c) (1) IND safety reports.

### 10.5 Reporting to the Institutional Review Board (IRB)

Investigative sites within DF/HCC will report all serious adverse events directly to the DFCI Office for Human Research Studies (OHRS).

Each investigative site will be responsible to report SAEs that occur at that institution to their respective IRB per their local IRB's policies and procedures in reporting adverse events. These sites will also complete a DF/HCC AE Reporting form and submit to the Overall PI and DFCI study team. The Overall PI and DFCI study team will then submit the DF/HCC AE Reporting form from outside institutions to the DFCI OHRS according to DFCI IRB policies and procedures in reporting adverse events.

### 10.6 Reporting to Regulatory Agencies

For multi-site trials where a DF/HCC investigator is serving as the principal investigator, each participating investigator is required to abide by the reporting requirements set by the DF/HCC. The study must be conducted in compliance with FDA regulations, local safety reporting requirements, and reporting requirements of the principal investigator.

The Overall PI, as study sponsor, will be responsible for all communications with the FDA and Health Canada. The Overall PI will report to the FDA and Health Canada, regardless of the site of occurrence, any serious adverse event that meets the FDA and Health Canada's criteria for expedited reporting following the reporting requirements and timelines set by the FDA and Health Canada.

### 10.7 Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any subject safety reports or sentinel events that require reporting according to institutional policy.

### 10.8 Pharmacovigilance Specifications and reporting to Sanofi

The sponsor-investigator Barbara Degar, M.D. of the Investigator-Sponsored Trial/Study (IST/ISS) will report the following information in English to the Sanofi Global Pharmacovigilance contact, **E-mail:** CL-CPV-Receipt@sanofi.com or **Fax:** +33 (0)1.60.49.77.77 or **Fax:** 1-908 -203-7783

1. Routine transmission of all Serious Adverse Events (SAEs) including pregnancy, overdose and Adverse Events of Special Interest (AESI), if any. These events must be transmitted within 1 business day of the ISS sponsor's awareness or identification of the event, *for Pre-marketing IST and post-marketing ISS with recently approved products.*
2. Routine transmission of SAEs related to the use of the Sanofi product must be transmitted within 1 business day of the ISS sponsor's awareness or identification of the event *for all other approved products*.
3. The reference safety information to be used by the ISS sponsor for evaluation of expectedness of adverse events shall be the current approved product label available in the country *(for an approved indication)/ the Investigator Brochure.*

4. Any Periodic reports (e.g. Development Safety Update Report (DSUR)), submitted to Regulatory Authority must be transmitted to Sanofi at the time of submission.
5. *New Safety Findings* in a study pertaining to safety of product must be transmitted within 1 business day. (e.g., Data Safety Monitoring Board recommendations)
6. The study reports of any ISS must contain a section describing safety review and conclusion and must be reviewed by Sanofi before finalization.

# 11 DATA AND SAFETY MONITORING

## 11.1 Data Reporting

### 11.1.1 Method

The ODQ will collect, manage, and perform quality checks on the data for this study.

### 11.1.2 Data Submission

Sites are responsible for submitting data and/or data forms to the ODQ according to the schedule set by the ODQ.

## 11.2 Safety Meetings

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this trial. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Principal Investigator and the Lead Site study team.
The DSMC will meet quarterly and/or as often as necessary, as determined by the DSMC, if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days for Phase I or II protocols; for gene transfer protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

## 11.3 Monitoring

Involvement in this study as a participating investigator implies acceptance of potential audits or inspections, including source data verification, by representatives designated by the DF/HCC Overall Principal Investigator (or Protocol Chair) or DF/HCC. The purpose of these audits or inspections is to examine study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported in accordance with the protocol, institutional policy, Good Clinical Practice (GCP), and any applicable regulatory requirements.

All data will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. Monitoring will begin at the time of participant registration and will continue during

protocol performance and completion.

Please refer to section 17 Appendix II for more details.

## 12 REGULATORY CONSIDERATIONS

### 12.1 Protocol Review and Amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing each study location.

Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The DF/HCC Overall Principal Investigator (or Protocol Chair) or his designee will disseminate protocol amendment information to all participating investigators.

All decisions of the IRB concerning the conduct of the study must be made in writing.

### 12.2 Informed Consent

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

### 12.3 Ethics

This study is to be conducted according to the following considerations, which represent good and sound research practice:

- US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki
    - Title 21 Part 50 – Protection of Human Subjects
      www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html
    - Title 21 Part 54 – Financial Disclosure by Clinical Investigators
      www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html
    - Title 21 Part 56 – Institutional Review Boards
      www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html

  - Title 21 Part 312 – Investigational New Drug Application
    www.access.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html

- State laws
- DF/HCC research policies and procedures
  http://www.dfhcc.harvard.edu/clinical-research-support/clinical-research-unit-cru/policies-and-procedures/

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB according to the local reporting policy.

### 12.4 Study Documentation

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified.

Original source documents supporting entries in the case report forms include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.

### 12.5 Records Retention

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

### 12.6 Multi-Center Guidelines

This protocol will adhere to the policies and requirements of the Dana-Farber/Harvard Cancer Center. The specific responsibilities of the DF/HCC Overall Principal Investigator (or Protocol Chair), Coordinating Center, and Participating Institutions are presented in the Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (see Appendix II).

- The DF/HCC Overall Principal Investigator/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports to all participating institutions for submission to their individual IRBs for action as required.
- Mechanisms will be in place to ensure quality assurance, protocol compliance, and adverse event reporting at each site.
- Except in very unusual circumstances, each participating institution will order the agent(s) directly from the supplier. A participating site may order the agent(s) only after the initial IRB approval for the site has been forwarded to the Coordinating Center.

# 13 STATISTICAL CONSIDERATIONS

## 13.1 Overview

This is a prospective study of clofarabine treatment for Histiocytosis patients. All patients will receive the same treatment with the standard dose of clofarabine (25 mg/m$^2$/d). A single-arm design test will be used to estimate the response rate in Stratum 1. In addition, in an exploratory fashion, we will estimate the rates of response and toxicity in patients with LCH-related disorders (Stratum 2). Stratum 2 is a heterogeneous group of patients, and we wish to gather data in order to generate hypotheses about the response rates of the subgroups of Stratum 2 which could be tested in a future protocol.

## 13.2 Sample Size/Accrual Rate

Twenty evaluable participants in Stratum 1 will be required in order to have sufficient power to address the study's primary objective. To account for participants who enroll and are subsequently determined to be ineligible or unevaluable, a total of up to 25 participants may be enrolled in order to obtain 20 evaluable patients. At an estimated accrual rate of 10 participants per year, the accrual goal of 20 evaluable participants can be achieved in less than 4 years. It is estimated that up to 10 patients per year meeting the eligibility criteria for Stratum 2 are seen across all study sites (personal communication from Drs. Degar and Jacobsen). Therefore, the estimated accrual rate of Stratum 2 patients is up to 5 patients per year, which allows for up to 20 patients in Stratum 2, though realistically, fewer of these rare patients are anticipated to be enrolled. We estimate a total study accrual of up to 45 patients (25 in Stratum 1, and 20 in Stratum 2).

Once the accrual goal of eligible patients for a given stratum is reached (with a 5-patient overage to account for potentially ineligible patients), that stratum will be closed to accrual. Once the accrual goal of evaluable patients is met within Stratum 1, the overall study will be closed even if fewer than 20 patients have been enrolled in Stratum 2. In the unlikely event that 20 patients are enrolled on Stratum 2 before Stratum 1 has met its accrual goal, Stratum 2 will be closed to accrual.

## 13.3 Study Design/Endpoints

The primary endpoint within each stratum will be the proportion of responders. A responder is defined as an eligible, evaluable participant who achieves either complete resolution or regression of disease, i.e., their disease gets "Better" per section 9.1, as the best overall response at any time up to and including the End of Cycle 2 assessment, which must be completed on Day 28 of Cycle 2 +/- 7 days, and must be completed prior to starting Cycle 3.

Secondary endpoints are:

a) Progression-free survival (PFS), where time to event for PFS is the time from study enrollment until the time of first occurrence of new lesions, progressive disease, or death from any cause, or until last contact if no event occurs;

b) Overall survival (OS), calculated as the time from enrollment until death or last contact;

c) Feasibility, which is assessed by the proportion of patients who experience a toxicity-event. Participants who have clofarabine stopped because of toxicity concerns will be considered to have experienced a toxicity-event. Otherwise, participants who complete therapy or who are removed from protocol therapy for reasons related to disease progression, second malignancy or death unrelated to protocol therapy will be considered to have successfully tolerated treatment; and,

d) The proportion of participants reporting grades 3-4 toxicity, for each CTCAE v4.0 toxicity code.

### 13.4 Evaluability

To be evaluable for inclusion in the analysis of response and toxicity, a patient must be eligible and have received at least one dose of protocol therapy. All evaluable participants must be assessed for response and toxicity to treatment, even if there are major protocol treatment deviations. Each participant should be assigned a category of response according to section 9 of the protocol.

### 13.5 Monitoring Rules

The study will be referred to the DSMC for review of dosing and toxicity at the first occurrence of a toxic death.

A Simon's two-stage group sequential design will be used to determine if there is sufficient evidence of efficacy to warrant further investigation of clofarabine.

**Rule A - Two-stage stopping rule for response in Stratum 1**

Stage 1: Accrue 13 evaluable participants. If 7 or fewer respond, then there is insufficient evidence to support further study of clofarabine in this cohort, and the study will be closed to further accrual. We would also close the trial if it became apparent prior to the accrual of all 13 that we would never achieve the 8 responders. If 8 or more out of 13 are responders, then proceed to stage 2.

Stage 2: A total of 20 evaluable patients will be studied. If 13 or fewer respond, then there is insufficient evidence to support further study of clofarabine in this cohort. If 14 or more are responders, then there is sufficient evidence to warrant further investigation of clofarabine within this cohort.

This rule has 91% power to detect a 27% difference (53% under the null to 80% under the alternative), with alpha = 0.093. If the response rates were actually higher, there would be even greater power to detect a 27% difference, for example 63% versus 90%.

**Rules for monitoring for toxicity associated with chemotherapy**

The study will be monitored to ensure the therapy can be delivered as planned ('chemotherapy feasibility'). Toxicities will be graded according to CTCAE version 4.0. Unacceptable toxicity will be defined as grade 5 toxicity and Grade 3 or 4 non-hematological toxicity that are possibly, probably, or definitely related to Clofarabine, with the specific exceptions of the following Grade 3 toxicities: anorexia, weight loss, nausea, vomiting, fatigue, mucositis, diarrhea, fever, electrolyte/metabolic abnormalities, menorrhagia, and

infection. Because all patients, regardless of stratum, receive the same treatment with the standard dose of clofarabine (25 mg/m$^2$/d), the stopping rule for toxicity will be applied to the overall cohort, i.e., combining Stratum 1 and Stratum 2. The toxicity monitoring rule will be applied to the first 25 evaluable participants, as this will provide sufficient evidence of safety/feasibility for the balance of the trial's accrual.

**Rule B – Three-stage stopping rule for toxicity events**

Stage 1: Accrue 7 evaluable participants. If at any time 2 or more participants experience a toxicity-event, enrollment will be suspended for DSMB review of dosage modifications or stopping the trial. If 1 or fewer have a toxicity-event, then proceed to stage 2.

Stage 2: Accrue an additional 8 evaluable participants for a total of 15. If at any time 3 or more participants experience a toxicity-event, enrollment will be suspended for DSMB review of dosage modifications or stopping the trial. If 2 or fewer have a toxicity-event, then proceed to stage 3.

Stage 3: Accrue an additional 10 evaluable participants for a total of 25. If 7 or more participants experience a toxicity-event, then there is insufficient evidence to support chemotherapy feasibility. If 6 or fewer have a toxicity-event, then there is sufficient evidence that the therapy can be delivered as planned, and this evidence supports continuation until the accrual goal for this trial is reached.
If all 25 participants are evaluated and the true toxicity-event rate is 5%, the therapy will be considered tolerable with a probability of 0.94. If all 25 participants are evaluated and true toxicity-event rate is 30%, the therapy will be considered tolerable with a probability of 0.1.

### 13.6 Statistical Methods to Address Objectives

Objective 1.3 - Monitoring Rule A will be used to address primary objective 1.3. The analysis will include all evaluable Stratum 1 participants. In addition, a 95% confidence interval will be placed on the response rate.

Secondary Objective 1.4.a – Descriptive analyses using the methods of Kaplan and Meier (with standard errors per Peto) will be performed to calculate the PFS and OS within each stratum and overall. Lifetables will also be constructed.

Secondary Objective 1.4.b – Monitoring Rule B will be used to address secondary objectives 1.4.b and 1.4.c. In addition, a descriptive tabulation of the proportion of participants reporting grade 3 and higher toxicity, separately by stratum (1 and 2) and by CTC toxicity code, will be generated for all evaluable patients. A given participant will be counted only one time per toxicity code at the maximum grade regardless of the number of times that participant experienced the toxicity.

Secondary Objective 1.4.c – Within Stratum 2 and within subgroups of Stratum 2, we will calculate the proportion of evaluable patients who are responders, and place 95% confidence intervals on these proportions. A descriptive tabulation of the proportion of participants reporting grade 3 and higher toxicity, by CTC toxicity code, will be generated for Stratum 2 patients. A given participant will be counted only one time per toxicity code at the maximum grade regardless of the number of times that participant experienced the toxicity.

## 14 PUBLICATION PLAN

A final report will be written regardless of the outcome of the study, within 24 months of its completion. The writing committee will be formed by all the study investigators; timing of the publication(s) and presentation to national and international meetings will be decided by the committee.

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## 16 APPENDIX I: Performance Status Criteria

Table 1: Performance Status Criteria

| **Percentage** | **Description** | |
|---|---|---|
| | **Lansky Performance Scale (< 16 yrs)** | **Karnofsky Performance Scale (> = 16 yrs)** |
| 100 | Fully active, normal. | Normal, no complaints, no evidence of disease. |
| 90 | Minor restrictions in physically strenuous activity. | Able to carry on normal activity; minor signs or symptoms of disease. |
| 80 | Active, but tires more quickly. | Normal activity with effort; some signs or symptoms of disease. |
| 70 | Both greater restriction of and less time spent in play activity. | Cares for self, unable to carry on normal activity or to do active work. |
| 60 | Up and around, but minimal active play; keeps busy with quieter activities. | Requires occasional assistance, but is able to care for most of his/her needs. |
| 50 | Gets dressed but lies around much of the day, no active play but able to participate in all quiet play and activities. | Requires considerable assistance and frequent medical care. |
| 40 | Mostly in bed; participates in quiet activities. | Disabled, requires special care and assistance. |
| 30 | In bed; needs assistance even for quiet play. | Severely disabled, hospitalization indicated. Death not imminent. |
| 20 | Often sleeping; play entirely limited to very passive activities. | Very sick, hospitalization indicated. Death not imminent. |
| 10 | No play; does not get out of bed. | Moribund, fatal processes progressing rapidly. |
| 0 | Unresponsive. | Dead. |

# 17 APPENDIX II: Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan

## 17.1 Introduction

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for conducting a DF/HCC Multi-Center research protocol. The DF/HCC DSMP should serve as a reference for any sites external to DF/HCC that will be participating in the research protocol.

### 17.1.1 Purpose

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center Multi-Center protocol will comply with Federal Regulations, Health Insurance Portability and Accountability Act (HIPAA) requirements and applicable DF/HCC Standard Operating Procedures.

### 17.1.2 Multi-Center Data and Safety Monitoring Plan Definitions

**DF/HCC Multi-Center Protocol**: A research protocol in which one or more outside institutions are collaborating with Dana-Farber/Harvard Cancer Center where a DF/HCC investigator is the sponsor. DF/HCC includes Dana-Farber/Partners Cancer Care (DF/PCC) Network Clinical Trial Affiliates.

**Lead Institution:** One of the Dana-Farber/Harvard Cancer Center consortium members (Dana-Farber Cancer Institute (DFCI), Massachusetts General Hospital (MGH), Beth Israel Deaconess Medical Center (BIDMC), Boston Children's Hospital (BCH), Brigham and Women's Hospital (BWH)) responsible for the coordination, development, submission, and approval of a protocol as well as its subsequent amendments per the DFCI IRB and applicable regulatory guidelines (CTEP, Food and Drug Administration (FDA), Office of Biotechnology Activities (OBA) etc.). The Lead Institution is typically the home of the DF/HCC Sponsor. The Lead Institution also typically serves as the Coordinating Center for the DF/HCC Multi-Center Protocol.

**DF/HCC Sponsor:** The person sponsoring the submitted Multi-Center protocol. Within DF/HCC, this person is the Overall Principal Investigator who takes responsibility for initiation, management and conduct of the protocol at all research locations. In applicable protocols, the DF/HCC Sponsor will serve as the single liaison with any regulatory agencies. The DF/HCC Sponsor has ultimate authority over the protocol and is responsible for the conduct of the study at DF/HCC and all Participating Institutions. In most cases the DF/HCC Sponsor is the same person as the DF/HCC Overall Principal Investigator; however, both roles can be filled by two different people.

**Participating Institution:** An institution that is outside the DF/HCC consortium that is collaborating with DF/HCC on a protocol where the sponsor is a DF/HCC Investigator. The Participating Institution acknowledges the DF/HCC Sponsor as having the ultimate authority and responsibility for the overall conduct of the study.

**Coordinating Center:** The entity (i.e. Lead Institution, Medical Monitor, Contract Research Organization (CRO), etc) that provides administrative support to the DF/HCC Sponsor in order that he/she may fulfill the responsibilities outlined in the protocol document and DSMP, and as specified in applicable regulatory guidelines (i.e. CTEP Multi-Center Guidelines). In general, the Lead Institution is the Coordinating Center for the DF/HCC Multi-Center Protocol. Should the DF/HCC Sponsor decide to use a CRO, the CRO will be deemed the Coordinating Center.

**DF/HCC Office of Data Quality (ODQ):** A group within DF/HCC responsible ensuring high-quality standards are used for data collection and the ongoing management of clinical trials, auditing, and data and safety monitoring. QACT also coordinates quality assurance efforts related to multi-center clinical research.

**DF/HCC Clinical Trials Research Informatics Office (CTRIO):** A group within DF/HCC responsible for providing a comprehensive data management platform for managing clinical trial data.

## 17.2 General Roles and Responsibilities

For DF/HCC Multi-Center Protocols, the DF/HCC Sponsor, the Coordinating Center, and the Participating Institutions are expected to adhere to the following general responsibilities:

### 17.2.1 DFCI/HCC Sponsor

The DF/HCC Sponsor, **Barbara Degar, MD** will accept responsibility for all aspects of conducting a DF/HCC Multi-Center protocol which includes but is not limited to:

- Oversee the coordination, development, submission, and approval of the protocol as well as subsequent amendments.
- Ensure that the investigators, study team members, and Participating Institutions are qualified and appropriately resourced to conduct the protocol.
- Include the Multi-Center Data and Safety Monitoring Plan as an appendix to the protocol.
- Ensure all Participating Institutions are using the correct version of the protocol.
- Ensure that each participating investigator and study team member receives adequate protocol training and/or a Site Initiation Visit prior to enrolling participants and throughout trial's conduct as needed.
- Ensure the protocol will be provided to each participating site in a language understandable to all applicable site personnel when English is not the primary language.
- Monitor progress and overall conduct of the study at all Participating Institutions.
- Ensure all DFCI Institutional Review Board (IRB), DF/HCC and other applicable reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.

- Act as the single liaison with FDA.
- Ensure compliance with all requirements as set forth in the Code of Federal Regulations, applicable DF/HCC requirements, HIPAA requirements, and the approved protocol.
- Commit to the provision that the protocol will not be rewritten or modified by anyone other than the DF/HCC Sponsor.
- Identify and qualify Participating Institutions and obtain accrual commitments prior to extending the protocol to that site.
- Monitor accrual and address Participating Institutions that are not meeting their accrual requirements.

### 17.2.2 Coordinating Center

The general responsibilities of the Coordinating Center may include but are not limited to:

- Assist in protocol development.
- Maintain FDA correspondence, as applicable.
- Review registration materials for eligibility and register participants from Participating Institutions in the DF/HCC clinical trial management system (CTMS).
- Distribute protocol and informed consent document updates to Participating Institutions as needed.
- Oversee the data collection process from Participating Institutions.
- Maintain documentation of Serious Adverse Event (SAE) reports and deviations/violation submitted by Participating Institutions and provide to the DF/HCC Sponsor for timely review.
- Distribute serious adverse events reported to the DF/HCC Sponsor that fall under the DFCI IRB Adverse Event Reporting Policy to all Participating Institutions.
- Provide Participating Institutions with information regarding DF/HCC requirements that they will be expected to comply with.
- Carry out plan to monitor Participating Institutions either by on-site or remote monitoring.
- Maintain Regulatory documents of all Participating Institutions which includes but is not limited to the following: local IRB approvals/notifications from all Participating Institutions, confirmation of Federal wide Assurances (FWAs) for all sites, all SAE submissions, Screening Logs for all sites, IRB approved consents for all sites

  Conduct regular communications with all Participating Institutions (conference calls, emails, etc) and maintain documentation all relevant communications.

### 17.2.3 Participating Institution

Each Participating Institution is expected to comply with all applicable federal regulations and DF/HCC requirements, the protocol and HIPAA requirements.

The general responsibilities for each Participating Institution may include but are not limited to:

- Document the delegation of research specific activities to study personnel.
- Commit to the accrual of participants to the protocol.
- Submit protocol and/or amendments to their local IRB.
- Maintain regulatory files as per sponsor requirements.
- Provide the Coordinating Center with regulatory documents or source documents as requested.
- Participate in protocol training prior to enrolling participants and throughout the trial as required (i.e. teleconferences).
- Update Coordinating Center with research staff changes on a timely basis.
- Register participants through the Coordinating Center prior to beginning research related activities.
- Submit Serious Adverse Event (SAE) reports to local IRB per institutional requirements and to the Coordinating Center, in accordance with DF/HCC requirements.
- Submit protocol deviations and violations to local IRB per local requirements and to the DF/HCC Sponsor in accordance with DF/HCC requirements.
- Order, store and dispense investigational agents and/or other protocol mandated drugs per federal guidelines and protocol requirements.
- Have office space, office equipment, and internet access that meet HIPAA standards.
- Participate in any quality assurance activities and meet with monitors or auditors at the conclusion of a visit to review findings.
- Promptly provide follow-up and/or corrective action plans for any monitoring queries or audit findings.

## 17.3 DF/HCC Requirements for Multi-Center Protocols

The following section will clarify DF/HCC Requirements and further detail the expectations for participating in a DF/HCC Multi-Center protocol.

### 17.3.1 Protocol Distribution

The Coordinating Center will distribute the final DFCI IRB approved protocol and any subsequent amended protocols to all Participating Institutions.

### 17.3.2 Protocol Revisions and Closures

The Participating Institutions will receive notification of protocol revisions and closures from the Coordinating Center. It is the individual Participating Institution's responsibility to notify its IRB of these revisions.

- **Non life-threatening revisions:** Participating Institutions will receive written notification of protocol revisions regarding non life-threatening events from the Coordinating Center. Non-life-threatening protocol revisions must be IRB approved and implemented within 90 days from receipt of the notification.
- **Revisions for life-threatening causes:** Participating Institutions will receive immediate notification from the Coordinating Center concerning protocol revisions required to protect lives with follow-up by fax, mail, e-mail, etc. Life-threatening protocol revisions will be implemented immediately followed by IRB request for approval.
- **Protocol closures and temporary holds:** Participating Institutions will receive notification of protocol closures and temporary holds from the Coordinating Center. Closures and holds will be effective immediately. In addition, the Coordinating Center, will update the Participating Institutions on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

### 17.3.3 Informed Consent Requirements

The DF/HCC approved informed consent document will serve as a template for the informed consent for Participating Institutions. The Participating Institution consent form must follow the consent template as closely as possible and should adhere to specifications outlined in the DF/HCC Guidance Document on Model Consent Language for PI-Initiated Multi-Center Protocols. This document will be provided separately to each Participating Institution.

Participating Institutions are to send their version of the informed consent document and HIPAA authorization, if a separate document, to the Coordinating Center for review and approval prior to submission to their local IRB. The approved consent form must also be submitted to the Coordinating Center after approval by the local IRB for all consent versions.

The Principal Investigator (PI) at each Participating Institution will identify the physician members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols. Participating institutions must follow the DF/HCC requirement that for all interventional drug, biologic, or device research, only attending physicians may obtain initial informed consent and any re-consent that requires a full revised consent form.

### 17.3.4 IRB Documentation

The following must be on file with the Coordinating Center:

- Initial approval letter of the Participating Institution's IRB.
- Copy of the Informed Consent Form(s) approved by the Participating Institution's IRB.
- Participating Institution's IRB approval for all amendments.
- Annual approval letters by the Participating Institution's IRB.

### 17.3.5 IRB Re-Approval

Verification of IRB re-approval from the Participating Institutions is required in order to continue research activities. There is no grace period for continuing approvals.

The Coordinating Center will not register participants if a re-approval letter is not received from the Participating Institution on or before the anniversary of the previous approval date.

### 17.3.6 Participant Confidentially and Authorization Statement

In 1996, congress passed the first federal law covering the privacy of health information known as the Health Insurance Portability and Accountability Act (HIPAA). Any information, related to the physical or mental health of an individual is called Protected Health Information (PHI). HIPAA outlines how and under what circumstances PHI can be used or disclosed.

In order for covered entities to use or disclose protected health information during the course of a study, the study participant must sign an authorization statement. This authorization statement may or may not be separate from the informed consent document. The Coordinating Center, with the approval from the DFCI IRB, will provide a consent template, with information regarding authorization for the disclosure of protected health information.

The DF/HCC Sponsor will use all efforts to limit its use of protected health information in its trials. However, because of the nature of these trials, certain protected health information must be collected. DF/HCC has chosen to use authorizations, signed by the participant in the trial, rather than limited data sets with data use agreements.

#### 17.3.6.1 DF/HCC Multi-Center Protocol Confidentiality

All documents, investigative reports, or information relating to the participant are strictly confidential. Whenever reasonably feasible, any participant specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Coordinating Center should be de-identified. It is recommended that the assigned protocol case number (as described below) be used for all participant specific documents. Participant initials may be included or retained for cross verification of identification.

### 17.3.7 DF/HCC Multi-Center Protocol Registration Policy

#### 17.3.7.1 Initiation of Therapy

Participants must be registered with the DF/HCC CTMS before receiving treatment. Treatment may not be initiated until the Participating Institution receives confirmation of the participant's registration from the Coordinating Center. The DF/HCC Sponsor and DFCI IRB must be notified of any violations to this policy. Please see section 4.4 of the protocol for more information regarding registration procedures.

#### 17.3.7.2 Eligibility Exceptions

No exceptions to the eligibility requirements for a protocol without DFCI IRB approval will be permitted. All Participating Institutions are required to fully comply with this requirement. The process for requesting an eligibility exception is defined below.

### 17.3.8 DF/HCC Protocol Case Number

At the time of registration, the following identifiers for all subjects: initials, date of birth, gender, race and ethnicity. Once eligibility has been established and the participant successfully registered, the participant is assigned a unique protocol case number. Participating Institutions should submit all de-identified subsequent communication and documents to the Coordinating Center, using this case number to identify the subject.

#### 17.3.8.1 Protocol Deviations, Exceptions and Violations

Federal Regulations require an IRB to review proposed changes in a research activity to ensure that researchers do not initiate changes in approved research without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the participant. DF/HCC requires all departures from the defined procedures set forth in the IRB approved protocol to be reported to the DF/HCC Sponsor, who in turn is responsible for reporting to the DFCI IRB.

For reporting purposes, DF/HCC uses the terms "violation", "deviation" and "exception" to describe departures from a protocol. All Participating Institutions must adhere to these requirements for reporting to the DF/HCC Sponsor and will follow their institutional policy for reporting to their local IRB.

#### 17.3.8.2 Definitions

Protocol Deviation: Any departure from the defined procedures set forth in the IRB-approved protocol which is *prospectively approved* prior to its implementation.

Protocol Exception: Any protocol deviation that relates to the eligibility criteria, e.g. enrollment of a participant who does not meet all inclusion/exclusion criteria.

Protocol Violation: Any protocol deviation that was not *prospectively approved* by the IRB prior to its initiation or implementation.

#### 17.3.8.3 Reporting Procedures

DF/HCC Sponsor: is responsible for ensuring that clear documentation is available in the medical record and/or regulatory documents to describe all protocol exceptions, deviations and violations. The DF/HCC Sponsor will also be responsible for ensuring that all protocol violations/deviations are promptly reported per DFCI IRB guidelines.

Participating Institutions: Protocol deviations require prospective approval from the DFCI IRB. The Participating Institution must submit the deviation request to the Coordinating Center who will then submit the deviation request to the DFCI IRB. Upon DFCI IRB approval the deviation is submitted to the Participating Institution IRB, per institutional policy. A copy of the Participating Institution's IRB report and determination will be forwarded to the Coordinating Center within 10 business days after the original submission. The deviation may not be implemented without all required approvals.

All protocol violations must be sent to the Coordinating Center in a timely manner. The Coordinating Center will provide training for the requirements for the reporting of violations.

Coordinating Center: Upon receipt of the violation/deviation report from the Participating Institution, the Coordinating Center will submit the report to the DF/HCC Sponsor for review. Subsequently, the Participating Institution's IRB violation/deviation report will be submitted to the DFCI IRB for review per DFCI IRB reporting guidelines.

### 17.3.9 Safety Assessments and Toxicity Monitoring

The study teams at all participating institutions are responsible for protecting the safety, rights and well-being of study participants. Recording and reporting of adverse events that occur during the course of a study help ensure the continuing safety of study participants.

All participants receiving investigational agents and/or other protocol mandated treatment will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical examination findings, and spontaneous reports of adverse events reported by participants. All toxicities encountered during the study will be evaluated according to the NCI criteria specified in the protocol. Life-threatening toxicities must be reported immediately to the DF/HCC Sponsor via the Coordinating Center.

Additional safety assessments and toxicity monitoring will be outlined in the protocol.

#### 17.3.9.1 Guidelines for Reporting Serious Adverse Events

Guidelines for reporting Adverse Events (AEs) and Serious Adverse Events (SAEs) are detailed in protocol section 10.

Participating Institutions must report the SAEs to the DF/HCC Sponsor and the Coordinating Center following the DFCI IRB Adverse Event Reporting Policy.

The Coordinating Center will review documentation of all Participating Institution Adverse Event reports and be responsible for communicating to all participating investigators, any observations reportable under the DFCI IRB Reporting Requirements.

Participating Institutions will review and submit to their IRB according to their institutional policies and procedures.

#### 17.3.9.2 Guidelines for Processing IND Safety Reports

The DF/HCC Sponsor will review all IND Safety Reports and ensure that all IND Safety Reports are distributed to the Participating Institutions. Participating Institutions will review and submit to their IRB according to their institutional policies and procedures.

### 17.3.10 Data Management

DF/HCC CTRIO develops case report forms (CRF/eCRFs), for use with the protocol. These forms are designed to collect data for each study. DF/HCC CTRIO provides a web based training for eCRF users.

#### 17.3.10.1 Data Forms Review

Data submissions are monitored for timeliness and completeness of submission. Participating Institutions are notified of their data submission delinquencies in accordance with the following:

Incomplete or Questionable Data
If study forms are received with missing or questionable data, the submitting institution will receive a written or electronic query from the DF/HCC Office of Data Quality, Coordinating Center or designee.

Responses to all queries should be completed and submitted within 14 calendar days.

Responses may be returned on the written query or on an amended paper case report form, or in the case of electronic queries, within the electronic data capture (eDC) system. In the case of a written query for data submitted on a paper case report form, the query must be attached to the specific data being re-submitted in response.

Missing Forms
If study forms are not submitted on schedule, the Participating Institution will periodically receive a Missing Form Report from the Coordinating Center noting the missing forms. These reports are compiled by the DF/HCC Office of Data Quality and distributed on a monthly basis.

## 17.4 Requisitioning Investigational Drug

The ordering of investigational agent is specified in the protocol section 7.10.

Ensure that the pharmacy will be able to receive and store the agent according to state and federal requirements. The local IRB should be kept informed of who will supply the agent (Sanofi) so that any regulatory responsibilities can be met in a timely fashion.

## 17.5 Monitoring: Quality Control

The quality control process for a clinical trial requires verification of protocol compliance and data accuracy. The Coordinating Center, with the aid of the DF/HCC Office of Data Quality, provides quality control oversight for the protocol.

### 17.5.1 Ongoing Monitoring of Protocol Compliance

#### 17.5.1.1 Site Qualification

Sites are invited to participate in this protocol if they are familiar with and have participated in prior Phase I studies, have an appropriate volume of patients to be able to contribute to study enrollment goals, and have appropriate resources, including IRB support, investigational pharmacists, clinical research coordinators, research nurses, and experienced physician investigators to conduct Phase II research. DF/HCC Site/Protocol Feasibility Questionnaires must be completed by each site. The Sponsor will assess that the investigators, study team members, and Participating Institutions are qualified and appropriately resourced to conduct the protocol. The DF/HCC Sponsor will have final approval of any and all participating sites on this trial.

#### 17.5.1.2 Regulatory Documents

DFCI will collect all required regulatory documentation prior to study activation. This includes but, is not limited to 1572, Site PI and Co-Investigator CVs, Financial Disclosure Forms, IRB approval documentation. The study team will work with all participating sites to ensure all updated / revised regulatory documentation is maintained at each site and forwarded to DFCI and maintained in the Trials Master File.

Once a proposed Participating Institution receives institutional IRB approval, all approval documentation and IRB-approved related documents will be emailed to the Coordinating Center study staff and an amendment to add a site will be submitted to the DF/HCC IRB.

Once approval is received to add the Participating Institution study materials will be sent to the Participating Institution. Study materials will include, but are not limited to, regulatory documents and participant tracking forms.

All Participating Institutions must maintain and update all essential regulatory documents in a regulatory binder. A designated member of the DF/HCC Lead Institution will be responsible for maintaining the Trial Master File which will include copied of all regulatory documentation for the Lead Site and all Participating Institutions.

All Participating Institutions are required to submit all institutional IRB correspondences and approvals to be retained in the Trial Master File at the Lead Institution. The Lead Institution will review all working study documents and ensure that most current IRB-approved protocol and study documents are being used by the Participating Institutions.

#### 17.5.1.3 Site Initiation Visit

A Site Initiation Visit (SIV) will be conducted with all participating sites via teleconference/webinar prior to enrolling participants. The SIV will cover study objectives and rationale, history of LCH-CLO, study design, eligibility, registration, required data, treatment schedule, side effects/AEs, SAE reporting, and dose modification. It will be led by the Coordinating Center and it is expected that the Site PI and all study staff will attend.

#### 17.5.1.4 Delegation of Authority/Responsibility

Participating Institutions will be instructed to complete a Delegation of Responsibility/ Authority Log which will be reviewed/approved by the DF/HCC Sponsor. A copy of this document will be retained in the Trial Master File. Participating Institutions will be instructed to inform the Coordinating Center immediately should there be a change in personnel. An updated training and Delegation of Authority/Responsibility log will need to be completed as soon as possible.

#### 17.5.1.5 Monitoring

The Participating Institutions will be required to submit participant source documents to the Coordinating Center for monitoring. Participating Institution may also be subject to on-site monitoring conducted by the Coordinating Center.

The Coordinating Center will implement ongoing monitoring activities to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and participant safety. Monitoring will occur before the clinical phase of the protocol begins, continue during protocol performance and through study completion. Additional monitoring practices may include but are not limited to; source verification, review and analysis of the following: eligibility requirements of all participants, informed consent procedures, adverse events and all associated documentation, study drug administration/treatment, regulatory files, protocol deviations, pharmacy records, response

assessments, and data management.

A study monitor will be available for monitoring all participating sites. All monitoring reports and ongoing progress reports for all participating sites will be provided to the DF/HCC Sponsor. Any major monitoring findings will be communicated to the DF/HCC Sponsor immediately.

Virtual Monitoring

The monitor will be responsible for on-going virtual monitoring of regulatory documents and data entered by participating sites. Participating sites will be responsible for providing necessary source documentation for virtual monitoring.

All eligibility source documentation from all participating sites will be reviewed by the Coordinating Center prior to registering participants on protocol. At the time of registration, all points of eligibility must be found in either source documentation or if eligibility points cannot be found in source documentation (i.e. lab reports etc.), **they must be included in an MD note**.

Registration documents (consent form and eligibility checklist) will also be reviewed via virtual monitoring at the time of registration. At the time of registration, the eligibility checklist(s) and all pages of the consent form(s) must be faxed or emailed to the DFCI Study Team for review (refer to protocol section 4 for participant registration process). The DFCI Study Team will review each consent form to ensure 1) it is the most appropriate and current version, 2) that the participant information is included on all pages of the consent and that all pages of the consent have been submitted, 3) that the participant has signed and dated the consent form, 4) that a physician has reviewed and signed the consent form on the same day/time as the participant, and that 5) all appropriate items have been completed.

Additional source documents that will be reviewed virtually include, but are not limited to:

- All results of the Required Assessments (Protocol Table 2).
- Any extra source documentation (i.e. admission notes, scans, culture results) pertaining to a serious adverse event (SAE).

In addition to enrollment documents, a subset of participants will have all data reviewed via virtual monitoring. This will occur once the participants complete cycle 1 of this study.

A list of items required to be virtually monitored will be provided to participating sites.

Virtual monitoring will be performed on an ongoing basis. The monitor will query within the Electronic Data Capture system. The DF/HCC Sponsor will be notified on an ongoing basis on the status of virtual monitoring, including which patients and what data has been virtually monitored. As part of virtual monitoring, if any significant non-compliance (i.e. if a patient is ineligible) is found during virtual monitoring this will be reported to the DF/HCC Sponsor immediately.

On-Site Monitoring
On-site monitoring may occur if sub-standard performance is discovered during virtual monitoring.

If sub-standard performance is discovered during routine monitoring (virtual or on-site) or auditing, more frequent on-site monitoring visits and/or audits will be made. Sub-standard performance includes, but is not limited to, data not entered on time, unreported adverse events, or enrolling ineligible participants. Participating Institutions that fail to meet the performance goals of accrual, submission of timely accurate data, adherence to protocol requirements, and compliance with state, federal, and Good Clinical Practice guidelines, will be recommended for a six- month probation period. Such institutions must respond with a corrective action plan and must demonstrate during the probation period that deficiencies have been corrected, as evidenced by the improved performance measures. Participating Institutions that fail to demonstrate significant improvement will be considered by the Sponsor for revocation of participation.

All submitted data will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. The Coordinating Center and if applicable, ODQ Data Analysts assigned to the protocol, will perform the ongoing protocol data compliance monitoring.

### 17.5.1.6 Adverse Event Reporting

Documentation of all adverse events must be included as part of source documentation. Documentation that a physician determined attribution of each event must also be included. AEs and SAEs must be reported as instructed in the protocol with the log serving as record

for all events at each Participating Institution. The DF/HCC Sponsor, Barbara Degar, MD, will be notified/report all AEs and SAEs as per protocol. Each Participating Institution will be instructed to keep an SAE log and submit it to the DF/HCC Lead Institution prior to each monthly teleconference. The DF/HCC Lead Institution will maintain a master SAE list.

### 17.5.1.7 Drug Accountability

Participating pharmacies will be required to submit Drug Accountability Logs at the time of monitoring documenting receipt and shipment of drug supply, dispensing/ordering of supply, and destruction of unused study medication and/or damaged or expired drug. Participating Institutional Pharmacies should destroy drug as per their institutional policy.

### 17.5.1.8 Ongoing Communication

Participating institutions will be required to participate in monthly Coordinating Center initiated teleconferences. This will be a forum to discuss study related issues not limited to the following: study accrual, SAE's/AE's, clinical response, deviations/violations, and monitoring A log of all SAEs and minor/major deviation/violation that have occurred on

study will be reviewed during each conference call. An agenda will be sent prior to each conference call and minutes will be taken. Calls will be held more or less regularly as needed based upon study accrual, necessary study updates or Sponsor request.

### 17.5.2 Monitoring Reports

The DF/HCC Sponsor will review all monitoring reports for on-site and remote monitoring of Participating Institutions to ensure protocol compliance. The DF/HCC Sponsor may increase the monitoring activities at Participating Institutions that are unable to comply with the protocol, DF/HCC Sponsor requirements or federal and local regulations. Participating Institutions may also be subject to an audit as determined by the DF/HCC Sponsor.

### 17.5.3 Accrual Monitoring

Prior to extending a protocol to an external site, the DF/HCC Sponsor will establish accrual requirements for each participating institution. Accrual will be monitored for each participating institution by the DF/HCC Sponsor or designee. Sites that are not meeting their accrual expectations may be subject to termination. The minimum accrual requirement is at least 1 patient per site annually.

## 17.6 Auditing: Quality Assurance

Auditing is a method of Quality Assurance. Its main focus is to measure whether standards and procedures were followed. Auditing is the systematic and independent examination of all trial related activities and documents. Audits determine if evaluated activities were appropriately conducted and whether data was generated, recorded and analyzed, and accurately reported per the protocol, Standard Operating Procedures (SOPs), and the Code of Federal Regulations (CFR).

### 17.6.1 Audit Plan: DF/HCC Sponsored Trials

All Participating Institutions are subject to audit by the DF/HCC Office of Data Quality (ODQ). Typically, approximately 3-4 participants would be audited at the site over a 2-day period. If violations which impact participant safety or the integrity of the study are found, more participant records may be audited.

### 17.6.2 Audit Notifications

It is the Participating Institution's responsibility to notify the Coordinating Center of all scheduled audit dates (internal or NCI) and re-audit dates (if applicable), which involve this protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the Coordinating Center, within 12 weeks after the audit date.

### 17.6.3 Audit Reports

The DF/HCC Sponsor will review all final audit reports and corrective action plans if applicable. The Coordinating Center, must forward these reports to the DF/HCC ODQ per DF/HCC policy for review by the DF/HCC Audit Committee. Based upon the audit assessments the DF/HCC Audit Committee could accept or conditionally accept the audit rating and final report. Conditional approval could require the DF/HCC Sponsor to implement recommendations or require further follow-up. For unacceptable audits, the DF/HCC Audit Committee would forward the final audit report and corrective action plan to the DFCI IRB as applicable.

### 17.6.4 Participating Institution Performance

The DF/HCC Sponsor, DFCI IRB, is charged with considering the totality of an institution's performance in considering institutional participation in the protocol.

Participating Institutions that fail to meet the performance goals of accrual, submission of timely and accurate data, adherence to protocol requirements, and compliance with state and federal regulations, may be recommended for a six-month probation period. Such institutions must respond with a corrective action plan and must demonstrate during the probation period that deficiencies have been corrected, as evidenced by the improved performance measures. Participating Institutions that fail to demonstrate significant improvement will be considered by the DF/HCC Sponsor for revocation of participation. A DF/HCC Sponsor and/or the DFCI IRB may terminate a site's participation if it is determined that a site is not fulfilling its responsibilities as described above.