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A Phase I Clinical Trial to Study the Safety, Pharmacokinetics, and Efficacy of BP1001 (L-Grb-2 Antisense Oligonucleotide) in Patients with Refractory or Relapsed Acute Myeloid Leukemia, Philadelphia Chromosome Positive Chronic Myelogenous Leukemia, or Acute Lymphoblastic Leukemia, and Myelodysplastic Syndrome

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Sponsor and Investigator Statements

Bio-Path Holdings, Inc. Statement:
As the Sponsor of this clinical research study, Bio-Path Holdings, Inc. hereby approves this protocol in its entirety:

_____
Authorized Bio-Path Holdings, Inc. Representative's Signature

_____
Authorized Bio-Path Holdings, Inc. Representative's Printed Name and Title

_____
Date

Investigator Statement:
I have read the protocol and agree that it contains all the details necessary for carrying out this study, and I will conduct the study as described herein.

_____
Investigator's Signature

_____
Investigator's Printed Name

_____
Date

TABLE OF CONTENTS

1.0 Objectives 5
2.0 Background 5
2.1 Inhibition of Grb-2 8
2.2 The Use of Lipid in Delivery of Grb-2 Antisense Oligonucleotides 8
3.0 Background Drug Information 8
3.1 P-ethoxy-oligonucleotide antisense therapy against Grb-2 8
3.2 Preparation of Liposomes 9
3.3 Mechanism of Action – Downregulation of Grb-2 expression 9
3.4 In vitro studies: 9
3.4.1 Studies in Philadelphia chromosome positive (Ph+) leukemic cells 9
3.4.2 Studies in AML cell lines 10
3.5 Preclinical Toxicology (Safety Studies) 10
4.0 Methodology 11
5.0 Patient Eligibility 12
5.1 Part A: Dose-Escalation Cohorts 12
5.1.1 Inclusion Criteria 12
5.1.2 Exclusion Criteria 13
6.0 Pretreatment Evaluation 13
7.0 Number of Patients 14
8.0 Treatment Plan 14
8.1 Part A: Dose-escalation 14
8.2 Part B: Dose-expansion Cohorts (DEC) 15
8.3 Definition of Dose-Limiting Toxicity (DLT) 15
8.4 Replacement of Patients 16
8.5 Concomitant Medications 16
8.6 Criteria for Dose Modification 16
8.7 Measurement of Biological Activity 16
8.8 Extension of Treatment 17
8.9 Statistical Considerations 17
9.0 Evaluation During Study 18
10.0 Evaluation of Toxicity 19
11.0 Clinical Pharmacology 19

11.1 Clinical Pharmacology Objectives for BP1001 19
11.2 Pharmacokinetic Studies 20
12.0 Criteria for Response 21
13.0 Criteria for Removal from the Study 25
14.0 Reporting Requirements 25
14.1 Adverse Events 25
14.2 Serious Adverse Events (SAEs) 25
14.3 Protocol-Specific Expedited Adverse Event Reporting Exclusions 26

Protocol Body

1.0 Objectives

The purpose of this study is to determine:

- The toxicity and tolerance of escalating doses of BP1001
- The maximum tolerated dose (MTD) of BP1001
- The optimal biologically active dose (OBAD) of BP1001, defined as a 50% reduction in Grb-2 expression in circulating leukemia cells (flow cytometry)
- The in vivo pharmacokinetics (PK) of BP1001
- Tumor response
- The PK data to correlate to the historical experience in order to demonstrate the liposomal delivery vehicle performs as expected
- The safety and toxicity of the combination of BP1001 and concurrent low-dose ara-C (LDAC) in patients with AML

2.0 Background

The Philadelphia (Ph) chromosome is present in approximately 90-95% of patients with chronic myelogenous leukemia (CML), and approximately 20-25% of patients with acute lymphocytic leukemia (ALL). It results from the reciprocal translation of chromosomes 9 and 22, which places the Abl gene on the 3' end of Bcr gene. The result is a chimeric gene, which is expressed as the p210 Bcr-Abl fusion protein in Ph+ CML cells, and the p185 Bcr-Abl fusion protein in Ph+ ALL cells. These fusion proteins cause dysregulation of tyrosine kinase activities, and lead to malignant transformation of fibroblasts and hematopoietic cells in culture. They have also been shown to prevent cells from undergoing apoptosis.

The ability of the Bcr-Abl oncoprotein to cause proliferation of Ph+ cells may relate to its capacity to activate the Ras and phosphatidylinositol-3 kinase (PI3K) signal transduction pathways. These signaling pathways are likely mediated by adaptor proteins, such as the growth receptor bound protein-2 (Grb-2). Adaptor proteins are made up of non-catalytic domains e.g. Src homology-2 (SH2), Src homology3 (SH3) and others. These domains enable the adaptor proteins to bind to a variety of other proteins, thereby facilitating the activation of multiple transduction pathways.

As with the product of the Bcr-Abl oncogene, that of c-Cbl, another proto-oncogene found in leukemia cells, is also constitutively tyrosine phosphorylated. This constitutive tyrosine phosphorylation is seen not only in CML cells in blast phase, but also in cells from acute myeloblastic leukemias (AMLs), Ph-negative acute T-lymphocytic leukemias (ALLs), and Ph-negative pre-B acute lymphoblastic leukemia (pre-B ALL). Grb-2 may also mediate c-CBL driven pathways. In both acute leukemic and CML blasts, c-Cbl is stably complexed with the N-terminal Src homology (SH) 3 domain of Grb-2. In blasts from ALL patients, it is complexed with the Grb-2 SH2 domain. This interaction may link the processes by which malignant transformation of lymphoid and myeloid progenitor cells occur.

The Grb-2 adaptor protein contains 1 SH2domain, flanked by 2 SH3 domains. Grb-2 uses its SH2 domain to bind to phosphotyrosine residues found in activated tyrosine kinases, such as Bcr-Abl, and epidermal growth factor receptor (EGFR), while it uses its SH3 domains to bind to praline-rich

motifs, such as those found in the guanine nucleotide exchange3 factor, Son of Sevenless. Ras, a GTPase protein, is active when bound to GTP, and inactive when bound to GDP. Guanine nucleotide exchange factors, such as SOS, increase the exchange of GDP for GTP on RAS. Upon growth factor stimulation, the Grb-2-SOS complex is recruited to the plasma membrane, where it uses its SH2 domain to bind to growth factor-stimulated tyrosine kinase receptors. This binding allows SOS to be in close proximity to RAS, which is localized to the plasma membrane. It is thus able to stimulate RAS activity. Ras activation will then in turn activate multiple downstream signaling pathways important for the regulation of diverse cellular processes.

The most well-known RAS signaling pathway is the MAP kinase cascade. In this cascade, RAS binds to RAF in a GTP-dependent manner. This binding leads to RAF activation. Activated RAF phosphorylates MEK, which in turn phosphorylates and activates ERK 1, 2. Activated ERK 1, 2 then translocates to the nucleus, and activates transcription by phosphorylating transcription factors (e.g. ERK-1 and MYC). By inhibiting Grb-2, the Grb2-SOS complex is no longer capable of exchanging GDP for GTP on Ras. Therefore down-regulation of the MAP kinase cascade and resultant transcription occur.

The Grb-2 gene has been mapped to the human chromosome region 17q22-qter, a region that is duplicated in leukemias and solid tumors. In the accelerated phase of CML, the occurrence of iso17q chromosome may result in an increased copy number of the Grb-2 gene product. As Grb-2 is important for the transformation of murine hematopoietic cells, and the proliferation of human leukemia cells that express high levels of the Bcr-Abl and the c-Cbl oncogenes, inhibition of Grb-2 may have a significant impact on the natural history of leukemias.

In addition, Grb-2 plays an important role in the activation of other tyrosine kinases that play a role in the pathogenesis and/or progression of CML and other myeloid disorders such as AML and myelodysplastic syndrome (MDS). Specific to AML, approximately 60% of AML blast samples have been demonstrated to have activated signaling genes which include tyrosine kinases such as Kit, Flt3, Janus-kinase-2 (JAK2), and c-Cbl (1). These tyrosine kinases utilize the adaptor protein Grb-2 to activate signaling pathways, resulting in cancer progression. Therefore, Grb-2 has a critical role in AML signaling, and inhibition of Grb-2 has therapeutic potential against AML.

Grb-2 utilizes its Src Homology 2 (SH2) domain to bind to the YXNX motif in activated tyrosine kinases (2). Both the Kit and the Flt3 receptor tyrosine kinases are expressed at high levels in AML cells (3-5). Upon ligand binding, the tyrosine kinase activities of Kit and Flt3 are stimulated, resulting in Grb-2 binding to the phosphotyrosine residues of KIT and FLT3 via its SH2 domain (6-9). In AML patients, mutations are rarely found in the *kit* gene but often in the *flt3* gene. The mutant *flt3* genes, which include the internal tandem duplication of the *flt3* gene (*FLT3/ITD*) and the *flt3* tyrosine kinase domain mutations (*FLT3/TKD)*, are found in 20 to 45% of AML patients (10-17). The mutant Flt3 kinases are constitutively activated and can bind to Grb-2. Recruitment of Grb-2 by Kit and Flt3 leads to increased guanine nucleotide exchange on Ras, thereby stimulating the activity of Ras and its downstream kinases like extracellular signals regulated kinases (Erk1,2) and Akt, which are crucial in inducing AML progression.

Grb-2 may also utilize its Src Homology 3 (SH3) domains to bind to proline-rich motifs on tyrosine kinases. The *JAK2* tyrosine kinase gene is commonly mutated in myeloid neoplasias, including AML (18). JAK2 constitutively associates with Grb2, through interaction with the SH3 domains of Grb-2 (19). The c-Cbl proto-oncogene is constitutively tyrosine phosphorylated in

AML (20). c-Cbl binds to Grb-2 via the N-terminal SH3 domain of Grb-2 (21, 22). Grb-2 is utilized by JAK2 and c-Cbl to the activation of Ras, Erk1,2, and Akt.

Thus, inhibition of Grb-2 has the potential to affect multiple other signal transduction pathways that play a role in myeloid disorders.

2.1 Inhibition of Grb-2

Multiple strategies for inhibiting the function of Grb-2 have been investigated. One strategy involves cloning an alternatively spliced form of Grb-2, which has a deleted non-functional SH2 domain. The encoded Grb3-3 will not bind to phosphorylated EGFR because the deleted residues are integral to the binding of Grb-2 to phosphotyrosine residues; Grb3-3 does, however, retain functional SH3 domains. Hence, Grb3-3 can compete with Grb-2 in the binding of guanine exchange factors. In a study by Fath et al., microinjection of Grb3-3 into Swiss 3T3 fibroblasts induced them to undergo apoptosis. A second strategy uses small molecule inhibitors to prevent the binding of growth factor receptors to the Grb-2 SH2 domain. These small molecule Grb-2 SH2 inhibitors are designed using molecular models, based on X-ray structures Grb-2, complexed with phosphopeptide ligands containing Tyr-X-Asn-X motif. These inhibitors contain elements able to recognize and selectively bind the Grb-2 SH2 domain. The goal of these inhibitors is to reverse oncogenic transformation, and prevent growth factor-induced cell motility. A third strategy involves the use of Grb-2 binding phosphopeptides. Treating cells with cell-permeable Grb-2 binding phosphopeptides results in their association with Grb-2, and inhibits growth factor receptor binding to Grb-2. This may halt growth factor stimulated mitogenesis. The strategy employed to inhibit Grb-2 in this study utilizes liposome-incorporated, nuclease-resistant antisense oligonucleotides specific for Grb-2 mRNA. The Grb-2 antisense (AS) molecule blocks binding of ribosomes to the Grb-2 mRNA, thereby impairing Grb-2 protein production. This ability of liposomal Grb-2 antisense oligonucleotides to reduce Grb-2 protein expression and induce growth inhibition has been demonstrated in several human leukemia and solid tumor cell lines.

2.2 The Use of Lipid in Delivery of Grb-2 Antisense Oligonucleotides

The poor cellular uptake of oligonucleotides has been one of the limitations of antisense therapies. In the past, ligands of transmembrane receptors such as transferrin and folate have been used to improve drug delivery. However, the approach taken in this study involves the incorporation of oligonucleotides into liposomes. These are a biodegradable, easily prepared vehicle for antisense transport. Because oligonucleotides are negatively charged molecules, cationic lipid complexes have been widely used. However, positively charged liposomes are toxic to the cell membrane, and have limited efficacy in oligonucleotide delivery. Tari et al., have demonstrated the successful delivery of antisense molecules to malignant cells via a neutral dioleoylphosphatidylcholine (DOPC) based liposomes. In one study, 50% of the oligonucleotides entered leukemic cells, and stayed in the cytoplasm for over 24 hours, allowing increased access of oligonucleotides intracellularly. This formulation did not show evidence of toxicity toward either peripheral blood mononuclear cells or bone marrow cells in animals. Accordingly, this study will make use of the neutral liposome formulation to deliver Grb-2 antisense molecules.

3.0 Background Drug Information

3.1 P-ethoxy-oligonucleotide antisense therapy against Grb-2

The antisense oligonucleotide drug substance in BP1001 used in this study is a nuclease-resistant phosphodiester analog that contains a P-ethoxy backbone. This structure was

chosen over one with phosphorothioate backbone, because it lacks a sulfur moiety. (The sulfur moiety of the phosphorothioate backbone has been associated with a bleeding diathesis.)

The oligonucleotide sequence being used is specific for the translation initiation site of human Grb-2 mRNA: 5'-ATATTTGGCGATGGCTTC-3'. This antisense has been shown to inhibit Grb-2 expression and cell growth in Bcr-Abl positive leukemic cells, as well as in breast cancer cells that express high levels of HER2/neu or EGFR. Minimal biological effects were seen in leukemic cell lines that lack Bcr-Abl oncoprotein.

Bio-Path Holdings, Inc. will provide BP1001.

3.2 Preparation of Liposomes

The lipid carrier used in this study is DOPC-based. The liposome formulation is non-ionic (neutral charge) and the lipid-to-drug ratio is 20:1 molar (approximately 2.7 to 1 mg). P-ethoxy oligonucleotides dissolved in DMSO are added to DOPC in the presence of an excess of tertiary-butanol (95% by volume). The mixture is vortexed, frozen in an acetone/dry ice bath and then it is lyophilized overnight. The lyophilized preparation will be kept at 4°-8°C for storage. When needed, the lyophilized liposomal oligonucleotides will be hydrated with 2.0 ml of 0.9% normal saline solution (NSS) to a final oligonucleotide concentration of 2.5 mg/ml.

The BP1001 will be manufactured by Lyophilization Services of New England, Inc., Manchester, NH.

3.3 Mechanism of Action – Down-regulation of Grb-2 expression

Inhibition of Grb-2 expression may be achieved with the use of antisense oligonucleotides complementary to specific regions of the Grb-2 mRNA. When the antisense oligonucleotides bind to the target mRNA, a DNA-RNA hybrid is formed. The hybrid formation inhibits the translation of the mRNA, and thus, the gene's expression of the protein. If the Grb-2 protein is essential for the survival of the cell, its inhibition may lead to cell death. Inhibition of Grb-2 expression may also overcome drug resistance, and promote chemotherapy-induced apoptosis in cancer cells.

3.4 In vitro studies:

3.4.1 Studies in Philadelphia chromosome positive (Ph+) leukemic cells

BP1001 has been shown to selectively inhibit Grb-2 Protein production in Ph+ leukemic cell lines BV173 and ALL-1, and was also found to inhibit the proliferation of Bcr-Abl+ leukemic cell lines (ALL-1, BV173, and K562 cells).

Summary of in vitro inhibition with BP1001 in Ph+ cell lines

Cell Line	BP1001 concentration (µM)	Incubation Time (days)	Decrease in viability (%)	IC 50(µM
ALL-1	6	5	100	4
BV173	10	5	70	8

K562	12	4	80	8
HL60 [a]	12	5	0	-

[a] Ph negative (Ph-) leukemia cell line (Bcr-Abl negative)

Inhibition of Grb-2 protein expression led to cell growth inhibition in Bcr-Abl+ cell lines derived from Philadelphia chromosome positive (Ph+) leukemic patients, demonstrating that Grb-2 plays a functional role in Bcr-Abl induced cell proliferation, and hence, a vital role in the maintenance of the tumorigenic potential of Ph+ leukemia.

These results show that down-regulation of the Grb-2 protein can lead to inhibition of CML cell growth as regulated by the Bcr-Abl tyrosine kinase.

3.4.2 Studies in AML cell lines

Bio-Path has recently completed an in vitro study evaluating the effects of co-incubating AML cell lines with BP1001 and ara-C. The study aimed to determine whether BP1001 would enhance or suppress the inhibitory effects of ara-C on AML cells. The co-incubation was performed in 3 different sequences: (1) BP1001 was added to cells 1 hour before adding ara-C (to mimic same day treatment); (2) BP1001 was added to cells 1 day after cells had been treated with ara-C (ara-C pretreatment); and (3) BP1001 was added to cells 1 day before cells were treated with ara-C (BP1001 pretreatment).

When BP1001 and ara-C were added to AML cell lines on the same day, the inhibitory effects of ara-C were mitigated or greatly reduced, indicating that AML cells should not be treated with BP1001 and ara-C on the same day. On the other hand, significant additional inhibition was observed when AML cells were pretreated with BP1001 before being treated with ara-C. In fact, this dosing schedule produced a greater degree of inhibition than cells pretreated with ara-C, followed by BP1001 treatment. These data suggest that patients with AML may receive a greater benefit from BP1001 pretreatment before being treated with ara-C.

Summary of in vitro co-incubation with BP1001 and ara-C

Cell Lines	% Decrease in ATP Production		
	Ara-C only	Ara-C Pretreatment [a]	BP1001 Pretreatment [b]
MV-4-11	0	30	71
Kasumi-1	23	28	53
KG-1	0	7	56

[a] AML cells were pretreated with 16 nM ara-C before being treated with 20 µM BP-100-1.101 (BP1001 and ara-C incubation was 3 days and 4 days, respectively).
[b] AML cells were pretreated with 20 µM BP-100-1.101 before being treated with 16 nM ara-C (BP1001 and ara-C incubation was 4 days and 3 days, respectively).

Additionally, preclinical studies have shown that BP1001 decreased Grb-2 levels in mouse tumors by 70% when mice were administrated with a total of 3 doses of BP1001 (given on days 1, 4 and 7). Paired with the results showing significant inhibition from combining BP1001 with ara-C in the in vitro AML cell line study, pretreatment with BP1001 prior to treatment with ara-C should be explored for maximum benefit.

3.5 Preclinical Toxicology (Safety Studies)

Data Summary

Studies of ICR mice (an outbred strain of mice from the Institute for Cancer Research) were performed in the laboratory of Dr. Ana Tari at M.D. Anderson Cancer Center to evaluate the pharmacokinetics and safety profile of intravenously administered BP1001. The data can be summarized as follows:

- The pharmacokinetics and tissue distribution of BP1001 were very similar to those of other liposome-incorporated P-ethoxy oligos. The $t_{½}$ α and β were 6 min and 4 h, respectively.
- The highest concentration of BP1001 was found in the spleen, followed by the liver and kidney.
- Administration of BP1001 at doses up to 40 mg/kg did not impair renal and hepatic functions in ICR mice.
- BP1001 did not affect the hemoglobin, hematocrit or platelets of treated mice.
- A diminution of the WBC was seen at higher dose levels of BP1001. However, no specific subpopulation of the WBC appeared to be affected.
- No significant histopathologic changes were observed at autopsy.
- In addition, a 28 day toxicity study in Dutch belted rabbits was performed by Charles River Laboratories. Study drug was administered twice weekly via the intravenous route at doses up to 7.5 mg/kg. There were no toxicological changes in clinical observations, body weights, bone marrow cytology, clinical pathology, organ weights, or microscopic findings. BP1001 also was demonstrated to have no significant activity in the Ames Mutagenicity test or the *In Vitro* Mammalian Chromosome Aberration Test (CHO cells).
- Details of the above studies and other information can be found in the Investigator Brochure.

4.0 Methodology

BP1001 is a neutral liposome formulation intended to deliver Grb-2 antisense molecules into cells to suppress the expression of Grb-2, subsequently interrupting the vital Grb-2 mediated signaling function and inhibiting cancer progression. This study is designed to characterize the safety, tolerability, pharmacokinetics, and antileukemic activity of BP1001 in patients with refractory or relapsed AML, CML ALL, or MDS.

This first-in-human study of BP1001 will be conducted in 2 parts: BP1001 dose escalation and BP1001 with concurrent LDAC dose expansion. For dose escalation (Part A), a standard "3+3" design will be used in which successive cohorts of 3 or more patients with hematologic malignancies will be treated at escalating doses from 5 to 135 mg/m^2 of BP1001 until a maximum tolerated dose (MTD) is identified. For the dose expansion portion of the study (Part B), 2 successive subsets of patients with AML will be treated with BP1001 at the MTD (or the highest dose tested [HDT] if the MTD is not defined) and 1 level below the MTD (or HDT) in combination with a fixed dose of low-dose ara-C (LDAC) to further characterize safety and biological effect, as well as identify the recommended phase 2 dose (RP2D). Both parts of the study will employ an open-label, sequential, dose-escalation design to assess safety, tolerability and toxicity, PK, tumor response and anti-leukemic activity, and PD effects.

5.0 Patient Eligibility

5.1 Part A: BP1001 Dose-Escalation Cohorts

5.1.1 Inclusion Criteria

1. Male or female patients 18 years of age or older
2. A diagnosis of refractory or relapsed AML, or Ph+ CML (in chronic, accelerated or blast phase, or acute lymphoblastic leukemia, or myelodysplastic syndrome.

   One of the following parameters is required to meet criteria for accelerated phase CML:

   - Blasts in Peripheral Blood or Bone Marrow ≥15%
   - Promyelocytes and Blasts in Peripheral Blood or Bone Marrow ≥30%
   - PB or BM basophils ≥20%
   - Thrombocytopenia <100 x 10^3/ml, not resulting from therapy

   Blast phase is defined as ≥30% blasts in peripheral blood or bone marrow, or presence of extramedullary disease, except for liver or spleen.

3. Patients with CML must have demonstrated resistance and/or intolerance to therapy with at least 2 tyrosine kinase inhibitors (TKI)
4. Patients with AML and ALL should have received at least 1 prior treatment regimen and either failed to achieve response or relapsed on treatment
5. Patients with MDS should have failed prior therapy with a hypomethylating agent or, if associated with a 5q- chromosomal abnormality, lenalidomide. **NOTE**: Patients with 5q- unable to receive or intolerant to lenalidomide are also eligible.
6.
7. Have clinically adequate hepatic and renal functions as defined by:
   - ALT<2x ULN
   - Serum creatinine concentration <2x ULN
   - Serum bilirubin <2x ULN
8. Patients must sign an informed consent
9. Women of childbearing age must have a negative serum or urine pregnancy test prior to the initiation of study drug.
10. Barrier contraceptive precautions are to be used throughout the trial by all study participants of child bearing potential.
11. Have not received anti-cancer therapy for at least 2 weeks prior to study entry, with the exception of low dose ara-C (LDAC) given as subcutaneous injections (no less than 15 days prior), hydroxyurea or anagrelide (no less than 24 hours prior), TKI (no less than 5 days prior), and interferon (no less than 2 weeks prior)
12. Have an ECOG Performance of 0-2
13. Have a life-expectancy ≥3 months

5.1.2 Exclusion Criteria

1. Serious intercurrent medical illnesses which would interfere with the ability of the patient to carry out the treatment program
2. Pregnant or breastfeeding women
3. Patients who have uncontrolled active infection
4. Patients who have received another investigational product within the longer of 14 days or 5 half-lives of the previous product
5. Any history of adverse reaction or hypersensitivity to LDAC

5.2 Part B: BP1001 with Concurrent LDAC Dose-Expansion Cohorts

Enrollment in the dose-expansion cohorts (DEC) will be limited to only those patients with a diagnosis of refractory or relapsed AML(except acute promyelocytic leukemia) or those who are refractory to at least 1 prior therapy regimen and no more than 1 prior salvage regimen.

Patients being considered for inclusion in the DEC must meet all other applicable eligibility criteria specified in §5.1.1 and §5.1.2.

6.0 Pretreatment Evaluation

Written informed consent must be obtained before any medical procedure(s) are performed. Screening assessments must be done within 7±3 days prior to administration of BP1001 (Day-7 to Predose), with the exception of the bone marrow evaluation, ECG, and Chest X-Ray, which may be performed up to 28 days prior to study drug, with ± 3 day window.

Assessments	**Includes**
Demographics	Date of birth, sex and race
Relevant Medical History/Current Medical Conditions	Relevant past medical history and current conditions not related to the study indication. Any new or worsening medical conditions at the start of the study must be documented. ECOG/Zubrod performance status and symptoms
Concomitant Medications/Significant Non-Drug Therapy	Medications and significant non-drug therapies at study entry and throughout the study.
Disease History	Date of initial diagnosis of leukemia, date when refractory or relapse status to prior therapy was established, summary of previous therapy for leukemia.
Bone Marrow Analysis and Cytogenetics	Karyotype, differential cell count
Vital Signs	Includes Performance Status according to ECOG/Zubrod criteria, and body surface area.
Diagnostic Imaging	Chest X-ray
ECG	Routine electrocardiogram.
Hematology	Hemoglobin, WBC, differential, and platelet count.
Pregnancy test	For women of child-bearing potential.
Coagulation profile	Prothrombin time, activated partial thromboplastin time
Urine	Urinalysis

Biochemistry	ALT, Total Bilirubin, BUN, Creatinine, Calcium, Phosphorous, Glucose, Magnesium, Sodium, Potassium, Chloride, Uric Acid

7.0 Number of Patients

This protocol will follow a standard 3+3 design format for patient enrollment. Accordingly, it is expected that up to 60 patients will be enrolled on study. Three patients will be treated at each dose level in the absence of grade ≥ 3 toxicity. When grade 3 toxicity is detected, the number of patients treated at that dose level will be expanded up to a maximum of 6 patients. The maximum tolerated dose (MTD) will be defined as the dose at which fewer than 2 of 6 patients experience grade ≥ 3 toxicity that is possibly related to the study drug. Once the dose above the MTD is reached, at least 3 additional patients will be treated at the MTD. (ie, a minimum of 6 patients will be treated at the MTD).

Summary of Dose-Escalation and Rules (all treatment cohorts)

Number of patients with DLT at a given dose level	**Escalation Decision Rule**
0 out of 3	Enter 3 patients at the next dose level
≥ 2	Dose escalation will be stopped. This dose level will be declared as the maximally administered dose (MAD). Three additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
1 out of 3	Enter at least 3 more patients at this dose level. If 0 of these patients experience Grade ≥ 3 experience DLT, proceed to next dose level, If 1 or more of this group experience DLT, then dose escalation is stopped, and this dose is declared as the maximally administered dose. Three additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose. Note – If this occurs in Cohort 1 (5 mg/m2), Cohort 0 will be opened, dosing at 3.75mg/m2.
≤ 1 out 6 at highest dose level below the maximally administered dose (MAD)	This is the maximally tolerated dose (MTD) level to be recommended for the Phase II trial.

8.0 Treatment Plan

The patient will be registered in the Clinical Oncology Research (CORe).

BP1001 will be supplied in 50 ml vials. Each vial contains 5 mg of oligonucleotide. The contents will have been lyophilized.

8.1 Part A: Dose-escalation

For those cohorts being evaluated in Part A, BP1001 will be administered intravenously (IV) twice weekly (every 3-4 days), with a ± 1 day window, over 2-3 hours for 28 days. The starting dose will be 5 mg/m^2. Drug administration must be completed within 6 hours

of reconstitution. Three patients will receive BP1001 at each dose level for 28 days in the absence of DLT.

Dose escalation will proceed as outlined above, until drug-related toxicity of grade 3 is detected. The next cohort of patients will be entered on study once 3 patients on the prior cohort have completed 28 days of treatment, and not exhibited DLT. Thereafter, dose escalation will proceed to 10, 20, 40, 60, 90 mg/m^2 and the highest dose at 135 mg/m^2. If an MTD cannot be determined at this dose, further doses may be considered at 33% dose escalation after discussion between the Sponsor and the Principal Investigator. All patients will be evaluated for toxicity at the end of treatment (28 days) using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE). Three patients will receive 56 days of therapy at the MTD to ascertain if cumulative toxicity develops.

8.2 Part B: Dose-expansion Cohorts (DEC)

For those cohorts being evaluated in Part B, patients will be screened, enrolled, and given study drug in the same fashion as in Part A, but will also be receiving concurrent LDAC. While the dose of BP1001 will be escalated with each cohort, the LDAC dose will remain constant.

Similar to the dose-escalation portion of the study (Part A), BP1001 will be administered intravenously (IV) twice weekly (every 3-4 days), with a ± 1 day window, over 2-3 hours for 28 days. The starting dose will be 60 mg/m^2 with the 1st dose of BP1001 to be given starting on Day 1 of each 28-day cycle. Drug administration of BP1001 should be completed within 6 hours of reconstitution. Patients will also receive 20 mg of LDAC, administered subcutaneously twice daily (approximately every 12 hours for 10 consecutive days) for 28 days. Regardless of the patient's LDAC dosing schedule prior to study entry, dosing of LDAC within the study will begin on Day 10 of each 28-day cycle.

Three patients will receive BP1001 at each dose level for 28 days in the absence of DLT.

Dose escalation within this part of the study will proceed as outlined in Section 7.0, until drug-related toxicity of grade 3 is detected. The next cohort of patients will be entered on study once 3 patients on the prior cohort have completed 28 days of treatment, without evidence of DLT. Thereafter, dose escalation will proceed to 90 mg/m^2. All patients will be evaluated for toxicity at the end of treatment (28 days) using the NCI CTCAE Criteria.

8.3 Definition of Dose-Limiting Toxicity (DLT)

8.3.1 Non-hematologic DLT is defined as grade 3 or 4 toxicity (NCI CTCAE v4.0) that is clinically significant and considered to be at least possibly related to study drug. Grade 3 or 4 nausea, vomiting, diarrhea or electrolyte abnormalities will be considered DLT only if not controlled by optimal therapy.

8.3.2 Hematologic DLT is defined as grade ≥3 neutropenia and/or thrombocytopenia with a normocellular or hypocellular bone marrow and no marrow blasts lasting for 6 weeks or more after the start of a course. For patients who start with neutrophil or platelet counts below those defining

grade ≥3 toxicity (i.e., neutrophils ≤1 $x10^9$/L, platelets ≤50 $x10^9$/L), hematologic dose-limiting toxicity will be defined as lack of recovery to at least pre-treatment levels within 6 to 8 weeks depending on the bone marrow cellularity and blast count as defined above. Anemia will not be considered for the definition of DLT.

8.4 Replacement of Patients

Patients who are taken off study before day 28 will be considered not evaluable for the purpose of defining dose-limiting toxicity and MTD and will be replaced. The only exception will be patients who discontinue therapy because of toxicity; these patients will be considered for the definition of MTD and will not be replaced.

8.5 Concomitant Medications

During the first 4 weeks of therapy, hydroxyurea will be allowed. Anagrelide will also be allowed at any time to manage thrombocytosis >500K. Doses of anagrelide used will be determined by the Investigator. After 28 days of study treatment, IT Chemotherapy may then be permitted only after discussion with, and approval of the Medical Monitor.

8.6 Criteria for Dose Modification

If toxicity grade 3-4 that is possibly related to the study drug is observed, treatment should be interrupted. Treatment can be re-started at the next lower dose level (or a 50% dose reduction if occurring with the first dose level) once toxicity has resolved to at least a grade 1. Patients with persistent grade 2 toxicity that is possibly related to the study drug and not responding to adequate management may have treatment interrupted until toxicity resolves to grade 1 or less. Treatment may then be re-started at the same dose. If toxicity recurs at grade 2, treatment may then be interrupted again and re-started at a 1 dose level reduction once resolved to grade 1 or less.

There will be no dose adjustments for hematologic toxicity during the first 28 day for patients with CML in blast phase, acute leukemias or high-risk myelodypslastic syndromes. For patients with chronic or accelerated phase CML who start with normal counts, neutropenia or thrombocytopenia grade 3-4 occurs, treatment should be interrupted. Treatment can be re-started at the same dose if recovery to neutrophils ≥1 $x10^9$/L and platelets to ≥50 $x10^9$/L within 2 weeks, or to the next lower dose level (or a 50% dose reduction if occurring with the first dose level) if recovery to these levels takes longer than 2 weeks. For patients with CML in blast phase, acute leukemias or high-risk myelodypslastic syndromes after the first 28 days of therapy, treatment may be interrupted for grade 3-4 toxicity that is possibly related to the study drug (ie, in the absence of active leukemia) following the guidelines mentioned above.

There will be no making up of missed doses. Dose- and schedule-adjustments different than those mentioned here should be considered in an individual case and discussed with the PI.

8.7 Measurement of Biological Activity

For both parts of the study, assays for Grb-2 and MAPK will be performed on samples taken from the peripheral blood and bone marrow. These assays will be performed on blood samples obtained from 3 patients per dose level, within 7 days (± 3 days) prior to the start of therapy, as well as on Days 1, 8, 15, and 22 of the first cycle and on Cycle 2 Day 1. An

assay will also be performed on a blood sample obtained at the end of the patient's treatment course. The blood specimen obtained prior to initiation of study drug will represent the baseline sample, and must be drawn prior to administering study drug. The Cycle 1 Day 1, 8, 15, and 22, and Cycle 2 Day 1 blood samples should be drawn prior to administration and within 2 hours after the end of study drug administration of these respective doses. A decrease in Grb-2 expression, as well as MAPK, as compared to baseline, will indicate inhibition of the target enzyme. At this time, it is not possible to specify the degree of inhibition that will be considered significant. Assays of these markers will also be performed on bone marrow samples obtained from these patients, within 28 days prior to the start of therapy (except in the event that an adequate sample is not available), on day 28 and every 56 days thereafter until the study concludes.

These measurements will provide preliminary information on any biologic changes induced by BP1001, as well as any association of these changes to clinical response. Specifically, the measurement will also allow assessment of the optimal biologically active dose (OBAD), and evaluation of the relationship between the OBAD and the maximum tolerated dose (MTD).

8.8 Extension of Treatment

Patients will receive 28 days of therapy in this study. In those patients who exhibit stable disease (i.e. less than a 50% increase in their WBC over the first 4 weeks of therapy), or else, have improvement of their disease, BP1001 antisense therapy may be continued until a reassessment of disease is performed after 3 months on treatment. Improvement of disease will be defined as hematologic improvement, or achievement of either a partial or complete hematologic remission. However, should the Investigator feel that progression of disease has occurred, or that the patient had an inadequate response to therapy, he/she may terminate the patient's participation in the study prior to the end of 3 months. Patients completing 3 months of therapy may continue to receive BP1001 for up to 6 months if they have achieved either a partial or complete hematologic response, until they have disease progression, if it occurs before the completion of the 6 months of therapy. After 6 months of therapy, those patients still receiving therapy will be re-evaluated. Patients deriving clinical benefit may continue to receive therapy at the same dose level that they were given during the induction phase of the study, provided that it is associated with ≤ grade 2 toxicity, until disease progression.

8.9 Statistical Considerations

This is a Phase I study to determine the MTD and OBAD of BP1001 among patients with certain hematologic malignancies. It will follow a standard 3+3 design format. Specifically, treatment of at least 3 patients at each dose will be necessary to fully evaluate that dose level. If 1 or more patients experience grade ≥ 3 toxicity, that level will be expanded to include up to 6 patients. If and when DLT has been determined, up to 6 patients will be treated at that dose level. The MTD is defined as the dose at which 2 of 6 patients experience ≥3 toxicity that is possibly related to study drug.
The OBAD will be that dose that achieves a ≥ 50% suppression of Grb-2 expression in patients with circulating leukemia cells. Grb-2 expression will be measured in these patients, before and after therapy, by assessing reduction in median fluorescence intensity.

In Part A of the study **only**, if at 3 consecutive dose levels the OBAD response is reached in at least 2/3 patients, dose escalation will stop and the middle dose that provides OBAD will be selected.

9.0 Evaluation during study

History and physical examination will be obtained once a week.

Bone marrow evaluation will be performed at Day 28 (± 3 days) of each odd-numbered cycle. In addition, bone marrow evaluation may also be performed if indicated, in the Investigator's judgment, at any time during the course of therapy as clinically indicated.

Pharmacokinetic testing is outlined in the clinical pharmacology section.

These laboratory studies may be performed at a higher frequency at the discretion of the Investigator. Also, a single set of samples can be collected at Day 28 of 1 cycle and Day 1 of the next cycle, provided there is ≤ 72 hours between the sample collection and Day 1 dosing. In this case, the values will be designated as Day 1 samples, with Day 28 designated as 'Not Done'.

Table of Events for Screening through Cycle 1

Event/Assessment	Day -7 to -1	Day 1	Day 4	Day 8	Day 10	Day 11	Day 15	Day 18	Day 19	Day 22	Day 25	Day 28
History, Physical	X			X			X			X		X
Bone Marrow Assessment	X *b*											X
CBC w/ differential	X	X	X	X		X	X	X		X	X	X
Chemistry *a*	X			X			X			X		X
Coagulation Profile	X											X
Urinalysis	X											X
Blood - MAPK and Grb-2 *e*	X	X		X			X			X		
EKG	X *b*											
CXR	X *b*											
Serum or urine pregnancy test	X *c*											
BP1001 Study Drug Administration *d*		X	X	X		X	X	X		X	X	
LDAC Administration *f*					X →				X			
Plasma for PK		X	X									
Urine for PK		X										

Note: All tests to be performed ±2 days, except where exceptions are specifically noted.

a - Chemistry: ALT, Total Bilirubin, BUN, Creatinine, Calcium, Phosphorous, Glucose, Magnesium, Sodium, Potassium, Chloride, Uric Acid

b - Bone Marrow Assessment, ECG, and Chest X-Ray to be conducted within 28 (± 3) days of first dose on C1D1.

c - Pregnancy test required for women of child-bearing potential only.

d - Study Drug Administration allows ± 1 day window.

e - Day 1, 8, 15, and 22 sample collection consists of 1 predose sample and 1 within 2 hours after completion of the dose.

f - LDAC administration applicable only to patients treated in Part B (dose-expansion cohorts). There is no window for drug administration for LDAC doses. LDAC should be given twice daily for 10 consecutive days (Days 10-19).

Table of Events for Cycle 2 through End of Treatment:

Event/Assessment	Day 1	Day 4	Day 8	Day 10	Day 11	Day 15	Day 18	Day 19	Day 22	Day 25	Day 28 & End of Treatment
Interim History & PE	X		X			X			X		X
Bone Marrow Assessment											X [c]
CBC w/ differential [a]	X		X			X			X		X
Chemistry [b]	X		X			X			X		X
Coagulation Profile	X										X
Urinalysis	X										X
Blood - MAPK and Grb-2 [g]	X										
Serum or urine pregnancy test											X [d]
BP1001 Study Drug Administration [f]	X	X	X		X	X	X		X	X	
LDAC Administration [h]				X →				→X			
Plasma for PK	X [e]										

Note: All tests to be performed ±2 days.

a - Differential may not be performed if WBC is 0.5 x 10^3/ml.

b - Chemistry: ALT, Total Bilirubin, BUN, Creatinine, Calcium, Phosphorous, Glucose, Magnesium, Sodium, Potassium, Chloride, Uric Acid.

c - Bone Marrow Assessment is to be conducted at the end of each odd-numbered cycle (i.e. – Cycle 1, Cycle3, etc.), unless clinically contra-indicated.

d- Pregnancy test required to be performed every 24 Weeks (i.e. – after 6 cycles), for women of child-bearing potential only.

e - Plasma for PK to be collected only at Cycle 2, Day 1 (Predose) – not thereafter.

f - Study Drug Administration allows ± 1 day window.

g - Cycle 2, Day 1 sample collection consists of 1 predose sample and 1 within 2 hours after completion of the dose.

h - LDAC administration applicable only to patients treated in Part B (dose-expansion cohorts). There is no window for drug administration for LDAC doses. LDAC should be given twice daily for 10 consecutive days (Days 10-19).

10.0 Evaluation of Toxicity

10.1 Toxicity shall be evaluated for each dose level and each course of therapy.

10.2 Acute toxicity will be assessed at the end of 1 month (28 days) of therapy.

10.3 Myelosuppression toxicity shall be reported as lowest observed WBC, PMN, and platelet counts. Anemia and red blood cell transfusion will be noted.

10.4 Renal and hepatic toxicity will be reported as changes in BUN, creatinine, ALT, and bilirubin during a course of therapy.

10.5 Other toxicities will be described according to NCI Toxicity Criteria, Version 4.

11.0 Clinical Pharmacology

11.1 Clinical Pharmacology Objectives

11.1.1 To study the pharmacokinetics of BP1001

11.1.2 To quantify the urinary excretion

11.1.3 To study in vivo drug metabolism

11.2 Pharmacokinetic Studies

11.2.1 All patients eligible for treatment on this study will have pharmacologic studies performed

11.2.2 All pharmacokinetic studies will be initiated in patients receiving the first intravenous dose of chemotherapy. The dose will be adjusted according to the total dose per course of drug utilized on the therapeutic schedule in this particular protocol

11.2.3 Plasma Collection: 9 ml of heparinized blood (green stopper vacutainer tube) will be collected for each sample. Samples will be centrifuged immediately. The resulting plasma will be placed into another labeled tube and inhibitor added to the sample prior to freezing. A baseline sample is to be collected before the drug is administered. Samples are then collected at 1, 2, 4, 6, 8, and 24 hours after drug administration. In addition, single samples will be collected prior to the Day 4 dose, and the Cycle 2, Day 1 dose. To facilitate collection of multiple samples, a heparin lock may be used. Care must be taken to clear the tubing of heparin before obtaining the sample, as excess heparin would dilute the plasma. This can be accomplished by withdrawing 3 ml of blood prior to sample collection. It is imperative that the drug be given through a separate intravenous line, so as not to contaminate the tubing of the heparin lock with the drug.

11.2.4 Urine samples are to be collected in dark bottles as voided, and stored (with inhibitor, if necessary) in a refrigerator for the first 24 hours following drug administration. The total volume collected should be noted for the following time periods: Dose through 4 hour post infusion start, 4-8 hours post-infusion start, and 8-24 hours post infusion start. An aliquot from each of these time points will be submitted for analysis. A baseline urine sample for use as a blank for interfering substances is to be collected prior to drug administration.

11.3 Clinical Pharmacology Data Evaluation

11.3.1 Pharmacokinetics: Upon completion of a study, results will be subjected to multiple linear regression analysis. Most results can be described by an open 2-compartment model. The various pharmacokinetic parameters are computed as follows:

A Intercept of the initial distribution slope, with ordinate usually in g/ml or ng/ml

P Intercept (in 3 compartment model) of back-extrapolated, second mono-exponential slope, describing distribution into second tissue compartment. Ordinate is usually given in g/ml or ng/ml.

B Intercept of back-extrapolated mono-exponential elimination slope, with ordinate usually given in g/ml or ng/ml.

a, b Slopes of these linear segments, with the dimension of t-1.

C	Drug concentration in the central (plasma) compartment, in g/ml or ng/ml.
Co	Drug concentration in the central compartment at time zero.
D	Dose (quantity) administered, in mg/kg or mg/m^2.
t	Time in min or hr.
t½	Half-life
t½	Half-life during the shallow tissue distribution () Phase.
t½	Half-life during the deep tissue distribution () Phase.
t½	Half-life during the terminal or elimination () Phase.
Vc	Volume of distribution of the drug in the open 1-compartment model, but volume of the central compartment in the 2- or 3-compartment models, in ml/kg or ml/ m^2.
Varea	Volume of distribution by the area method.
Vdss	Volume of distribution at steady state.
k12	Specific first-order rate constant (in t-1) for drug transfer from the central compartment to the peripheral compartment (2-compartment model), or to the first ("shallow") peripheral compartment (3-compartment model).
k21	Rate constant of the reverse process.
ke	Elimination constant (2-compartment model).
k13	Rate constant for drug transfer from the central compartment to second ("deep") peripheral compartment.
k31	Rate constant of the reverse process.
k10	Rate constant (in t-1) for elimination of drug from central compartment (3-compartment model).

12.0 Criteria for Response

This Phase I trial is not designed to formally evaluate clinical efficacy of BP1001, although it is intended to reach potentially therapeutic dose level, and gain preliminary evidence of the agent's anti-leukemic effects of treatment. Clinical and pharmacodynamic assessments will be performed

and recorded in order to detect potential anti-leukemic effects of treatment. The following parameters will be used to evaluate for response:

MDS: Response criteria will be according to the International Working Group (Blood 2006; 108: 419-425). Responders are patients who obtain a CR, CRi, or PR, with or without cytogenetic response, hematologic improvements, and morphologic leukemia-free state. Briefly, criteria are as follows:

Morphologic Complete Response (CR)

- **Peripheral blood counts:**
  - No circulating blasts
  - Neutrophil count >1.0 $x10^9$/L
  - Platelet count >100 $x10^9$/L
- **Bone marrow aspirate and biopsy:**
  - < 5% blasts
  - No extramedullary leukemia

Partial Response (PR)

- All CR criteria if abnormal before treatment except:
  - ≥50 % reduction in bone marrow blast but still >5%

Marrow CR

- Bone marrow: ≤5% myeloblasts and decrease by ≥50% over pretreatment
- Peripheral blood: if HI responses, they will be noted in addition to marrow CR

Hematologic Improvement (HI): Hematologic response must be described by the number of positively affected cell lines.

- **Erythroid response (E)** (pretreatment Hgb <11 g/dL): Hgb increase by ≥1.5 g/dL

- **Platelet response (P)** (pretreatment platelets <100 $x10^9$/L)
  - Absolute increase of ≥30 x 10^9/L for patients starting with > 20 x 10^9/L platelets
  - Increase from < 20 x 10^9/L to > 20 x 10^9/L and by at least 100%

- **Neutrophil response (N)** (pretreatment ANC <1.0 $x10^9$/L): At least 100% increase and an absolute increase > 0.5 x 10^9/L

CML:
Hematologic Response (HR)

1. Complete Hematologic Response (CHR):
   a. WBC ≤ institutional upper limit of normal (ULN)
   b. Platelets ≤ 450,000 $x10^9$/L
   c. No blasts or promyelocytes in peripheral blood.
   d. < 5% myelocytes plus metamyelocytes in peripheral blood

e. Peripheral blood basophils < 2%
f. No extra-medullary involvement including no splenomegaly or hepatomegaly
g. <5% blasts in bone marrow

2. No Evidence of Leukemia (NEL) - meet the same criteria as CHR except for:
    a. Platelets ≥ 20,000/mm3 and < 100,000 mm3, and/or
    b. ANC > 500/mm3 and < 1,000/mm3
3. Minor Hematologic Response (MiHR) - meet all of the following:
    c. < 15% blasts in BM and in PB
    d. < 30% blasts + promyelocytes in BM and PB
    e. < 20% basophils in PB
    f. No extra-medullary disease other than spleen and liver
4. Major Hematologic Response (MHR) is defined as CHR or NEL
5. Overall Hematologic Response (OHR) is defined as CHR, NEL or MiHR

A **confirmed** HR is obtained when all above criteria are fulfilled at least 28 days after they are first met.

Cytogenetic Response (CyR): classified according to suppression of the Philadelphia chromosome (Ph) by cytogenetics (FISH if cytogenetic analysis not informative, e.g., insufficient metaphases)

1. No cytogenetic response - Ph positive >95%
2. Minimal cytogenetic response - Ph positive 66-95%
3. Minor cytogenetic response - Ph positive 36-65%
4. Partial cytogenetic response - Ph positive 1-35%
5. Complete cytogenetic response - Ph positive 0%

* Major cytogenetic response = complete + partial (Ph positive ≤35%)

Molecular response

1. Major (MMR): BCR-ABL/ABL ratio $\leq$ 0.02%
2. Complete: Undetectable BCR-ABL

AML:

Complete remission (CR): The patient must achieve a morphologic leukemia-free state and must have an absolute neutrophil count >1 × 10^9/L and platelet count >100 × 10^9/L, and normal marrow differential with < 5% blasts with no Auer rods in a normo- or hypercellular marrow. There should be no evidence of extramedullary leukemia.

• Partial remission: Requires all the same hematologic values as a CR but with a decrease of at least 50% in the percentage of blasts in the bone marrow aspirate to 5% to 25% in the bone marrow aspirate. A value of < 5% blasts may be considered a PR if Auer rods are present. A repeat bone marrow aspiration after several weeks may be required to distinguish between a PR and increased blasts caused by bone marrow regeneration.

• CRp: As per CR but platelet count < 100 × 10^9/L.

• CRCi: Morphologic CR with incomplete blood recovery. After chemotherapy some patients fulfill all the criteria for CR except for residual neutropenia (<1,000/microL) or thrombocytopenia (<100,000/microL).

• Hematologic Improvement (HI): Hematologic improvement should be described by the number of individual, positively affected cell lines (e.g., HI-E; HI-E + HI-N; HI-E+ HI-P + HI-N).

• Erythroid response (HI-E)

Major response: For patients with pretreatment hemoglobin less than 11 g/dL, greater than 2 g/dL increase in hemoglobin; for RBC transfusion-dependent patients, transfusion independence.

Minor response: For patients with pretreatment hemoglobin less than 11g/dL, 1 to 2 g/dL increase in hemoglobin; for RBC transfusion-dependent patients, 50% decrease in transfusion requirements.

• Platelet response (HI-P)

Major response: For patients with a pretreatment platelet count less than 100×10^9/L, an absolute increase of 30×10^9/L or more; for platelet transfusion-dependent patients, stabilization of platelet transfusion independence.

Minor response: For patients with a pretreatment platelet count less than 100×10^9/L, a 50% or more increase in platelet count with a net increase greater than 10×10^9/L but less than 30×10^9/L.

• Neutrophil response (HI-N)

Major response: For absolute neutrophil count (ANC) less than 1.5×10^9/L before therapy, at least a 100% increase, or an absolute increase of more than 0.5×10^9/L, whichever is greater.

Minor response: For ANC less than 1.5×10^9/L before therapy, ANC increase of at least 100%, but absolute increase less than 0.5×10^9/L.

For all diseases:

- Stable disease will be classified as a lack of clinically significant change in the disease status in the patient, in the judgment of the treating physician.
- Progressive disease, similarly, will be defined as a Clinically Significant deterioration in the disease status of the patient, as noted by the treating physician.

Duration of hematologic or major cytogenetic response will be calculated for all responders as the time from the first reported date of response to the earliest date of reported relapse or death. Duration of response will be censored at the last examination date for patients with ongoing response or patients who discontinued treatment for reasons other than adverse events, progression, or death.

A single determination not fulfilling the criteria for "return to chronic phase" will be considered a relapse. Time to disease progression will be calculated for patients as the time from treatment start to the onset of blast crisis, relapse (for responding patients), discontinuation of therapy, or death from any cause. This time will be censored at the last examination date for patients without progression or patients who discontinued treatment for reasons other than adverse events, progression, or death. Overall survival will be calculated as the time from treatment start to the date of death from any cause. Survival will be censored at the time treatment is discontinued to all BMT, or at the last recorded contact or evaluation when patients were alive at time of analysis.

13.0 Criteria for Removal from the Study

- Progressive disease, as defined above
- Development of Grade 4 toxicity, or other toxicity deemed medically unacceptable by the Principal Investigator
- Patient noncompliance or request to withdraw
- Completion of 28 days of therapy
- Development of serious intercurrent illness during the course of treatment, at the discretion of the Principal Investigator

Note: Those patients achieving a benefit from BP1001 antisense therapy beyond 28 days may receive an extension of treatment for a maximum of 6 months.

14.0 Reporting Requirements

14.1 Adverse Events

The M.D. Anderson Cancer Center's *"Guidelines for Filling Reports of Adverse Experiences at M.D. Anderson Cancer Center"* will be followed in the reporting of adverse experiences.

All new or worsening clinical complaints and/or signs/symptoms a patient experiences while on the study or during the follow-up period (defined as 28 days after the last dose of study drug, or commencement of a subsequent therapy, whichever occurs first), regardless of relationship to study drug will be recorded by the Investigator in the patient's medical record and on case report forms.

In case of emergency, the patient should contact the Principal Investigator:

Jorge Cortes, MD
MD Anderson Cancer Center
1515 Holcombe Boulevard
Houston, Texas 77030
Office: 713-794-5783

ALL SERIOUS AND UNEXPECTED ADVERSE EXPERIENCES, INCLUDING DEATH OR SERIOUS INJURY, WILL BE REPORTED TO THE IRB ACCORDING TO REGULATIONS AND MDACC IRB REQUIREMENTS.

14.2 Serious Adverse Events (SAEs)

If an SAE occurs (other than the excluded SAEs listed below in section 14.3), the Principal Investigator or his/her designee must notify BioPath Holdings, Inc. in writing (via fax of the completed "Serious Adverse Event Report" form), within 24 hours of learning of the SAE. The SAE will be reported to:

Brad Somer, MD
Ph – 901-683-0055

Cell- 901-268-5101
Fax – 901-685-2969

Information regarding SAEs will be transmitted to Bio-Path Holdings using the Serious Adverse Event Form providedd by the sponsor.

14.3 Protocol-Specific Expedited Adverse Event Reporting Exclusions

Certain AEs/grades are exceptions to the Expedited Reporting Guidelines and do not require expedited reporting. The following AEs must be reported through the routine reporting mechanism:

Myelosuppression and associated complications are expected events in patients with leukemia, with or without therapy. Myelosuppression and associated complications such as fever, infections, bleeding and related hospitalizations, will not be reported as individual AEs, but will be summarized in annual report to the IRB.

Note: All deaths on study must be reported using expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

Information regarding serious adverse events will be transmitted to Bio- Path Holdings using the Serious Adverse Event Form provided by the sponsor.

Bio-Path Holdings assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. Bio-Path Holdings will also report to the Investigator all SAEs that are unlisted and associated with the use of the drug.