Effect of Omega-3 Fatty Acid (EPA) and its Metabolites in Combination with Tyrosine Kinase Inhibitors (TKIs) in Chronic Myeloid Leukemia (CML) in Stable Chronic Phase

PSCI # 17-085

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SUPPLIED AGENT: GoldAID Eicosapentaenoic acid (EPA) (Omegatex 1640TG, Lifeomega, Solutex8000TG EMOX)

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PROTOCOL SYNOPSIS

Title of Study	Effect of Omega-3 Fatty Acid, Eicosapentaenoic Acid and its Metabolites in Combination with Tyrosine Kinase Inhibitors in Chronic Myeloid Leukemia in Stable Chronic Phase
PI and Sponsor	Seema Naik, M.D.
Sub-Investigators	David Claxton, M.D. Christopher Ehmann, M.D. Hong Zheng, M.D. Shin Mineishi, M.D. Kevin Rakszawski, M.D. Myles Nickolich, MD
Objectives	**Primary Objectives:** Phase I: Establish toxicity, dose-limiting toxicities (DLT) and a maximum tolerated dose (MTD) recommended Phase 2 dose (RP2D) of GoldAID Eicosapentaenoic Acid (EPA) in combination with Tyrosine Kinase Inhibitors (TKI) for therapy of stable chronic phase (CP) Chronic Myeloid Leukemia (CML) with stable molecular response. Phase II: To determine the anti-CML efficacy at the RP2D dose of GoldAID EPA in combination with tyrosine kinase inhibitors in subjects with CML in chronic phase in stable molecular response without complete molecular response (CMR). **Secondary Objectives Phase II:** Observe molecular responses including complete molecular response of CML CP to combination therapy with these agents. Assess the impact of GoldAID EPA in combination with TKI in induction of apoptosis in CML leukemia stem cell by formation of Δ12- Prostaglandin J3 (PGJ3) and other metabolites.
Background	In addition to its well-known anti-inflammatory benefits, eicosapentaenoic acid (EPA), a long-chain ω-3 polyunsaturated fatty acid (n-3 PUFA) is associated with cancer prevention. Cyclooxygenase-2 (COX-2) metabolizes EPA to a novel set of autocoids called E-series resolvins or prostaglandin H3 (PGH3). 15d-Prostaglandin J2 (15d-PGJ2) inhibits anti-apoptotic NF-κB, to mediate apoptosis [1-3] and may potentially lead to the eradication of Acute Myeloid Leukemia (AML) and CML stem cells based on cDNA microarray gene-expression profiles base.[4] Selective targeting of cancer stem cells (CSCs) may be potentially a highly effective treatment for cancer. The endogenous formation of Δ12-PGJ3 from EPA has been investigated to target leukemia stem cells (LSCs) in 2 murine models of leukemia. [1] As most CML patients treated with a TKI will reach a complete cytogenetic response (CCyR), quantification of residual *BCR-ABL* p210 transcripts by quantitative reverse transcription polymerase chain reaction (RT-qPCR) is a critical tool to further monitor response kinetics. The amount of *BCR-ABL* p210 transcripts mirrors the number of residual *BCR-ABL* Philadelphia chromosome-positive (Ph+) cells. After 18 months of imatinib mesylate (IM) treatment, the probability of losing CCyR after achieving MMR is 0% compared to 25% for patients with a CCyR but no MMR. Patients who achieve MMR at 6, 12 or 18 months on IM

	treatment have 93%, 69% and 37%, probabilities to evolve in a lasting CCyR.
Background *Continued*	Rapidity in obtaining an MMR correlates with a higher probability of achieving a CMR. Molecular monitoring may allow early recognition of acquired resistance. Increasing levels of *BCR-ABL* p210 transcripts or suboptimal molecular responses, fluctuations at high *BCR-ABL* p210 levels are associated with increased risk of resistance due to mutations and loss of CCyR. A French study, Stop Imatinib Trial (STIM study) showed that the patients who achieved and maintained CMR for a period of 2 years remained in CMR after IM discontinuation, and this practice has now become standard of care. Targeting CML leukemia stem cells is of paramount importance in successfully preventing cancer relapse. Δ^{12}-PGJ_3 may represent a new chemotherapeutic agent for leukemia that targets LSCs. It is hypothesized that GoldAID EPA together with TKIs may yield more responses and more CMR, thereby allowing more patients to discontinue TKIs and potentially cure CML.
Study Design	A Phase I/II study of the safety and efficacy of GoldAID EPA in combination with TKI for CML subjects with stable molecular response.
Study Population	**<u>Inclusion Criteria</u>** 1. Male or female ≥ 18 years of age 2. Confirmed diagnosis of CML ≥ 18 months from diagnosis 3. Current concomitant treatment with TKI therapy (Imatinib, Dasatinib, Nilotinib or Bosutinib; excluding Ponatinib). TKI therapy should be stable (same drug and dose) for at least 3 months prior to study enrollment. 4. One of the following confirmed: a. *BCR-ABL* p210 at stable molecular disease (e.g. MMR stable but not CMR) b. Hematologic remission (HR) but no MMR 5. Stable molecular response defined as 2 sequential *BCR-ABL* p210 levels done in the same lab with less than ½ log variation of *BCR-ABL* p210 3-6 months apart. 6. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) score of ≤ 3 (See Appendix A) 7. Adequate organ system function, as defined by the following: • Absolute neutrophil count (ANC) ≥500 cells/mm^3 • Platelet count ≥ 50,000 cells/mm^3 • Serum bilirubin ≤ 1.5 × upper limits of normal (ULN) • AST and ALT ≤ 2.5 × ULN • Alkaline phosphatase ≤ 2.5 × ULN 8. Women of childbearing potential (WOCP) as defined as not surgically sterile or not one year postmenopausal, must have a negative result for a serum or urine pregnancy test within 7 days of receipt of study drug. Surgically sterile is defined as having had a hysterectomy, tubal ligation, or oophorectomy. 9. WOCP must use a medically accepted method of contraception and must agree to continued use of this method for the duration of the study and for 30 days

	after last dose of study drug. Acceptable contraception include abstinence, barrier method with spermicide, intrauterine device (IUD) known to have a
Study Population *continued*	failure rate of less than 1% per year, or steroidal contraceptive (oral, transdermal, implanted, or injected) in conjunction with a barrier method. 10. Male subjects capable of producing offspring must use a medically accepted method of contraception and agree to continued use of this method for the duration of the study and for 30 days after last dose of study drug because of the possible effects on spermatogenesis. Acceptable methods of contraception include abstinence, barrier method with spermicide, WOCP partner's use of an IUD known to have a failure rate of less than 1% per year, WOCP partner's use of steroidal contraceptive (oral, implanted or injected) in conjunction with a barrier method, or WOCP partner is surgically sterile or at least 1 year post-menopausal. In addition, male subjects may not donate sperm for the duration of the study and for 30 days after last dose of study drug. **Exclusion Criteria** 1. Current malignancy requiring active treatment 2. Active infection requiring antibiotic treatment 3. Documented history of HIV, Hepatitis C, or known active Hepatitis B on therapy (HIV, Hepatitis B or C testing are part of usual care testing absent a trial). 4. Known symptomatic congestive heart failure (CHF), unstable angina or cardiac arrhythmia 5. Current concomitant use of NSAIDs (including Aspirin) or COX-1; a washout period of 4 weeks prior to enrollment is permitted 6. Known non-compliance with medications 7. In the opinion of the PI or sub-I, an uncontrolled medical or psychiatric disorder 8. History of active central nervous system (CNS) leukemia 9. Preceding allogeneic HSCT 10. Known T315I mutation. 11. Current concomitant use of fish oil at EPA dose >500 mg; a washout period of 4 weeks prior to enrollment is permitted 12. Known hypersensitivity to EPA 13. Pregnant or breastfeeding 14. An implanted defibrillator 15. Fish or seafood allergy
Treatment Regimen	A Phase I/II study with a 3+3 cohort design and inter-subject dose escalation. *Dose 1:* GoldAID EPA 1500 mg by mouth (p.o.) daily with TKI for 2 years. *Dose 2*: GoldAID EPA 2000 mg p.o. daily with TKI for 2 years. *Dose 3:* GoldAID EPA 3000 mg p.o. daily with TKI for2 years. In the event of excessive dose limiting toxicity (DLT) in Dose 1, Dose -1 and Dose -2 will be explored: *Dose -1*: GoldAID EPA 1000 mg p.o. daily with TKI for 2 years.

	Dose -2: GoldAID EPA 500 mg p.o. daily with TKI for 2 years.
Toxicity Criteria	Version 5.0 National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE)
Endpoint	The primary endpoint of the Phase I is the determination of a RP2D. For Phase II, the primary endpoint is a one-log decrease (improvement) in *BCR-ABL* p210 blood quantitation after 1 year of combined GoldAID EPA and TKI therapy. The primary *efficacy* endpoint is the one-year response rate, defined as a stable one-log decrease (improvement) in *BCR-ABL* p210 transcript level, as measured by RT-qPCR. A single stage design will be used for the Phase II portion of the study based on the assumption that the complete molecular response rate is 25% for subjects on TKI alone.[5-7] The design involves a maximum of n = 30 subjects, has a type I error rate (α) of 0.05, and provides statistical power ≥ 80% when the response rate for subjects on the combination therapy of TKI and GoldAID EPA is at least 50%. Assuming a 10% drop-out rate, a total of n = 34 subjects will be enrolled in Phase II.
Primary Assessments	*BCR-ABL* p210 quantitative RT-PCR studies will be used to identify degrees of molecular response that predict both complete cytogenetic response and long term stability, as well as, patterns of response that provide an early indication of relapse and Imatinib resistance.
Special Lab Studies	Correlative studies will be performed at baseline, at 3, 6, 9, 12, 18 and 24 months. Correlative studies with measurement of differential expression of genes and modulated pathways in CML leukemic progenitors, PG isoforms, omega-3 index and Specialized pro-resolving mediators (SPMs) would define in vivo response to GoldAID EPA and TKI combination therapy.
Sample Size	A minimum of 9 subjects and a maximum of 52 subjects will be enrolled in this study (phase I and II). Once a recommended Phase 2 dose **(**RP2D) is established, an expanded cohort will be opened at that dose to generate an RP2D experience with a total of 34 subjects (phase II).
Site(s)	This is a single site clinical trial. It will take place at Penn State Cancer Institute (PSCI) in Hershey, Pennsylvania.
Study Duration	24 months
Participant Duration	24 months

ACRONYMS:

Acute Myeloid Leukemia (AML)

Adverse Event (AE)

Cancer Stem cells (CSCs)

Central Nervous System (CNS)

Chronic Myeloid Leukemia (CML)

Complete Molecular Response (CMR)

Clinical Trial Office (CTO)

Complete Cytogenetic Response (CcyR)

Complete Molecular Response (CMR)

Cyclooxygenase (COX)

Dose-limiting toxicities (DLT)

Eastern Cooperative Oncology Group (ECOG)

Eicosapentaenoic Acid (EPA)

Gene for Hematopoietic- prostaglandin D synthase (HGDS)

Glutathione S-transferases (GST)

Hematologic Response (HR)

Hematopoietic- prostaglandin D synthase (H-PGDS)

Hematopoietic stem cell transplantation (HSCT)

15-hydroxyprostaglandin dehydrogenase (PGDH)

Imatinib mesylate (IM)

Institutional Review Board (IRB)

Leukemia Stem Cells (LSCs)

Major Molecular Response (MMR)

Maximum tolerated dose (MTD)

Nonsteroidal anti-inflammatory drug (NSAID)

Penn State Cancer Institute (PSCI)

Performance Status (PS)

Polyunsaturated fatty acid (PUFA)

Prostaglandin J3 (PGJ3)

Prostaglandin H3 (PGH3)

Recommended Phase II dose (RP2D)

Reverse transcription- quantitative polymerase chain reaction (RT-qPCR)

Serious Adverse Event (SAE)

Stop Imatinib Trial (STIM study)

Tyrosine Kinase Inhibitors (TKI)

US Food and Drug Administration (FDA)

1.0. BACKGROUND AND RATIONALE

In addition to its well-known anti-inflammatory benefits, EPA, a long-chain ω-3 polyunsaturated fatty acid (n-3 PUFA), is associated with cancer prevention. Cyclooxygenase-2 (COX-2) metabolizes EPA to autocoids from prostaglandin H3 (PGH3). The arachidonic-acid derived 15d-Prostaglandin J2 (15d-PGJ2) inhibits pro-apoptotic factors, including NF-κB and Bcl6, to mediate apoptosis.[1-3]

Selective targeting of CSCs may be potentially a highly effective treatment for cancer. The endogenous formation of Δ^{12}-PGJ_3 from EPA has been investigated to target LSCs in 2 murine models of leukemia.[1] EPA-derived Δ^{12}-PGJ_3 and 15d-PGJ_3 metabolites selectively activate p53 in LSCs with its up-regulation at the transcript level. Only Δ^{12}-PGJ_3, and 15d-PGJ_3 target LSCs for apoptosis in murine models of CML.[4, 8] Splenic tissue, rich in monocytes and T cells, expresses high amounts of H-PGDS (Hematopoietic- prostaglandin D synthase) that may aid in the metabolism of dietary EPA to Δ^{12}-PGJ_3 to activate proapoptotic pathways in LSCs in a paracrine mechanism through ataxia-telangiectasia mutated (ATM)/p53–signaling axis, which leads to complete ablation of leukemia *in vivo*.[4, 8, 9]

As most CML patients treated with a TKI will reach a CCyR, quantification of residual *BCR-ABL* p210 transcripts by RT-qPCR is a great tool to further monitor response kinetics.[10, 11] The amount of *BCR-ABL* p210 transcripts mirrors the number of residual *BCR-ABL* Ph+ cells. After 18 months of IM treatment, the probability of losing CCyR after achieving MMR is 0% compared to 25% for patients with a CCyR but no MMR. Patients who achieve MMR at 6, 12 or 18 months on IM treatment have 93%, 69% and 37%, probabilities to evolve in a lasting CCyR. Rapidity in obtaining an MMR correlates with a higher probability of achieving a CMR. Molecular monitoring may allow early recognition of acquired resistance. Increasing levels of *BCR-ABL* p210 transcripts or suboptimal molecular responses, fluctuations at high *BCR-ABL* p210 levels are associated with increased risk of resistance due to mutations and loss of CCyR. In contrast, fluctuations at low *BCR-ABL* p210 levels from ≤ 0.1% to undetectable levels are associated with maintenance of the molecular response. An absolute clearance of *BCR-ABL*$^+$ cells as detected by the most sensitive methodology (4.5 log by RT-qPCR) MMR comprises patients with tumor burden at 0.1% - 0.001% on the IS. The latter (MMR ≤ 0.001%) includes patients with undetectable levels by the most sensitive techniques such as Nested-PCR and RT-qPCR are classified as CMR.

A French study, Stop Imatinib (IM) Trial (STIM study) showed that the patients who achieved and maintained CMR for a period of 2 years remained in CMR after IM discontinuation. Although 50% of patients who stopped IM remained in CMR, the IM discontinuation was until recent years not recommended outside clinical trials.[6, 7] Current National Comprehensive Cancer Network (NCCN) guidelines provide clear criteria and guidelines for TKI discontinuation in patients achieving sustained CMR (https://www.nccn.org/professionals/physician_gls/pdf/cml.pdf).

Targeting CML leukemia stem cells is of paramount importance in successfully preventing cancer relapse. Δ^{12}-PGJ_3 may represent a new chemotherapeutic agent for leukemia that targets LSCs. The goal is to demonstrate the ability of macrophages to produce endogenous Δ^{12}-PGJ_3 with a potent proapoptotic activity toward LSCs in CML by activating the ATM-p53 pathway. In this study, the effect of combination of tyrosine kinase inhibition followed by novel inhibition by EPA products to cause selective leukemia cell death will be explored. Additionally, correlative studies will be conducted to identify potential biomarker to predict response with this novel combination approach.

Rationale for Study Design with Combination of TKI and EPA: Preliminary data suggests that Δ12-PGJ_3 has the ability to activate the transcription of p53 in LSCs. Such a regulatory control could initiate a positive feedback loop leading to the increased expression and consequent nuclear translocation of p53 protein causing apoptosis of LSCs. It is known that increased oxidative stress and chemotherapeutic agents can increase transcription of p53 to maintain cell cycle checkpoints, where the

activation of ATM kinase plays a pivotal role. Preliminary data suggests that PGD3 metabolites produced by macrophages and T-cells which express COX-2 and H-PGDS from EPA bind to DP1/DP2 GPCRs on LSCs activate p53-dependent apoptotic pathway.

In this study, we will explore effect of combination of tyrosine kinase inhibition followed by EPA on the burden of leukemia cells. Correlative studies may identify potential biomarkers predicting response with this novel combination approach.

Rationale for TKI without Ponatinib: First, second and third generation TKIs exhibit efficacy in CML but none consistently achieve CMR. Thus Imatinib, Nilotinib, Dasatinib and Bosutinib are usually well tolerated and are not expected to interact with EPA in a toxic way. Ponatinib (the third generation agent), though effective in treatment of CML, has significant toxicity which may confound the assessment of toxicity in combination with EPA.

Rationale for Dose Escalation: As explained earlier, significant doses of EPA are required to maximize the production of Δ^{12}-PGJ_3. Previous studies conducted by the Penn State University Prabhu laboratory have demonstrated a linear dose response of CML-LSCs for D12-PGJ3 with an IC50 of 10-20 nM. [1] While EPA has been well tolerated in a number of clinical settings, its interactions with TKIs are generally unknown. While no toxic interactions are expected, it is reasonable to carefully escalate from moderate to more significant doses of EPA.

Rationale for *Subject* Dose Escalation: EPA is metabolized by enzymes, COX-2 and H-PGDS (as well as lipocalin type-PGDS). PGD3 produced from this pathway is further non-enzymatically converted to Δ^{12}-PGJ_3. Active levels of Δ^{12}-PGJ_3 are regulated by the levels of two primary catabolic enzymes, 15-PGDH (15-prostaglandin dehydrogenase) and GSTs (Glutathione S-transferases) that convert Δ^{12}-PGJ_3 to 13, 14dihydro 15-keto- PGJ2 and D12-PGJ3-glutathione conjugate, respectively. Most importantly, there is evidence for inter-individual variation of COX-2 activity due to the presence of SNPs in the COX-2 gene. [7] To account for the changes in the activity and metabolism of PUFA by COX-2 followed by downstream catalysis by HGDS (Gene for Hematopoietic- prostaglandin D synthase) isozymes and catabolic inactivation by 15-PGDH and GSTs, we will use dose escalation as a means to maximize the endogenous metabolism of EPA production of D12-PGJ3. In other words, stated simply, the goal is to offer patients the best tolerated but most efficacious EPA dose available.

Rationale for Dose: Dietary EPA is esterified in phospholipids within the membrane. Once incorporated into the membrane, EPA is then released by the action of phospholipase A2 (PLA2) as a substrate for COX-2 and other enzymes. Previous studies have shown that membrane incorporation of EPA increases with increased dietary intake, but readily saturates at 4 g of n-3 fish oil (containing 2.6-3.0 g of EPA) to increase the membrane composition (n-3 index) by 15-18 %. [12, 13] Such a seemingly small increase in membrane levels of n-3 is still sufficient to mediate the effects of dietary EPA on leukemia, as well as, effectively treat hypertriglyceridemia. Thus, a maximum dose of 3 g of EPA will be used, which is well within the MTD for EPA. Such doses have been well tolerated in other clinical contexts when used alone without TKIs.[14-17]

Overall Rationale and Potential Impact: This study of CML with incomplete *BCR-ABL* p210 response to TKIs has the potential to increase the number of CML patients entering and sustaining CMR. Patients sustaining CMR for two years may stop their TKIs, as some of these patients may be considered cured. This concept is validated by the current planned national studies in the same patient group of TKIs and the use of much more toxic PD1 inhibitors.

2.0. OBJECTIVES

2.1. Primary Objective:

Phase I: Establish toxicity, DLT and a MTD RP2D of GoldAID EPA in combination with TKI for therapy of CP CML with stable molecular response.

Phase II: To determine the anti-CML efficacy at the RP2D dose of GoldAID EPA in combination with tyrosine kinase inhibitors in subjects with CML in chronic phase in stable molecular response without CMR.

2.2. Secondary Objectives:

Phase II:

2.2.1 Observe molecular responses including complete molecular response of CML CP to combination therapy with these agents.

2.2.2 Assess the impact of GoldAID EPA in combination with TKI in induction of apoptosis in CML leukemia stem cell by formation of Δ12-PGJ3 and other metabolites

2.3. Primary Endpoints:

2.3.1. Phase I Study: Determination of a RP2D.

2.3.2. Phase II Study**:** One log decrease (improvement) in *BCR-ABL* blood quantitation after 1 year of combined GoldAID EPA and TKI therapy.

2.4. Secondary Endpoints:

2.4.1. Phase I Study:

- Evaluate safety and adverse events (AEs).
- Evaluate compliance – proportion of doses taken as per protocol, DLTs.

2.4.2. Phase II Study**:**

- Evaluate MMR and CMR rate based on *BCR-ABL* p210 level for monitoring of CML at one month (+/-5 days) then at approximately every 3 month intervals up to and including Year 2.
- Correlation of levels of EPA metabolites with *BCR-ABL* p210 level at RP2D of EPA.

3.0. PATIENT SELECTION

3.1. Inclusion Criteria:

1. Male or female ≥18 years of age.
2. Confirmed diagnosis of CML ≥ 18 months from diagnosis.
3. Current concomitant treatment with TKI therapy (Imatinib, Dasatinib, Nilotinib or Bosutinib; excluding Ponatinib). TKI therapy should be stable (same drug and dose) for at least 3 months prior to study enrollment.
4. One of the following confirmed:
   a. *BCR-ABL* p210 at stable molecular disease (e.g., MMR stable but not CMR)
   b. HR but no MMR.
5. Stable molecular response defined as 2 sequential *BCR-ABL* p210 levels done in the same lab with less than ½ log variation of *BCR-ABL* (BA) 3-6 months apart.
6. ECOG PS of ≤ 3
7. Adequate organ function, as defined by the following:
   - ANC ≥ 500 cells/mm^3

- Platelet count ≥ 50,000 cells/mm^3
- Serum bilirubin ≤ 1.5 × ULN
- AST and ALT ≤ 2.5 × ULN
- Alkaline phosphatase ≤ 2.5 × ULN

8. WOCP as defined as defined as not surgically sterile or not one year post-menopausal, must have a negative result for a serum or urine pregnancy test within 7 days of initial receipt of study drug. Surgically sterile is defined as having had a hysterectomy, tubal ligation, or oophorectomy.
9. WOCP must use a medically accepted method of contraception and must agree to continued use of this method for the duration of the study and for 30 days after last dose of study drug. Acceptable methods of contraception include abstinence, barrier method with spermicide, intrauterine device (IUD) known to have a failure rate of less than 1% per year, or steroidal contraceptive (oral, transdermal, implanted, or injected) in conjunction with a barrier method.
10. Male subjects capable of producing offspring, must use a medically accepted method of birth control and agree to continued use of this method for the duration of the study and for 30 days after last dose of study drug because of the possible effects on spermatogenesis. Acceptable methods of contraception include abstinence, barrier method with spermicide, WOCP partner's use of an IUD known to have a failure rate of less than 1% per year, WOCP partner's use of steroidal contraceptive (oral, implanted or injected) in conjunction with a barrier method, WOCP partner is surgically sterile or 1 year post-menopausal. In addition, male subjects may not donate sperm for the duration of the study and for 30 days after last dose of study drug.

3.2. Exclusion Criteria

1. Current malignancy requiring active treatment.
2. Active infection requiring antibiotic treatment.
3. Documented history of HIV, Hepatitis C, or known active Hepatitis B on therapy (HIV, Hepatitis B or C testing are part of usual care testing absent a trial).
4. Known symptomatic CHF, unstable angina or cardiac arrhythmia.
5. Current concomitant use of NSAIDs (including Aspirin) or COX-1; a washout period of 4 weeks prior to enrollment is permitted.
6. Known non-compliance with medications.
7. In the opinion of a PI or Sub-I, an uncontrolled medical or psychiatric disorder.
8. History of active CNS leukemia.
9. Preceding allogeneic HSCT.
10. Known T315I mutation.
11. Current concomitant use of fish oil at EPA dose > 500 mg; a washout period of 4 weeks prior to enrollment is permitted.
12. Known hypersensitivity to EPA.
13. Pregnant or breastfeeding.
14. An implanted defibrillator.
15. Fish or seafood allergy.

Subjects must be informed of the investigational nature of this study in accordance with

institutional and federal guidelines. Subject must also be able to provide written informed consent prior to initiation of any study-related procedures, and in the opinion of the PI, must be able to comply with all of the requirements of the study.

Inclusion of Women and Minorities: Both men and women and members of all races and ethnic groups are eligible for this trial. Pregnant females are excluded due to the unknown effects that the study drug may have on the fetus.

3.3. Definitions of Therapeutic Response:

3.3.1. MMR is 3-log reduction in *BCR-ABL* p210 also known as MR 3.0.[6, 7, 18]

3.3.2. CMR is 4.5-log reduction in *BCR-ABL* p210, also known as, MR 4.5 or molecularly undetectable leukemia.[6, 7] Criteria for Molecular Response is located in Appendix D.

3.3.3. Disease progression with molecular relapse is defined as increase in *BCR-ABL* p210 quantitative PCR by one log.[19]

3.3.4. Stable molecular response defined as 2 sequential BCR-ABL p210 levels done in the same lab with less than ½ log variation of *BCR-ABL* p210 3-6 months apart.

3.4. Sample Size:

A minimum of 9 subjects for phase I and a maximum of 52 subjects (for phase I and phase II) will be enrolled in this study. Once a RP2D is established, an expanded cohort will be opened at that dose to generate an RP2D experience with a total of 34 subjects.

3.5. Study Design: A Phase I/II study of the safety and efficacy of GoldAID EPA in combination with TKI CML subjects with stable molecular response.

3.5.1. Tyrosine Kinase Inhibitors: Subjects will continue to receive their TKI daily at a stable dose with *BCR-ABL* p210 monitoring every 3 months. TKI will continue indefinitely per the recommendations of treating physicians.

3.5.2. GoldAID EPA: One of the primary objectives of Phase I of this study is to determine a RP2D of GoldAID EPA. During Phase I, subjects will be monitored closely for evidence of DLTs. The NCI CTCAE, version 5.0, will be used to determine DLT terms, definitions (descriptions) and grades for DLT reporting. Additionally, subjects will be monitored for signs of objective response vs. stable disease. Subjects will continue taking GoldAID EPA for up to two years, if tolerated (Appendix B).

4.0. REGISTRATION PROCEDURES:

General Guidelines: Eligible subjects will be registered on study by the PSCI Clinical Trials Office (CTO). Issues that would cause treatment delays should be discussed with the sponsor investigator or designated physician sub-Investigator (Sub-I) and documented in the research record.

5.0. TREATMENT PLAN:

5.1. Phase I Study Scheme:

The Phase I study is designed as a single center, single arm trial to evaluate the safety and toxicity profile of the combination therapy of TKI and GoldAID EPA. Treatment with TKI will continue indefinitely under the direction and at the discretion of treating physicians. A 3+3 subject per cohort design will be used as described in the Section 12.0 Statistical Considerations. Subjects will receive TKI daily at their pre-study dose and will be monitored initially at one month for any DLT with *BCR-ABL* p210 quantitative PCR and every 3 months. In the event of excessive DLTs in Dose 1, Dose -1 will be explored. In the event of excessive DLTs in Dose -1, Dose -2 will be explored.

Table 1. Treatment doses should be as follows:

Dose Level	Dose
Dose 1	GoldAID EPA 1500 mg p.o.
	TKI
Dose 2	GoldAID EPA 2000 mg p.o.
	TKI
Dose 3	GoldAID EPA 3000 mg p.o.
	TKI
Dose -1	GoldAID EPA 1000 mg p.o.
	TKI
Dose -2	GoldAID EPA 500 mg p.o.
	TKI

5.2 Progression between Dose Levels (Modified Fibonacci Scheme), Dose Adjustment due to Toxicity, and RP2D:

Dose levels are schematically shown in Table 1. The subjects will receive GoldAID EPA in a classic "3 + 3" dose escalation design. Initially, 3 patients will be treated using dose level 1. If 0 out of 3 patients experience dose limiting toxicity (DLT) at dose 1, then the next level (dose 2) will be used. If 1 out of 3 patients experience DLT at dose 1, then an additional 3 patients will be treated at the same dose level. If 1 out of 6 patients have a DLT at dose 1, then dose 2 will be used following the same algorithm as dose 1. If more than 1 out of 6 patients experience DLT at dose 1, then dose level -1 will be used for an additional 3 patients following the same algorithm as dose 1. The maximum tolerated dose (MTD) will be defined as the highest dose level where no more than 1 of 6 patients experiences DLT, and this dose will be recommended for Phase II. There will be no intra-patient dose escalation. Subjects will be monitored closely for evidence of DLTs. The NCI CTCAE, version 5.0, will be used to determine DLT terms, definitions (descriptions) and grades for DLT reporting. For the stopping rule for excess toxicity we will use the DLT criteria. An interim analysis for excess toxicity will be performed based on the presence of DLTs and their grades. In brief, once half of the phase II cohort has been accrued (n = 17), the proportion of patients exhibiting DLTs greater than grade 2 will be computed. We will suspend the trial if n = 3 or more patients exhibit a DLT of grade greater than 2 in the interim analysis. This stopping threshold corresponds to approximately 18% of the number of accrued patients at the time of the interim analysis and is within the FDA's suggested range (15% - 25%).

5.3 Expanded Cohort: Once the RP2D is established, the cohort will be expanded to a total of 34 subjects for Phase II of the study.

5.4 Phase II Study Schema: The subjects from phase II will administer GoldAID EPA at the RP2D established in Phase I study for the duration of two years in combination with the TKI dose. *BCR-ABL* p210 quantitative PCR will be performed every 3 months while the subjects are on the study. Treatment with TKI will continue for up to 2 years after molecular remission or until disease progression or development of unacceptable AEs.

5.5 Definition of Dose Limiting Toxicity (DLT)

DLT is defined as any NCI CTCAE version 5.0 grade 3 or higher treatment related toxicity that occurs within 30 days from starting study drug.

5.6 Dose Modification of the Study Drug out of DLT Window

CTCAE Grade	GoldAID EPA Dose Modifications
Grade 2	Dose reduction to the next lower dose level, if toxicity resolves within 14 days then resume at the original dose.
Grade 3 or 4	Suspend dose until toxicity resolves to ≤ Grade 2, then resume at next lower dose level, if toxicity resolves within 30 days then resume at the original dose.

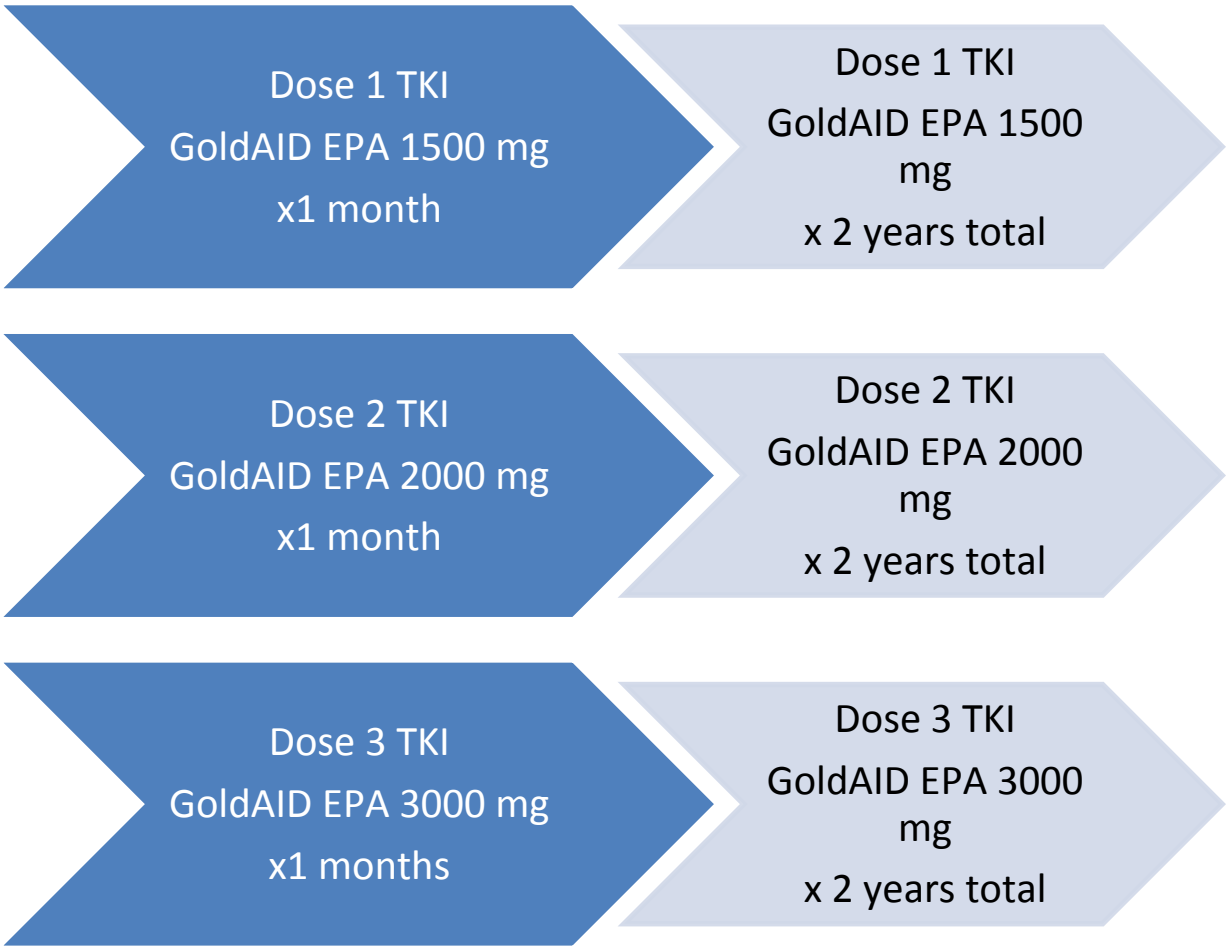
Dose level	3000 mg	2000 mg	1500 mg
1st dose reduction	2000 mg	1500 mg	1000 mg
2nd dose reduction	1500 mg	1000 mg	500 mg

Note: 1. Patients requiring a delay of 30 days will be removed from study.
2. Patients must be compliant with ≥ 75% of the GoldAID EPA dose. Patients who are less than 75% compliant will be removed from the study and replaced.
3. No re-challenges after second dose reduction.

6.0. **TREATMENT SCHEMA:**

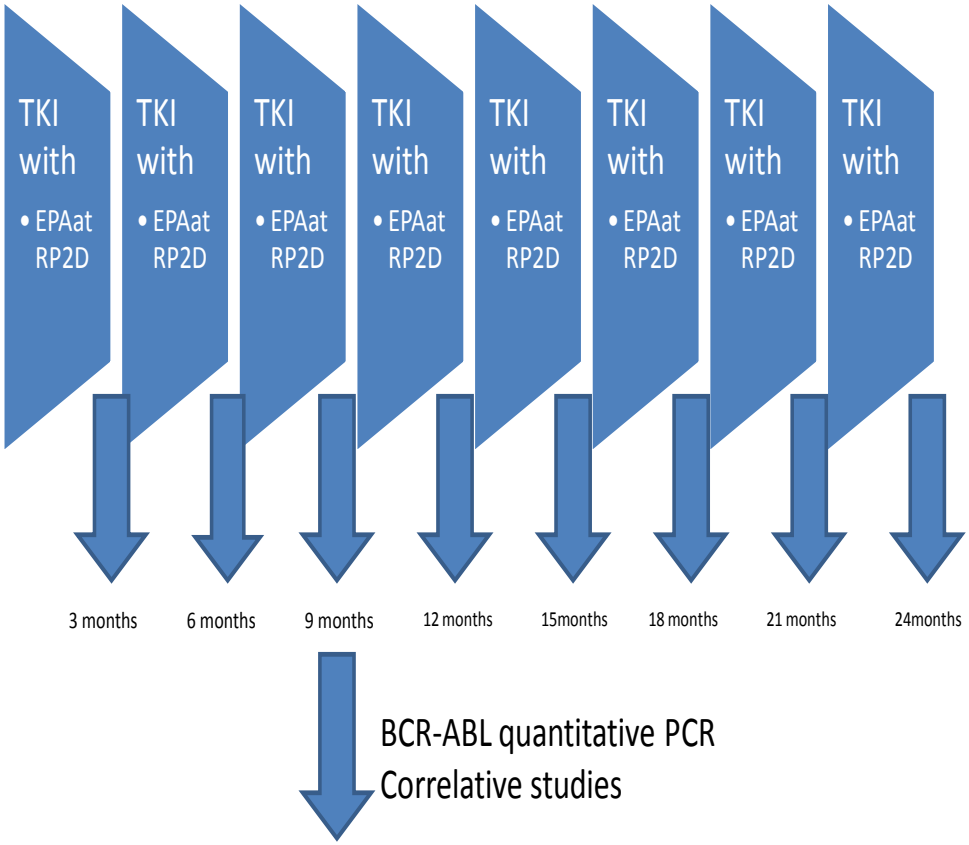
6.1. Phase I Study:

Figure 1.Dose escalation of EPA on Phase I study


Dose 1 TKI
GoldAID EPA 1500 mg
x1 month
Dose 1 TKI
GoldAID EPA 1500 mg
x 2 years total
Dose 2 TKI
GoldAID EPA 2000 mg
x1 month
Dose 2 TKI
GoldAID EPA 2000 mg
x 2 years total
Dose 3 TKI
GoldAID EPA 3000 mg
x1 months
Dose 3 TKI
GoldAID EPA 3000 mg
x 2 years total

6.2. Phase II Study:

Figure 2. Phase II study Schema with Combination of TKI and RP2D GoldAID EPA dose with 3 monthly *BCR-ABL* p210 and correlative studies. The study medication will be administered approximately 24 months.



7.0 STUDY PROCEDURES

	Screening D -28 to D0	Day 0	Day 28-30	Month 3,6,9,12,15, 18,21	Unscheduled visits	Month 24/ EOT	30 days post EOT	Year 3, 4, 5 Follow Up
Informed Consent	X							
Medical History and Physical Exam[1]	X	X	X	X	X	X	X	X
ECOG PS (Appendix A)	X	X	X	X	X	X	X	X
CBC with differential	X	X[7]	X	X	X	X	X	X
Chemistry Testing[2]	X	X[7]	X	X	X	X	X	
Pregnancy Testing[3]	X							
BCR-ABL p210 PCR	X	X[7]		X		X		X
Correlative Studies [4,5]		X		X		X		
AE Assessment		X	X	X	X	X	X	
Concurrent Medications Assessment	X	X	X	X	X	X		
Dispensing of Study Medication and diary card[6]		X	X	X		X		

1. Medical history includes any prior surgical history. All physical exams will include vital signs and weight. Vital signs include blood pressure, heart rate, respiratory rate, and temperature. Initial physical exam will be a full assessment. Subsequent exams may be limited. Height will be required at screening/baseline only.
2. Chemistry testing = complete metabolic profile (CMP), magnesium, phosphorous, and LDH.
3. Pregnancy testing (urine or serum) for WOCP to be collected within 7 days prior to administration of first dose of investigational GoldAID EPA medication.
4. A total of three 5 ml tubes of blood will be obtained for correlative studies. Of these three tubes, plasma and mononuclear cell layer/buffy coat will be sent to Dr. Prabhu's lab at University Park.
5. GoldAID EPA metabolites will be measured at screening and subsequent visits (on month 3,6,9,12,18, and 24, not month 15 and 21).
6. Documentation of GoldAID EPA dosing will be recorded in a Study Medication Diary provided by the study team. Dosing noncompliance is defined as a patient missing ≥ 75%of medication in a 28-day window for 2 consecutive visits for a non-protocol-specified reason.
7. CBC with differential, chemistry testing and *BCR-ABL* p210 PCR to be performed only once if day 0 is within one week from screening visit.

- A window of +/- 4 business days will be allowed for Day 28 visit. A window of +/- 10 business days will be allowed for Month 3, 6, 9, 12, 15, 18, 21, 24 and EOT and 30 days post EOT visits. A window of +/- 21 business days will be allowed for Year 3, 4, and 5 Follow-Up visit.

7.1 Screening Visit – Day -28 to Day 0

The following assessments and procedures will be obtained during the Screening visit:

- Informed consent: written informed consent using an IRB approved consent document must be obtained prior to initiation of any study-related procedures.

- Medical history (including any prior surgical history): documentation of all medical history must be maintained in the source documents.
- Physical exam. A full physical examination will be completed at Screening.
- ECOG PS
- Pregnancy test for WOCP only.
- CBC with differential
- Chemistry testing
- *BCR-ABL* p210 PCR by peripheral blood
- Concurrent medications assessment

7.2 Day 0 (first day of investigational medication administration)

- Interval medical history (including any interval surgical history)
- Physical exam (a limited exam may be performed).
- ECOG PS
- CBC with differential (performed only once if day 0 is within one week from screening visit)
- Chemistry testing (performed only once if day 0 is within one week from screening visit)
- *BCR-ABL* p210 PCR(performed only once if day 0 is within one week from screening visit)
- Correlative studies
- Concurrent medications assessment
- AE assessment (start after receipt of first dose)
- Subjects will be asked to complete a Study Medication Diary while taking the study medication

7.3 Day +28-30

- Interval medical history (including any interval surgical history).
- Physical exam (a limited exam may be performed).
- ECOG PS
- CBC with differential
- Chemistry testing
- Concurrent medications assessment
- AE assessment
- The Study Medication Diary will be collected and reviewed.

7.4 Month +3, 6, 9, 12, 15, 18, 21

- Interval medical history (including any interval surgical history).
- Physical exam (a limited exam may be performed).
- ECOG PS
- CBC with differential
- Chemistry testing
- *BCR-ABL* p210 PCR
- Correlative studies (only on Month 3, 6, 9, 12, 18)
- Concurrent medications assessment
- AE assessment
- The Study Medication Diary will be collected and reviewed.

7.5 Unscheduled visits

- Interval medical history (including any interval surgical history).

- Physical exam (a limited exam may be performed).
- ECOG PS
- CBC with differential
- Chemistry testing
- Concurrent medications assessment
- AE assessment

7.6 Month 24 (End of Treatment)

- Interval medical history (including any interval surgical history).
- Physical exam (a limited exam may be performed).
- ECOG PS
- CBC with differential
- Chemistry testing
- *BCR-ABL* p210 PCR
- Correlative studies
- Concurrent medications assessment
- AE assessment
- The Study Medication Diary will be collected and reviewed.

7.7 30 days post End of Treatment

- Interval medical history (including any interval surgical history).
- Physical exam (a limited exam may be performed).
- ECOG PS
- CBC with differential
- Chemistry testing
- AE assessment

7.8 Year 3 4, 5 (Follow-Up)

- Interval medical history (including any interval surgical history).
- Physical exam (a limited exam may be performed).
- ECOG PS
- CBC with differential
- *BCR-ABL* p210 PCR

7.9 Off treatment criteria (rendered off treatment but remains on follow up)

a. Completion of the full protocol prescribed treatment regimen.
b. Excessive or intolerable toxicity resulting in discontinuation of treatment as described.
c. Pregnancy
d. Subject withdraws consent for treatment but agrees to continue to be followed until off study criteria is met.
e. Subject non-compliance with medication regimen and/or required clinical follow up per PI or physician Sub-I judgement.
f. Disease progression which requires discontinuation of the study drug.
g. PI or physician Sub-I determine it is not in the best clinical interest of the subject to continue treatment.
h. Participant unable to receive GoldAID EPA for 28 days.

7.10 Off study criteria

a. Does not meet initial eligibility criteria
b. Completes all study requirements and follow up
c. Death
d. Voluntary withdrawal of consent.
e. Subject non-compliance with protocol required follow up.
f. Lost to follow up despite 3 documented contact attempts followed by non-response to certified mail.
g. Study closure/premature study closure.

8.0. DRUG INFORMATION

GoldAID EPA will be provided to subjects by Solutex free of charge.

8. 1. GoldAID EPA Formulation: GoldAID EPA is a fluid emulsion of white color, strawberry flavored (Solutex; USP grade), high-potency EPA formulation as triglyceride (for higher bioavailability) containing 3000 mg EPA and 3320 mg of Omega-3 (purified by supercritical CO_2 technology) per sachet with superior organoleptic properties. The product is tested for stability for >24 months and has no detectable heavy metals, saturated fatty acids, or monounsaturated fatty acids. A stability study was initiated on March 2, 2018 for the product GOLDAID EPA which is still active. The product is packaged in sachets and evaluated under normal (25°C ± 2°C/60% RH ± 5% RH) and accelerated (40°C ± 2°C/75% RH ± 5%) storage conditions. The testing covers all those features susceptible to change during storage and likely to influence physical, chemical and quality characteristics of the product. In this respect, the stability studies include all tests on the product´s technical data sheet "TDS GOLDAID EPA" with specific values for the product shown on "(certificate of analysis (COA) GOLDAID EPA". Stability tests are conducted following USP and internal methods. The stability study design is summarized on Appendix B.

8.1.1 Administration: GoldAID EPA is the natural omega-3 fatty acid formula that contains flavoring agents and stabilizers, which are normally Generally Recognized as Safe (GRAS). The GoldAID EPA provided is of extremely high quality and a strong contender with its 3000 mg serving sizes. The GoldAID EPA provided is in the form of triglyceride, which is more bioavailable compared to ethyl esters. Furthermore, the GoldAid EPA provided is in the form of uniformly-sized particular emulsion that easily dissolves in aqueous solutions.

Study drug is supplied in a 20 ml sachet package. Each sachet will include a label indicating the name of the product, date, and lot number. Per 21CFR 312.1, The Penn State Pharmacy will add a label noting "Caution: New Drug--Limited by Federal (or United States) law to investigational use." Each sachet provided will contain 3000 mg in 20 ml of emulsion; therefore, 1500 mg = 10 ml (Dose 1) and 2000 mg = 13.3 ml (Dose 2). A small syringe will be provided to each subject to facilitate accurate dosing.

8.1.2 Geriatric Use: Safety and efficacy findings of EPA in subjects older than 60 years did not appear to differ from those of subjects younger than 60 years.

8.1.3 Pharmacokinetics: Females tended to have more uptake of EPA into serum phospholipids than males; however, the clinical significance of this is unknown. Pediatric: Pharmacokinetics of EPA has not been studied. Renal or Hepatic Impairment: EPA has not been studied in patients with renal or hepatic impairment.

8.1.4 Toxicity: Fish oil is **LIKELY SAFE** for most people when taken by mouth in low doses (3 grams or less per day). There are some safety concerns when fish oil is taken in high doses. Taking more than 3 grams per day might keep blood from clotting and can increase the chance of bleeding.

High doses of fish oil might also reduce the immune system's activity, reducing the body's ability to fight infection. This is a special concern for people taking medications to reduce their immune system's activity (organ transplant patients, for example) and the elderly.

High doses of fish oil should only be taken under medical supervision. Fish oil can cause side effects including belching, bad breath, heartburn, nausea, loose stools, rash, and nosebleeds. Taking fish oil supplements with meals or freezing them can often decrease these side effects.

Fish oil is **POSSIBLY SAFE** when injected intravenously (IV) in the short-term. Fish oil or omega-3 fatty acid solutions have been safely used for 1 to 4 weeks.

Consuming large amounts of fish oil from some dietary sources is **POSSIBLY UNSAFE**. Some fish meats (especially shark, king mackerel, and farm-raised salmon) can be contaminated with mercury and other industrial and environmental chemicals. Fish oil supplements typically do not contain these contaminants.

Special Warnings and Precautions:

Children: Fish oil is **POSSIBLY SAFE** when taken by mouth appropriately. Fish oil has been used safely through feeding tubes in infants for up to 9 months. But young children should not eat more than two ounces of fish per week. Fish oil is **POSSIBLY UNSAFE** when consumed from dietary sources in large amounts. Fatty fish contain toxins such as mercury. Eating contaminated fish frequently can cause brain damage, mental retardation, blindness and seizures in children.

Pregnancy and breastfeeding: Fish oil is **LIKELY SAFE** when taken by mouth appropriately. Taking fish oil during pregnancy or while breastfeeding does not seem to affect the fetus or baby. As stated previously, fatty fish contain toxins such as mercury. Women who are pregnant or who may become pregnant, and nursing mothers should avoid shark, swordfish, king mackerel, and tilefish (also called golden bass or golden snapper), as these may contain high levels of mercury. Limit consumption of other fish to 12 ounces per week (about 3 to 4 servings per /week). Fish oil supplements typically do not contain these contaminants.

POSSIBLY UNSAFE when dietary sources are consumed in large amounts.

Bipolar disorder: Taking fish oil might increase some of the symptoms of this condition.

Liver disease: Fish oil might increase the risk of bleeding in people with liver scarring due to liver disease.

Depression: Taking fish oil might increase some of the symptoms of this condition.

Diabetes: There is some concern that taking high doses of fish oil might make the control of blood sugar more difficult.

Familial adenomatous polyposis: There is some concern that fish oil might further increase the risk of getting cancer in people with this condition.

High blood pressure: Fish oil can lower blood pressure and might cause blood pressure to drop too low in people who are being treated with blood pressure-lowering medications.

HIV/AIDS and other conditions in which the immune system response is lowered: Higher doses of fish oil can lower the body's immune system response. This could be a problem for people whose immune system is already weak.

An implanted defibrillator: Some, but not all, research suggests that fish oil might increase the risk of irregular heartbeat in patients with an implanted defibrillator. These patients should avoid taking fish oil supplements.

Fish or seafood allergy: People who are allergic to seafood, such as fish, might also be allergic to fish oil supplements. There is no reliable information showing how likely people with seafood allergy are to have an allergic reaction to fish oil. Until more is known, patients with an allergy to seafood should use fish oil supplements cautiously or avoid the use altogether**.**

Side Effects:

Common Side effects – as defined as found to occur in < 1% of recipients**.**

- Gastrointestinal: Eructation, dyspepsia, nausea, gastrointestinal disorders (abdominal distension, pain, constipation, diarrhea, flatulence, GERD, vomiting) : <1% GI hemorrhage, gastroenteritis
- Other: Infection, pain, bad breath
- Dermatologic: Rash; < 1%: Atopic dermatitis
- Cardiovascular: 0.1% to 1%: Hypotension
- Musculoskeletal: Back pain
- Metabolic :< 1%: Hyperglycemia, gout, high triglycerides
- Nervous system: Taste perversion ; < 1%: Dizziness, dysgeusia, headache, hyperactivity
- Respiratory: < 1%: Epistaxis
- Psychiatric : < 1%: Tics, tantrum, insomnia

Less common side effects - as defined as found to occur in < 0.1% of recipients.

- Hepatic: increased ALT, AST, transaminases
- Hypersensitivity
- Anaphylactic reaction
- Gastrointestinal pain
- Urticaria
- Acne
- Rash Pruritic

Uncommon side effects as defined as found to occur in <.001% of recipients.

- Lower GI hemorrhage
- Hematologic: WBC increased
- LDH increased
- Respiratory: Nasal dryness

Drug-Drug Interactions In vitro studies using human liver microsomes indicated that clinically significant cytochrome P450-mediated inhibition by EPA/DHA combinations are not expected in humans.

Nonclinical toxicology: Omega-3-acid ethyl esters were not mutagenic or clastogenic. Omega-3-acid ethyl esters were negative in the *in vivo* mouse micronucleus assay. **8.2 TKI: (Labeling and package inserts for TKIs are located in Appendix C).**

8.2.1. Imatinib: Imatinib is indicated for newly diagnosed adult patients with Philadelphia chromosome positive (Ph+) CML in chronic phase.

Available Forms: 400 mg tablets

Administration: The recommended dose is 400 mg per day for adult patients in chronic phase CML and 600 mg per day for adult patients in accelerated phase or blast crisis. In CML, a dose increase from 400 mg to 600 mg in adult patients with chronic phase disease, or from 600 mg to 800 mg (given

as 400 mg twice daily) in adult patients in accelerated phase or blast crisis may be considered in the absence of severe adverse drug reaction and severe non-leukemia related neutropenia or thrombocytopenia in the following circumstances: disease progression (at any time), failure to achieve a satisfactory hematologic response after at least 3 months of treatment, failure to achieve a cytogenetic response after 6 to 12 months of treatment, or loss of a previously achieved hematologic or cytogenetic response.

Toxicity: Common Side Effects of Imatinib include: fluid retention (holding water), muscle cramps, pain, bone pain, abdominal pain, anorexia (loss of appetite), vomiting, diarrhea, decreased hemoglobin, hemorrhage (abnormal bleeding), nausea, fatigue and rash.

Toxicities with expected incidences of 1% to 10% include: cardiac disorders (palpitations and pericardial effusion), vascular disorders (flushing, hemorrhage, blood CPK, and blood amylase increased), skin abnormalities (dry skin, alopecia, face edema, erythema, photosensitivity reaction, nail disorder and purpura), gastrointestinal disorders (abdominal distention, gastro esophageal reflux, dry mouth, and gastritis), weakness, anasarca, chills, pancytopenia, febrile neutropenia, lymphopenia, eosinophilia, hepatobiliary disorders (hepatitis and jaundice) immune system disorders (angioedema, weight decreased, decreased appetite and joint swelling) and nervous system (paresthesia, hypoesthesia; epistaxis conjunctivitis, vision blurred, orbital edema, conjunctival hemorrhage and dry eye).

8.2.2. Dasatinib: Dasatinib is indicated for the treatment of adults with chronic, accelerated, or myeloid or lymphoid blast phase CML with resistance or intolerance to prior therapy including Imatinib.

Available Forms: 50 mg or 100 mg tablets

Administration: The recommended starting dosage of Dasatinib for chronic phase CML is 100 mg administered orally once daily. Tablets should not be crushed or cut; they should be swallowed whole. Dasatinib can be taken with or without a meal, either in the morning or in the evening. In clinical studies, treatment with Dasatinib was continued until disease progression or until no longer tolerated by the patient. The effect of stopping treatment after the achievement of a complete cytogenetic response (CCyR) has not been investigated.

Toxicity: Myelosuppression, bleeding related events, fluid retention and QT prolongation

8.2.3. Nilotinib: Nilotinib is indicated for the treatment of adult patients with newly diagnosed Philadelphia chromosome positive (Ph+) CML in chronic phase.

Available Forms: 150 mg red opaque hard gelatin capsules with black axial imprint and 200 mg light-yellow opaque hard gelatin capsules with a red axial imprint.

Administration: Nilotinib should be taken twice daily at approximately 12-hour intervals and must be taken on an empty stomach. The bioavailability of Nilotinib is increased with food; therefore, no food should be consumed for at least 2 hours before the dose is taken and for at least 1 hour after the dose is taken. Patients should be advised to swallow the capsules whole with water. The recommended dose of Nilotinib for newly diagnosed Ph+ CML CP patients is 300 mg orally twice daily. The recommended dose of Nilotinib for resistant or intolerant PH+ CML CP and CML AP patients is 400 mg orally twice daily.

Contraindications: Nilotinib is contraindicated in patients with hypokalemia, hypomagnesemia, or long QT syndrome. Concomitant use of strong CYP3A4 inhibitors has been known to cause QT interval prolongation; therefore, concomitant use of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) and grapefruit products should be avoided.

Toxicity: Myelosuppression, QT prolongation, sudden deaths, cardiac and arterial vascular occlusive events, pancreatitis and elevated serum lipase, hepatotoxicity, and electrolyte abnormalities. The use of Nilotinib can also cause hypophosphatemia, hypokalemia, hyperkalemia, hypocalcemia, and hyponatremia, hepatic impairment, tumor lysis syndrome, hemorrhage, total gastrectomy, and/or lactose intolerance.

. **8.2.4. Bosutinib:** Bosutinib is indicated for the treatment of adult patients with chronic, accelerated, or blast phase Philadelphia chromosome–positive (Ph+) CML with resistance or intolerance to prior therapy.

Available Forms: **100 mg and 500 mg tablets**

Administration: The recommended dose of Bosutinib is 500 mg orally once daily with food. Dose escalation to 600 mg daily should be considered in patients who do not reach complete hematologic response by week 8 or complete cytogenetic response by week 12 and do not have Grade 3 or greater adverse reactions. Dosage should be adjusted for toxicity and organ impairment.

Contraindications: In patients with a history of hypersensitivity to Bosutinib, anaphylaxis reactions of occurred. Anaphylactic shock occurred in less than 0.2% of treated patients in clinical trials. Concurrent use of strong or moderate CYP3A inhibitors or inducers should be avoided. The use of proton pump inhibitors may decrease Bosutinib drug levels; therefore, short acting antacids should be considered in place of proton pump inhibitors.

Most common adverse reactions (incidence ≥20%): diarrhea, nausea, thrombocytopenia, rash, vomiting, abdominal pain, respiratory tract infections, anemia, pyrexia, liver test abnormalities, fatigue, cough, and headache**.**

Toxicity Management:

- Gastrointestinal Toxicity: Monitor and manage, as necessary. If appropriate, withhold, reduce dose of, or discontinue Bosutinib.
- Myelosuppression: Monitor blood counts and manage, as necessary.
- Hepatic Toxicity: Monitor liver enzymes at least monthly for the first three months and as needed. If appropriate, withhold, reduce dose of, or discontinue Bosutinib.
- Fluid Retention: Monitor and manage using standard of care treatment. If appropriate, withhold, reduce dose of, or discontinue Bosutinib.
- Renal Toxicity: Monitor renal function at baseline and during therapy with Bosutinib.
- Embryo Fetal Toxicity: Females of reproductive potential should avoid becoming pregnant while being treated with Bosutinib, as it may cause fetal harm.

9.0. LABORATORY STUDIES:

The following laboratory studies listed below will be completed at time points specified in Section 7.0.

9.1. BCR-ABL p210 PCR test.

Objective response versus stable disease will be monitored on/about Month 3, 6, 9 and 12 time period during Year 1 and Month 15, 18, 21 and 24 time periods during the Year 2. We will use *BCR-ABL* p210 gene rearrangement assay by quantitative PCR at screening visit, on/about Month 3, 6, 9 and 12 during Year 1

and Month 15, 18, 21 and 24 during Year 2. This is a standard of care assay and will be executed through available laboratories at HMC.

9.2. Correlative Studies.

The following correlative studies will be studied through the laboratories of Drs. Prabhu and Paulson at University Park at Penn State University at screening visit, on/about Month 3, 6, 9 and 12 during Year 1 and Month 18 and 24 during Year 2: The research blood processing refers to the PSCI-17-085 lab manual. Differential expression of genes and modulated pathways in CML leukemic progenitors will be studied. Specifically, *in vivo* correlation by measurement of PG isoforms, omega-3 index and SPMs will be studied.

10.0 ADVERSE EVENT REPORTING

AE collection will be initiated at the time of the first dose of GoldAID EPA. Any AEs occurring following study registration but prior to initiation of the investigational medication (Day 1) will be reported as medical history.

For the Phase I portion, all AEs that are not related to the underlying disease, will be assessed and entered in the study database. : Lab and test abnormalities that are >/= grade 2 or higher regardless of clinical significance will be assessed and entered into the study database. The period of time for AE collection will be from the time of initiation of the study medication to 30 days after last dose of study medication.

In the Phase II portion, disease progression will not be recorded as an AE. Any non-serious AEs that continue when the subject has completed the specified AE collection time period will be identified as ongoing and no end date will be identified. SAEs will be followed until resolution or until an off study criterion is met (whichever occurs first).

Adverse events will be recorded and entered into the database individually, except when considered manifestations of a medical condition or disease state. When such a diagnosis is made, all related signs, symptoms, and any test findings will be recorded collectively as a single diagnosis. A precise medical diagnosis will be recorded, whenever possible.

When known, the onset and end dates, duration, overall action taken regarding study drug (e.g. supportive medication given, dose decreased, medication discontinued, etc.), and outcome for each AE should be recorded on the source documentation and entered in the study database. The expectedness and relationship of each AE to study drug and/or study procedures, and the severity and seriousness of each AE, as judged by the PI is described below.

10.1. AE Characteristics

The NCI CTCAE, version 5.0, will be used to determine AE terms, definitions and grades for AE reporting. A copy can be downloaded from the CTEP website: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Expectedness of the AE:

AEs will be identified in the database as ‘unexpected’ or ‘expected’

Attribution of the AE:

The relationship of AE to study medication will be defined 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.

10.2. Serious AE Reporting Procedures

An SAE is defined as an AE that occurs and results in ANY of the following outcomes:

- Death.
- A life-threatening adverse drug experience. An AE or suspected adverse reaction is considered "life-threatening" if, in the view of the PI, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected AE that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization. Emergency room visits that do not result in admission to the hospital are not SAEs unless they meet one of the other criteria noted. Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) should not be recorded as an AE or SAE.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly or birth defect.
- Important medical events (IME) that may not result in death, be life-threatening, or require hospitalization may be considered a SAE when, based upon medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

The clinical research staff and Regulatory Associates of PSCI CTO will coordinate the reporting process between the sponsor-investigator and IRB. Copies of all correspondence and reporting documents will be maintained in the protocol specific regulatory binder maintained in the PSCI CTO. The SAEs must report to the sponsor-investigator within 24 hours of knowledge SAEs.

10.3. Required AEs Reporting

10.3.1 Reporting Adverse Reactions and Unanticipated Problems to the IRB

In accordance with applicable policies of The Pennsylvania State University Institutional Review Board (IRB), the PI or designated physician Sub-I will report to the IRB any observed or reported harm (i.e. AE) experienced by a subject or other individual. This includes those SAEs which in the opinion of the PI are determined to be unanticipated, i.e. unexpected and possibly, probably, or definitely related to the research medication. AEs of this nature as well as SAEs will be reported to the IRB within 5 business days in accordance with the IRB policies and procedures as noted in the Investigators Manual.

10.3.2 Reporting Adverse Reactions and Unanticipated Problems to the FDA

As the study Sponsor, the PI will be responsible for notifying the FDA of certain unanticipated events. Unexpected and related (possibly, probably, definitely) fatal or life-threatening events require reporting to the FDA within 7 days of study teams notification of the event. A written follow-up must be provided within 15 calendar days after becoming aware of the event, when necessary. Those SAEs that are not life threatening or fatal must be reported within 15 calendar days of becoming aware of the event.

All safety reports to the FDA must be submitted on a MedWatch Form (Form FDA 3500A) and be accompanied by the Investigational New Drug Application (IND) (Form FDA1571). The type of report (initial or follow-up) should be checked in the respective boxes on each form. The submission must be identified as:

- "IND safety report" for 15-day reports, or
- "7-day IND safety report" for unexpected fatal or life-threatening suspected adverse reaction reports, or
- "Follow-up IND safety report" for follow-up information.

The report must be submitted to the designated FDA reviewer(s) at the Center for Drug Evaluation and Research (CDER) that has the responsibility to review the IND application under which the safety report is submitted. FDA recommends that safety reports are submitted electronically through the FDA system. Other means of rapid communication to the respective review division's Regulatory Project Manager (e.g., telephone, facsimile transmission, email) may also be used.

10.3.3 Reporting SAEs to Solutex, Inc.

Solutex, the manufacturer of the study medication will be notified of any unanticipated (serious, unexpected, and related to the GoldAID EPA– possibly, probably, definitely) SAE within 72 hours of becoming aware of the event. A copy of MedWatch 3500A will be provided to Solutex, Inc. representative Julio Boza, General Manager, Azur Global Nutrition, email: jboza@azur-gn.com.

11. DATA REPORTING, REGULATORY REQUIREMENTS AND CONFIDENTIALITY

11.1. Confidentiality of Records: The original data collection forms will be stored in Oncore, a highly secure, web-based, CTMS. Any research related paper documents will be stored in the limited access, locked PSCI CTO. Institutional policies and guidance outlining the requirements for managing appropriate levels of safeguard to ensure the confidentiality, integrity and availability of clinical research data will be followed.

Subjects will be identified using a protocol specific unique patient identification number in all reports (e.g., statistical analyses, DSMC reports, annual reports to Solutex and the IRB, SAE reports). The corresponding name "key" for this unique code will be maintained in the OnCore system. A copy of the annual continuing review report submitted to the IRB will be provided to Solutex for the purposes of providing updates on the overall status of the study. A mutually agreed upon contractual agreement will be in place to allow for this transfer of information.

11.2. Informed Consent:

Prior to commencement of any screening activities, written, signed and dated informed consent must be obtained. A copy of the signed and dated informed consent form must be provided to the subject. The original signed consent form will be filed in the subject's research chart. Additionally, a copy of the signed consent form will be maintained in the protocol specific regulatory files, as well as, uploaded in the Cerner electronic medical record per institutional standards.

11.3. Registration Eligibility Checklist:

At the time of registration, the information requested on the Eligibility Checklist will be completed. Confirmation of eligibility will be confirmed by CI CTO research team members. A second verification of the eligibility should be completed by another research team member but is not required in the event that a second team member is not available. The PI will review and sign the completed Eligibility Checklist as confirmation that only those subjects who have met protocol

eligibility criteria are enrolled on the study.

11.4. Data Collection and Submission Schedule:

Study management activity and research data will be entered and stored in the Cancer Institute Oncore CTMS. Data will be entered into OnCore® which was developed by Forte, Inc., and is a highly secure, web-based, customizable system that provides fully integrated statistical data management capabilities.

The data to be collected and transcribed into the OnCore database will include but is not limited to those required for the primary and secondary objectives. In addition, demographics, safety data, prior and concomitant medication use, and past medical history will be transcribed into the database. Eligibility assessment will be coded as "met" or "not met" with reason(s) explaining why the subject was ineligible. Information related to general assessments including but not limited to dates and results of physical exams, vital signs, ECOG PS, laboratory values and weight will not be entered into the database. However, any abnormal results of the assessments will be captured as an AE according to the criteria noted in Section 10.0. For those who consent but are not eligible (screen failure) only data related to failure reason and demography will be captured.

The resultant data collected will be approved by the PI or designated physician Sub-I. Evidence of the PI/Sub-I review and approval may be done electronically in the OnCore CTMS or in a paper document format. This approval acknowledges the PI's review and acceptance of the data as being, to the best of her knowledge, complete, accurate, and up to the date.

11.5. Protocol Non-Compliance and Deviations

A protocol departure is any non-compliance with the clinical trial protocol, ICH GCP, or federal and local regulations. Non-compliance may be either on the part of the subject, the PIs or Sub-Is, or the study site staff. As a result of protocol deviations within the control of the study staff, corrective actions must be developed and subsequently implemented. Reporting of protocol non-compliance to the IRB will be completed as directed in the Penn State IRB *Investigator Manual*. A Log will be maintained in the OnCore system identifying the protocol departures. Study subjects will be notified of any significant departure. Documentation of the departure and the notification discussion with the subject will be included in the subject's research record.

11.6 Data Safety Monitoring Plan

The Penn State Hershey Cancer Institute Data and Safety Monitoring Committee (PSCI DSMC) will serve as the internal DSMC for data and safety review for this protocol. The principal investigator (PI) will continuously monitor study progress for safety and will hold routine meetings with the study team and disease center personnel to review overall conduct and progress of this study. The frequency of such meetings will be dependent upon accrual to the trial and issues that arise. Study team and disease team meetings will include discussion of accrual, adverse events/safety issues, response and overall progress of the trial.

The DSMC will review all data prior to each DLT review for dose escalation. The DSMC will determine if the next cohort will be opened, expanded, de-escalated or the protocol be placed on hold. Additionally all exception and/or prospective deviations must be approved by the DSMC prior to execution. On an annual basis, the PI will provide the PSCI DSMC with reports showing the number of subjects enrolled, SAE assessments, information on any protocol deviations or breaches of confidentiality, response if appropriate, and overall status of the trial. The PSCI DSMC meets quarterly as well as on an ad hoc basis. The investigator will be asked for a report for the DSMC sufficiently in advance of annual IRB renewal in order to include DSMC findings with annual IRB submission. Adverse event reporting to the IRB will occur in compliance with IRB guidelines. A summary of all adverse events will be reported to

the IRB annually; unexpected adverse events will be reported as they arise as well as any significant literature reporting developments that may affect the safety of participants in this study. Serious and unexpected adverse events will be reported to PSCI DMSC simultaneously with the IRB reporting.

11.7 Audit and Inspection

Applicable federal, state and local entities may request an audit or inspection at any time. The PI will ensure all requested documentation is provided to auditors and inspectors, including appropriate access to the study database, source documentation and Case Report Forms (CRFs).

11.8 Study Monitoring

It is the responsibility of the PI to ensure that this study is conducted and that the data are generated, documented (recorded) and reported in compliance with this protocol, with institutional and IRB policies, with Good Clinical Practice guidelines and with any other applicable regulatory requirements. The study will be monitored by the Clinical Trial Monitoring Team from the Department of Public Health Sciences at Penn State Hershey College of Medicine. The monitors will provide an independent review of the subject records, regulatory records and the data collected to assure compliance with the protocol, GCP, and applicable local and federal regulations. The monitoring will occur at regular intervals after the enrollment of the first subject predetermined by the monitoring plan developed by the Clinical Trial Monitoring Team.

11.9. Records Retention:

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harmonization (ICH) region and until there are no pending or contemplated marketing applications or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations.

12.0. STATISTICAL CONSIDERATIONS

Study Design/Endpoints: The primary *efficacy* endpoint is the one-year response rate, where response is defined as a one-log decrease (improvement) in *BCR-ABL* p210 transcript level, as measured by RT-qPCR. Single stage design will be used for the Phase II portion of the study based on the assumption that the complete molecular response rate is 25% for subjects on TKI alone vs. 50% for TKI + GoldAID EPA. The design involves a maximum of n = 30 subjects, has a type I error rate (α) of 0.05, and provides statistical power $\geq$ 80% when the response rate for subjects on the combination therapy of TKI and GoldAID EPA is at least 50%. Assuming a 10% drop-out rate, a total of n = 34 subjects will be enrolled. An interim analysis for excess toxicity will be performed based on the presence of DLTs and their grades. In brief, once half of the phase II cohort has been accrued (n = 17), the proportion of patients exhibiting DLTs greater than grade 2 will be computed. We will suspend the trial if n = 3 or more patients exhibit a DLT of grade greater than 2 in the interim analysis. This stopping threshold corresponds to approximately 18% of the number of accrued patients at the time of the interim analysis and is within the FDA's suggested range (15% - 25%).

In the *in vivo* studies, Spearman rank correlations will be used to quantify associations between *BCR-ABL* p210 transcript levels and serum D12-PGJ3, the oxidation product 13, 14-dihydro 15-keto-PGJ3, and metabolites including COX-1 and COX-2. For the studies involving cryopreserved peripheral blood cells, the normality of the expression levels of p53 and other pro-apoptotic and anti-apoptotic genes will be assessed. Repeated measures ANOVA models will be used to compare the effect of multiple D12-PGJ3 treatment levels on expression levels at multiple time points depending on whether the expression levels are normally distributed or can be appropriately

transformed; otherwise, non-parametric methods will be applied. One-way ANOVA or Kruskal-Wallis tests will be used to compare the effect of D12-PGJ3 concentrations on expression levels at any fixed time point and also in the colony formation assays depending on whether or not the normality assumptions hold. Because of the exploratory nature of the study, no correction for multiple testing will be performed. R and SAS (Cary, NC) will be used to perform all data analyses.

13.0 SHARING STUDY RESULTS

13.1 Study Subjects

Results will be shared with subjects upon request at the completion of the trial in the form of the final publication when publically available.

13.2 Solutex, Inc.

Solutex, Inc. is the manufacturer of the study medication. As a result of this relationship, a contractual agreement will be in place for this study between Penn State Hershey Cancer Institute and Solutex. Results of the study will be shared with Solutex. In order to protect confidentiality, subjects will be identified by a unique code number only. .

14.0 SUBJECT STIPEND (COMPENSATION) AND/OR TRAVEL REIMBURSEMENTS

Subjects will not receive any compensation for taking part in this study. The investigational medication, GoldAID EPA, will be provided to them at no cost.

15.0 COMPENSATION FOR RESEARCH-RELATED INJURY

It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Costs for the treatment of research-related injuries will be charged to subjects or their insurance carriers.

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APPENDIX A: ECOG PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale	
Grade	**Descriptions**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B. GOLDAID EPA STABILITY STUDY DATA, TDS AND COA

Stability Study Design

Interval	RT	25°/60%RH	40°C/75%RH
T0	XZ	--	--
3-month	--	XZ	XZ
6-month	--	XZ	XZ
9-month	--	XZ	--
12-month	--	XZ	--
18-month	--	XZ	--
24-month	--	XZ	--
36-month	--	XZ	--

RT = Ambient Room Temperature
X indicates that all Chemistry testing will be performed.
Z indicates that Microbial Limits testing will be performed.
(X) indicates that Chemistry testing will only be performed in the event of a failure at 40°C/75%RH.
(Z) indicates that Microbial Limits testing will only be performed in the event of a failure at 40°C/75%RH.

Stability data of final product GOLDAID EPA at 25ºC ± 2ºC, 60/+5% RH

Test	Analytical method	Specification	T0	T1 (3-month)	T2 (6-month)
Appearance	Visual	Homogeneous liquid	Pass	Pass	Pass
EPA-TG	Internal	Min3000 mg /dose	3190	3085	3073
Total Omega-3-TG	Internal	Min. 3320 mg /dose	3640	3520	3496
pH	Internal	Report	5.9	5.7	5.3
Total Plate Count	Eur. Ph. 2.6.12	NMT 10.000 cfu/g	<10	<10	<10
Yeast and Molds	Eur. Ph. 2.6.12	NMT 100 cfu/g	<10	<10	<10
Bacteria Gram Negative	Eur. Ph. 2.6.12	NMT 100 cfu/g	<10	<10	<10
E. coli	Eur. Ph. 2.6.12	Absent	Absent	Absent	Absent
S. aureus	Eur. Ph. 2.6.12	Absent	Absent	Absent	Absent
Salmonella spp	Eur. Ph. 2.6.12	Absent	Absent	Absent	Absent

Stability data of final product GOLDAID EPA at 40ºC ± 2ºC, 75 ±5% RH

Test	Analytical method	Specification	T0	T1 (3-month)	T2 (6-month)
Appearance	Visual	Homogeneous liquid	Pass	Pass	Pass
EPA-TG	Internal	Min3000 mg /dose	3190	3078	3072
Total Omega-3-TG	Internal	Min. 3320 mg /dose	3640	3515	3495
pH	Internal	Report	5.9	5.4	5.6
Total Plate Count	Eur. Ph. 2.6.12	NMT 10.000 cfu/g	<10	<10	<10
Yeast and Molds	Eur. Ph. 2.6.12	NMT 100 cfu/g	<10	<10	<10
Bacteria Gram Negative	Eur. Ph. 2.6.12	NMT 100 cfu/g	<10	<10	<10
E. coli	Eur. Ph. 2.6.12	Absent	Absent	Absent	Absent
S. aureus	Eur. Ph. 2.6.12	Absent	Absent	Absent	Absent
Salmonella spp	Eur. Ph. 2.6.12	Absent	Absent	Absent	Absent

Solutex®
Delivering TailorMade Value

TECHNICAL DATA SHEET

Product name: **GOLDaid® EPA**
Product description: SolutexE2EPA18TG Oral Lipidic Emulsion
Reference: 30.033
Observations: Sachet of 20 ml
Shelf life / retest period: 18 months

General Information	
Appearance	Liquid emulsion, pinky coloured, strawberry and berries flavoured and with slightly fishy note
General information	Homogeneous fluid emulsion. Sachet of 20 ml (20.1 g)

DETERMINATIONS	SPECIFICATION	METHOD
Fatty Acid Profile		
EPA mg/sachet (as TG)	Min. 3000	Internal
Total Omega-3 mg/sachet (as TG)*	Min. 3320	Internal
*(Sum of 18:3 ω3, 18:4 ω3, 20:4 ω3, 20:5 ω3, 21:5 ω3, 22:5 ω3, 22:6 ω3)		
Contaminant Data		
Arsenic (mg/kg)	Max. 0.1	AOAC 986.15
Cadmium(mg/kg)	Max. 0.1	AOCS Ca18d-01
Lead (mg/kg)	Max. 0.1	AOCS Ca18c-91
Mercury (mg/kg)	Max. 0.1	AOAC971.21
Contaminant Data		
Total Aerobic Microbial Count (CFU/g)	Max. 10^4	Eur. Ph. 2.6.12
Total combined Yeasts/Moulds Count (CFU/g)	Max. 10^2	Eur. Ph. 2.6.12
Bacteria Gram negative (CFU/g)	Max. 10^2	Eur. Ph. 2.6.12
Escherichia coli (Absent/g)	Absent	Eur. Ph. 2.6.13
Staphylococcus aureus (Absent/g)	Absent	Eur. Ph. 2.6.13
Salmonella spp. (Absent/10g)	Absent	Eur. Ph. 2.6.13

This product is in accordance with the European legislation and does not contain any GMO.

Storage
Shelf life can be guaranteed if the oil is kept in the original unopened sealed container, protected from light and heat

QA Manager:

TDS 30.033	Revision date: 25-Jul-2018	Rev. 5

www.solutex.es

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CERTIFICATE OF ANALYSIS

Product Name:	**GOLDaid® EPA**	Product Reference: 30.03 3	TDS Rev: 5
Product Description:	SolutexE2EPA18TG Oral Lipidic Emulsion Sachet of 20 ml		Coa Rev: 2
Observations:			
Lot:	00003181		
Manufacturing Date:			

General Description	
Appearance:	Liquid emulsion, pinky coloured, strawberry and with slightly fishy note and berries flavoured
General Information:	Homogeneo us fluid emulsion. Sachet of 20 ml (20.1 g)

This product is in accordance with the European legislation and does not contain any GMO.

DETERMINATIONS	Storage	SPECIFICATION	RESULT	METHOD
Fatty Acid Profile				
EPA mg/sachet (as TG)		Min. 3000	3190	Internal
Total Omega-3 mg/sachet (as TG)* • (Sum of 18:3 *w* 3; t8:4 *w* 3, 20:4 *w* 3, 20:5 *w*3, 21:5 *w* 3, 22:5 *w* 3, 22:6 *w* 3)		Min. 3320	3640	Internal
Contaminant Data				
Arsenic (mg/kg)		Max. 0.1	<0.05	AOAC 986.15
Cadmium (mg/kg)		Max. 0.1	0.04	AOCS Ca18d-01
Lead (mg/kg)		Max. 0.1	<0.025	AOCS Ca18c-91
Mercury (mg/kg)		Max. 0.1	<0.10	AOAC 971.21
Microbial Contaminants				
Total Aerobic Microbial Count (CFU/g)		Max. 10^4	<10	Eur. Ph. 2.6.12
Total combined yeasts/moulds count (CFU/g)		Max. 10:1	<10	Eur. Ph. 2.6.12
Bacteria Gram negative (CFU/g)		Max. 10:1	< 10	Eur. Ph. 2.6.12
Escherichia coli (Absent/g)		Absent	Conforms	Eur. Ph. 2.6.13
Staphylococcus aureus (Ab$ent/g)		Absent	Conforms	Eur. Ph. 2.6.13
Salmonellaspp. (Absent/g)		Absent	Conforms	Eur. Ph. 2.6.13

Shelf life can be guaranteed if the oil is kept in the original unopened sealed container, protected from light and heat	17 - Jan - 2018 Shelf Life/ Retest Period: Jul-2019

F/QA-11/01
Rev 1

Date: 18-Jan-2019
QA Approval:

APPENDIX C. FDA APPROVED LABELS FOR TKI USE:

Imatinib: GLEEVEC (imatinib mesylate) tablets for oral use Initial U.S. Approval: 2001

INDICATIONS AND USAGE: Gleevec is a kinase inhibitor indicated for the treatment of: Newly diagnosed adult patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase. Follow-up is limited to 5 years • Patients with Ph+ CML in blast crisis (BC), accelerated phase (AP), or in chronic phase (CP) after failure of interferon-alpha therapy • Pediatric patients with Ph+ CML in chronic phase who are newly diagnosed or whose disease has recurred after stem cell transplant or who are resistant to interferon-alpha therapy. There are no controlled trials in pediatric patients demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival • Adult patients with relapsed or refractory Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) • Adult patients with myelodysplastic/ myeloproliferative diseases (MDS/MPD) associated with PDGFR (platelet-derived growth factor receptor) gene re-arrangements • Adult patients with aggressive systemic mastocytosis (ASM) without the D816V c-Kit mutation or with cKit mutational status unknown • Adult patients with hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) who have the FIP1L1-PDGFRα fusion kinase (mutational analysis or FISH demonstration of CHIC2 allele deletion) and for patients with HES and/or CEL who are FIP1L1-PDGFRα fusion kinase negative or unknown • Adult patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans (DFSP) • Patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST).

DOSAGE AND ADMINISTRATION• Adults with Ph+ CML CP : 400 mg/day • Adults with Ph+ CML AP or BC : 600 mg/day • Pediatrics with Ph+ CML CP : 340 mg/m2 /day • Adults with Ph+ ALL (2.4): 600 mg/day • Pediatrics with Ph+ ALL : 340 mg/m2 /day • Adults with MDS/MPD : 400 mg/day • Adults with ASM : 100 mg/day or 400 mg/day • Adults with HES/CEL .: 100 mg/day or 400 mg/day • Adults with DFSP : 800 mg/day • Adults with metastatic and/or unresectable GIST : 400 mg/day • Adjuvant treatment of adults with GIST : 400 mg/day • Patients with mild to moderate hepatic impairment : 400 mg/day • Patients with severe hepatic impairment : 300 mg/day All doses of Gleevec should be taken with a meal and a large glass of water. Doses of 400 mg or 600 mg should be administered once daily, whereas a dose of 800 mg should be administered as 400 mg twice a day. Gleevec can be dissolved in water or apple juice for patients having difficulty swallowing. Daily dosing of 800 mg and above should be accomplished using the 400 mg tablet to reduce exposure to iron.

DOSAGE FORMS AND STRENGTHS: Tablets (scored): 100 mg and 400 mg

CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS • Edema and severe fluid retention have occurred. Weigh patients regularly and manage unexpected rapid weight gain by drug interruption and diuretics • Cytopenias, particularly anemia, neutropenia, and thrombocytopenia, have occurred. Manage with dose reduction or dose interruption and in rare cases discontinuation of treatment. Perform complete blood counts weekly for the first month, biweekly for the second month, and periodically thereafter • Severe congestive heart failure and left ventricular dysfunction have been reported, particularly in patients with comorbidities and risk factors. Monitor and treat patients with cardiac disease or risk factors for cardiac failure • Severe hepatotoxicity including fatalities may occur. Assess liver function before initiation of treatment and monthly thereafter or as clinically indicated. Monitor liver function when combined with chemotherapy known to be associated with liver dysfunction, Grade 3/4 hemorrhage has been reported in clinical studies in patients with newly diagnosed CML and with

GIST. GI tumor sites may be the source of GI bleeds in GIST • Gastrointestinal perforations, some fatal, have been reported • Cardiogenic shock/left ventricular dysfunction has been associated with the initiation of Gleevec in patients with conditions associated with high eosinophil levels (e.g., HES, MDS/MPD and ASM) • Bullous dermatologic reactions (e.g., erythema multiforme and Stevens-Johnson syndrome) have been reported with the use of Gleevec • Hypothyroidism has been reported in thyroidectomy patients undergoing levothyroxine replacement. Closely monitor TSH levels in such patients • Fetal harm can occur when administered to a pregnant woman. Apprise women of the potential harm to the fetus, and to avoid pregnancy when taking Gleevec • Growth retardation occurring in children and pre-adolescents receiving Gleevec has been reported. Close monitoring of growth in children under Gleevec treatment is recommended. Tumor lysis syndrome. Close monitoring is recommended • Reports of motor vehicle accidents have been received in patients receiving Gleevec. Caution patients about driving a car or operating machinery

ADVERSE REACTIONS: The most frequently reported adverse reactions (greater than or equal to 30%) were edema, nausea, vomiting, muscle cramps, musculoskeletal pain, diarrhea, rash, fatigue and abdominal pain.

DRUG INTERACTIONS• CYP3A4 inducers may decrease Gleevec Cmax and AUC • CYP3A4 inhibitors may increase Gleevec Cmax and AUC • Gleevec is an inhibitor of CYP3A4 and CYP2D6 which may increase the Cmax and AUC of other drugs. • Patients who require anticoagulation should receive low-molecular weight or standard heparin and not warfarin.

SPRYCEL® (dasatinib)

Tablet for Oral Use Initial U.S. Approval: 2006

RECENT MAJOR CHANGES Indications and Usage 10/2010

Dosage Adjustment for Adverse Reactions

Warnings and Precautions, Bleeding Related Events 10/2010 Congestive Heart Failure, Left Ventricular Dysfunction, and Myocardial Infarction 10/2010

INDICATIONS AND USAGE: SPRYCEL is a kinase inhibitor indicated for the treatment of newly diagnosed adults with Ph+CML in chronic phase. The trial is ongoing and further data will be required to determine long-term outcome. Adults with chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy including imatinib. Adults with Philadelphia chromosome-positive ALL (Ph+ ALL) with resistance or intolerance to prior therapy.

DOSAGE AND ADMINISTRATION • Chronic phase CML: 100 mg once daily. Accelerated phase CML, myeloid or lymphoid blast phase CML, or Ph+ ALL: 140 mg once daily. Administered orally, with or without a meal. Tablets should not be crushed or cut.

DOSAGE FORMS/STRENGTHS: Tablets: 20 mg, 50 mg, 70 mg, 80 mg, 100 mg, and 140 mg.

CONTRAINDICATIONS: None.

Tasigna® (nilotinib) Capsules

Initial U.S. Approval: 2007

WARNING: QT PROLONGATION AND SUDDEN DEATHS See full prescribing information for complete boxed warning. Tasigna prolongs the QT interval. Sudden deaths have been reported in patients receiving nilotinib. Tasigna should not be used in patients with hypokalemia, hypomagnesemia, or long QT syndrome. Hypokalemia or hypomagnesemia must be corrected prior to Tasigna administration and should be periodically monitored. Drugs known to prolong the QT

interval and strong CYP3A4 inhibitors should be avoided. Patients should avoid food 2 hours before and 1 hour after taking dose. A dose reduction is recommended in patients with hepatic impairment. ECGs should be obtained to monitor the QTc at baseline, seven days after initiation, and periodically thereafter, as well as following any dose adjustments.

RECENT MAJOR CHANGES

Indications and usage: Newly diagnosed Ph+ CML-CP 06/2010 Dosage and administration: Recommended Dosing, Dose Adjustments or Modifications 06/2010 Warnings and precautions: myelosuppression, sudden deaths, elevated serum lipase, total gastrectomy 06/2010

INDICATIONS AND USAGE

Treatment of newly diagnosed adult patients with Philadelphia chromosome positive CML (Ph+ CML) in chronic phase. The study is ongoing and further data will be required to determine long-term outcome. (1.1) Treatment of chronic phase (CP) and accelerated phase (AP) Ph+ CML in adult patients resistant to or intolerant to prior therapy that included imatinib. Clinical benefit, such as improvement in disease-related symptoms or increased survival, has not been demonstrated.

DOSAGE AND ADMINISTRATION • Recommended Dose: Newly diagnosed Ph+ CML-CP: 300 mg orally twice daily. Resistant or intolerant Ph+ CML-CP and CML-AP: 400 mg orally twice daily Administer Tasigna approximately 12 hours apart and must not take with food. • Swallow the capsules whole with water. Do not consume food for at least 2 hours before the dose is taken and for at least one hour after. • Dose adjustment may be required for hematologic and non-hematologic toxicities, and drug interactions. • A lower starting dose is recommended in patients with hepatic impairment (at baseline).

DOSAGE FORMS AND STRENGTHS: 150 mg and 200 mg hard capsules

CONTRAINDICATIONS: Do not use in patients with hypokalemia, hypomagnesemia, or long QT syndrome.

WARNINGS AND PRECAUTIONS • Myelosuppression: Associated with neutropenia, thrombocytopenia and anemia. CBC should be done every 2 weeks for the first 2 months, then monthly. Reversible by withholding dose. Dose reduction may be required. • QT Prolongation: Tasigna prolongs the QT interval. Correct hypokalemia or hypomagnesemia prior to administration and monitor periodically. Avoid drugs known to prolong the QT interval and strong CYP3A4 inhibitors. Use caution in patients with hepatic impairment. Obtain ECGs at baseline, seven days after initiation, and periodically thereafter, as well as following any dose adjustments. • Sudden deaths: Sudden deaths have been reported in patients with resistant or intolerant Ph+ CML receiving nilotinib. Ventricular repolarization abnormalities may have contributed to their occurrence. • Elevated serum lipase: Check serum lipase periodically. In case lipase elevations are accompanied by abdominal symptoms, interrupt doses and consider appropriate diagnostics to exclude pancreatitis. Caution is recommended in patients with history of pancreatitis. • Liver function abnormality: Tasigna may result in elevations in bilirubin, AST/ALT, and alkaline phosphatase. Check hepatic function tests periodically. • Electrolyte abnormalities: Tasigna can cause hypophosphatemia, hypokalemia, hyperkalemia, hypocalcemia, and hyponatremia. Correct electrolyte abnormalities prior to initiating Tasigna and monitor periodically during therapy. • Hepatic impairment: Nilotinib exposure is increased in patients with impaired hepatic function. A dose reduction is recommended in these patients and QT interval should be monitored closely. • Drug interactions: Avoid concomitant use of strong inhibitors or inducers of CYP3A4. If patients must be co-administered a strong CYP3A4 inhibitor, dose reduction should be considered and the QT interval should be monitored closely. • Food Effects: Food increases blood levels of Tasigna. • Avoid food 2 hours before and 1

hour after a dose. • Total Gastrectomy: More frequent follow-up of these patients should be considered. If necessary, dose increase may be considered. • Pregnancy: Fetal harm can occur when administered to a pregnant woman. Women should be advised not to become pregnant when taking Tasigna.

ADVERSE REACTIONS: The most commonly reported non-hematologic adverse drug reactions (≥10%) in patients with newly diagnosed Ph+CML-CP, resistant or intolerant Ph+CML-CP, or resistant or intolerant Ph+CML-AP were rash, pruritus, headache, nausea, fatigue, myalgia, nasopharyngitis, constipation, diarrhea, abdominal pain, vomiting, arthralgia, pyrexia, upper urinary tract infection, back pain, cough, and asthenia. Hematologic adverse drug reactions include myelosuppression: thrombocytopenia, neutropenia and anemia.

DRUG INTERACTIONS: Tasigna is an inhibitor of CYP3A4, CYP2C8, CYP2C9, and CYP2D6. It may also induce CYP2B6, CYP2C8 and CYP2C9. Therefore, Tasigna may alter serum concentration of other drugs CYP3A4 inhibitors may affect serum concentration (7.2) CYP3A4 inducers may affect serum concentration

USE IN SPECIFIC POPULATIONS: Sexually active female patients should use effective contraception during treatment. Should not breast-feed. No data to support use in pediatrics. A lower starting dose is recommended in patients with hepatic impairment.

BOSULIF. BOSULIF® (bosutinib) tablets, for oral use Initial U.S. Approval:

INDICATIONS AND USAGE BOSULIF is a kinase inhibitor indicated for the treatment of adult patients with chronic, accelerated, or blast phase Ph+ CML with resistance or intolerance to prior therapy.

DOSAGE AND ADMINISTRATION • Recommended Dose: 500 mg orally once daily with food. Consider dose escalation to 600 mg daily in patients who do not reach complete hematologic response by week 8 or complete cytogenetic response by week 12 and do not have Grade 3 or greater adverse reactions. Adjust dosage for hematologic and non-hematologic toxicity. Hepatic impairment (at baseline): reduce BOSULIF dose to 200 mg daily.

DOSAGE FORMS AND STRENGTHS: Tablets: 100 mg and 500 mg.

CONTRAINDICATIONS: Hypersensitivity to BOSULIF.

WARNINGS AND PRECAUTIONS • Gastrointestinal toxicity: Monitor and manage as necessary. Withhold, dose reduce, or discontinue BOSULIF. • Myelosuppression: Monitor blood counts and manage as necessary. • Hepatic toxicity: Monitor liver enzymes at least monthly for the first three months and as needed. Withhold, dose reduce, or discontinue BOSULIF. • Fluid retention: Monitor patients and manage using standard of care treatment. Withhold, dose reduce, or discontinue BOSULIF. • Embryo-fetal toxicity: May cause fetal harm. Females of reproductive potential should avoid becoming pregnant while being treated with BOSULIF.

ADVERSE REACTIONS: Most common adverse reactions (incidence greater than 20%) are diarrhea, nausea, thrombocytopenia, vomiting, abdominal pain, rash, anemia, pyrexia, and fatigue.

DRUG INTERACTIONS• CYP3A Inhibitors and Inducers: Avoid concurrent use of BOSULIF with strong or moderate CYP3A inhibitors and inducers. • Proton Pump Inhibitors: May decrease bosutinib drug levels.

APPENDIX D1. CRITERIA FOR EVALUATION OF SUBJECT ELIGIBILITY

BCR-ABL Level in %	*BCR-ABL* Response in log	Stable Range 1 log difference	Stable Range 1/2 log difference	MR Levels	Type of MR	Progression Range
1	-2	0.1-10	(0.32, 3.2)	MR2	<MMR	>=10
0.1	-3	0.01-1.0	(0.032, 0.32)	MR3	MMR	≥ 1.0
0.01	-4	0.001-0.1	(0.0032, 0.032)	MR4	MMR	≥ 0.1
0.003	-4.5	0.0003-0.03	(0.001, 0.01)	MR4.5	MMR	≥ 0.032
0.001	-5	0.0001-0.01	(0.0003, 0.003)	MR5	CMR	≥ 0.01

D2. CRITERIA FOR MOLECULAR RESPONSE

Initial *BCR-ABL* Level	Stable Range	Response Range	Progression Range
1.0	0.1-10	≤ 0.10	≥ 10
0.1	0.01 – 0.1	≤ 0.01	≥ 1.0
0.01	0.001 – 0.1	≤ 0.001	≥ 0.1
0.003	0.0003 – 0.03	≤ 0.0003	≥ 0.03
indeterminate	indeterminate	negative	≥ 0.003

APPENDIX E. Detailed Summary of Protocol Changes
PSCI Number: _17-085___ IRB Number: _STUDY00010945_ Principal Investigator: _Seema Naik__

Protocol Title: Effect of Omega-3 Fatty Acid, Eicosapentaenoic Acid, and its Metabolites in Combination with Tyrosine Kinase Inhibitors in Chronic Myeloid Leukemia in Stable Chronic Phase

	Version Date
FDA Approved Protocol	12-06-2019
Amended Protocol	7-6-2020

Section and page numbers are references to the (17-085 protocol VERSION dated 7-6-2020) amended protocol.

1. **<Title Page, Page Number 1>**
   Old Text: dated 12/06/2019

   New Text: dated 7/6/2020

   Rationale for change: Updating document version date

2. **<Title Page, Page Number 1; Protocol Synopsis, Page Number 4>**

   New Text: Sub-I: Myles Nickolich, MD

   Rationale for change: Dr. Myles Nickolich is a qualified hematologist/oncologist for this study.

3. **<Clinical Study Protocol Synopsis, Page Number 5; Section 3.1. Inclusion Criteria, Page Number 12>**
   Added Text: 5. Stable molecular response defined as 2 sequential BCR-ABL p210 levels done in the same lab with less than ½ log reduction of BCR-ABL p210 **3-6 months apart.**

   Rationale for change: Clarification per discussion with the study team on 6/15/2020.

4. **<Clinical Study Protocol Synopsis, Page Number 6>**
   Changed Text: 3. ~~Known~~ **Medical documented or self-reported history of** HIV, Hepatitis B, or Hepatitis C infection

   Rationale for change: Clarification from the discussion with PSCI CTO Clinical Research Nurse Educator Doris Shank on 6/2/2020.

5. **<Clinical Study Protocol Synopsis, Page Number 6; Section 3.1. Exclusion Criteria, Page Number 13>**
   Added Text: 8. **No history of active** central nervous system (CNS) leukemia.

   Rationale for change: Clarification per discussion with the study team on 6/2/2020.

6. **<Clinical Study Protocol Synopsis Endpoint, Page Number 7>**
   Changed Text: A single stage ~~Simon's optimal two-stage~~ design will be used for the Phase II portion of the study based on the assumption that the complete molecular response rate is 25% for subjects on TKI alone. The design involves a maximum of n = **30**~~24~~ subjects, has a type I error rate (α) of 0.05, and provides statistical power ≥ 80% when the response rate for subjects on the combination therapy of TKI and GoldAID EPA is at least 50%. Assuming a 10% drop-out rate, a total of n = **34**~~27~~ subjects will be enrolled in Phase II.

   Rationale for change: Clarification from the discussion with the statistician Dr. Vonn Walter Doris Shank on 6/15/2020.

7. **<Clinical Study Protocol Synopsis Endpoint, Page Number 7; Section 3.4 Sample Size, Page Number 14>**
   Changed Text: A minimum of 9 subjects and a maximum of **52** ~~45~~ subjects will be enrolled in this study (phase I and II). Once a recommended Phase 2 dose (RP2D) is established, an expanded cohort will be opened at that dose to generate an RP2D experience with a total of ~~30~~ **34** subjects (phase II).
   Rationale for change: Clarification from the discussion with the statistician Dr. Vonn Walter Doris Shank on 6/15/2020.

8. **<Acronym, Page Number 8>**
   Added Text: Hematological Response (HR)

   Rationale for change: Add missed acronyms from the protocol.

9. **<Section 4.0. Registration Procedures, Page Number 14>**
   Changed Text: Eligible subjects will be registered on study by the PSCI Clinical Trials Office (CTO) ~~by the Study Coordinator~~. ~~The subject's Eligibility Checklist will be completed in its entirety prior to registration, and source documentation verifying each eligibility criterion must be available. Subjects are considered registered on study after they are entered into the Online Collaborative Research Environment (OnCore) system as "On-Study." Every effort will be made to ensure that the s~~**S**ubject begins treatment within ~~30~~ **15** days of registration. Issues that would cause treatment delays should be discussed with the ~~PI~~ **sponsor investigator** or designated physician sub-Investigator (Sub-I) and documented in the research record.

   Rationale for change: Clarification per discussion with the study team on 6/2/2020. The study treatment should begin 15 days not 30 days after registration.

10. **<Section 5.1 Phase I Study Scheme, Page Number 15>**
    Deleted Text: ~~Phase I subjects will be included if RP2D was administered.~~

    Rationale for change: Clarification from the discussion with Dr. Vonn Walter, the statistician

of this study, on 6/4/2020, phase I subjects will not be cross-over to phase II.

11. **<Section 5.2 Progression between Dose Levels (Modified Fibonacci Scheme), Dose Adjustment due to Toxicity, and RP2D, Page Number 15; Section 12.0 Statistical consideration, Page Number 33>**
Changed Text: ~~The stopping boundaries representing a MTD of 20% with a range of 15%-25%. Thus, if more than 25% patients developed DLT more than grade 1, it will be considered stopping rule for the study.~~ **An interim analysis for excess toxicity will be performed based on the presence of DLTs and their grades. In brief, once half of the phase II cohort has been accrued (n = 17), the proportion of patients exhibiting DLTs greater than grade 2 will be computed. We will suspend the trial if n = 3 or more patients exhibit a DLT of grade greater than 2 in the interim analysis. This stopping threshold corresponds to approximately 18% of the number of accrued patients at the time of the interim analysis and is within the FDA's suggested range (15% - 25%).**

Rationale for change: Clarification from the discussion with Dr. Walter in regards to interim analysis and stopping rule in phase II, the statistician of this study, on 6/4/2020.

12. **<Section 5.3 Expanded Cohort, Page Number 16>**
Changed Text: Once the RP2D is established, the cohort will be expanded to a total of **34** ~~27~~ subjects for Phase II of the study.

Rationale for change: Clarification from the discussion with Dr. Walter in regards to interim analysis and stopping rule in phase II, the statistician of this study, on 6/15/2020.

13. **<Section 5.4 Phase II Study Schema, Page Number 15>**
Changed Text: The subjects **from phase II** will ~~continue~~ **administer** GoldAID EPA at the RP2D established in Phase I study for the duration of ~~one~~ **two** year**s** in combination with the TKI dose. BCR-ABL p210 quantitative PCR will be performed every 3 months while the subjects are on the study.

Rationale for change: Clarification from the discussion with the study team on 6/4/2020. The phase I subjects will not be cross-over to phase II.

14. **<Section 5.5 Definition of Dose Limiting Toxicity (DLT), Page Number 16>**
Changed Text: DLT is defined as any NCI CTCAE version 5.0 ~~(https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50) higher than~~ grade ~~1(except alopecia)~~ **3 or higher treatment related toxicity that occurs within 30 days from starting study drug.**
~~DLT can be defined as follows:~~
~~• Treatment emergent toxicity, defined as related to use of the investigational treatment regimen, of Grade 2 or greater not resolving to < Grade 2 after 7 days.~~
~~• Inability to take or resume the initial dose level of assigned cohort because of treatment emergent toxicity (e.g., toxicity > Grade 3).~~
~~Toxicities will be considered related to the study drug unless there is a clear, documented, alternative explanation for the AE. A DLT will be defined as any NCI CTC Grade 3 or higher treatment -related toxicity that occurs during the DLT evaluation period, including but not limited to:~~

~~• Any Grade 2 or greater toxicity felt to be related to GoldAID EPA, or the development of a ≥ Grade 2 dysfunction of a vital organ felt to be secondary to an AE.~~
~~• Grade 2 or greater AST, ALT, and/or total bilirubin elevations not explained by other causes.~~
~~• Any Grade 3-4 neutropenia or thrombocytopenia that does not resolve to ≤ Grade 2 within ≤ 7 days or ≤ Grade 3 thrombocytopenia associated with any clinically significant bleeding defined by NCI CTCAE criteria as grade 2 bleeding or higher.).~~
~~• Grade ≥ 2 nausea/vomiting, dehydration or diarrhea while taking optimal supportive medications.~~
~~• Any other Grade ≥ 2 non-hematologic toxicity except alopecia or electrolyte abnormalities unable to be treated with supportive therapy.~~

Rationale for change: Clarification of the definition of DLT and duration of DLT evaluation period, from the discussion with the study team on 6/2/2020.

15. <Section 5.6 Dose Modification of the Study Drug out of DLT Window, Page Number 16>

Deleted Text: ~~Subjects with Grade ≤ 2 toxicity or AEs thought to be study treatment-related may reduce their dose by 1 dose level and continue medication, if tolerated. If symptoms resolve after one or more weeks of this reduced dose, dose may re-escalate to the original dose as desired. Subjects with Grade 3 - 4 study treatment emergent toxicities should interrupt GoldAID EPA and not resume until resolution of symptoms to ≤ Grade 2. Dosing may then resume at one dose level reduction. If after 30 days this dose is tolerated, dose may be re-escalated to original dose.~~

~~NOTE: Any AEs that require permanent discontinuation of GoldAID EPA should be considered DLTs.~~

New Text:

CTCAE Grade	GoldAID EPA Dose Modifications
Grade 2	Dose reduction to the next lower dose level, if toxicity resolves within 14 days then resume at the original dose.
Grade 3 or 4	Suspend dose until toxicity resolves to ≤ Grade 2, then resume at next lower dose level, if toxicity resolves within 30 days then resume at the original dose

Dose level	3000 mg	2000 mg	1500 mg
1st dose reduction	2000 mg	1500 mg	1000 mg
2nd dose reduction	1500 mg	1000 mg	500 mg

Note: 1. Patients requiring a delay of 30 days will be removed from study.
2. Patients must be compliant with ≥ 75% of the GoldAID EPA dose. Patients who are less than 75% compliant will be removed from the study and replaced.
3. No re-challenges after second dose reduction.

Rationale for change: Clarification of the definition of DLT and duration of DLT evaluation period, from the discussion with the study team on 6/2/2020.

16. **<Section 7.0 Study Procedures, Page Number 19>**
Changed Text: 6. Documentation of **GoldAID EPA** dosing will be recorded in a Study Medication Diary provided by the ~~treating physician~~ **study team**. Dosing noncompliance is defined as a patient missing **≥ 75%** ~~> 14~~ days of medication in a 28-day window for 2 consecutive visits for a non-protocol-specified reason. ~~The Principal Investigator may require patients meeting noncompliance criteria to discontinue study treatment.~~

Rationale for change: Clarification from the discussion with PSCI CTO Clinical Research Nurse Educator Doris Shank on 6/2/2020.

17. **<Section 7.0 Study Procedures, Page Number 19; Section 7.1 Screening Visit –Day -30 to Day 0, Page Number 20>**
Old Text: Screening D-30 to D 0

New Text: Screening D-28 to D 0

Rationale for change: Clarification from the discussion with Dr. Naik on 6/15/2020.

18. **<Section 7.1 Screen viist, Page Number 21>**

Deleted Text: • Medical history (including any prior surgical history): ~~includes any AEs that occur following study registration but prior to initiation of the investigational medication. D~~**d**ocumentation of all medical history must be maintained in the source documents.

Rationale for change: Clarification from the discussion with PSCI CTO Clinical Research Nurse Educator Doris Shank on 6/2/2020.As there is no investigational drug given during the screening period, the statement about collecting AEs prior to registration is removed.

19. **<Section 7.1 Screen viist, Page Number 21>**

Deleted Text: ~~HIV, HBC, HCV testing for subjects with a known, documented prior history of positive tests only. Testing is not required for those subjects that do not have a known, documented prior history of positive tests.~~

Rationale for change: Clarification from the discussion with PSCI CTO Clinical Research Nurse Educator Doris Shank on 6/2/2020.

20. **<Section 7.1 Screen viist, Page Number 21>**
Added Text: *BCR-ABL* p210 **by peripheral blood**

Rationale for change: Clarification from the discussion with PSCI CTO Clinical Research Nurse Educator Doris Shank on 6/2/2020.

21. **<Section 8.1.1 Administration, Page Number 23>**
Deleted Text: ~~The emulsion was designed to be palatable. Subjects may empty the contents~~

~~of each sachet into a glass and add approximately 50 ml water. Subjects may also drink it directly without any other liquids. As the product is an emulsion, stirring is not necessary.~~

Rationale for change: Clarification from the discussion with PSCI CTO Clinical Research Nurse Educator Doris Shank on 6/2/2020. Redundant information was removed.

22. **<Section 9.0. Correlative Studies, Page Number 28>**
Changed Text: ~~• The PSCI CTO laboratory staff will spin the blood to obtain plasma and mononuclear cells (MNC) and buffy coat at the PSCI. After processing, specimens will be shipped to University Park on dry ice.~~ **The research blood processing refers to the lab manual.**

Rationale for change: Clarification from the discussion with PSCI CTO Clinical Research Nurse Educator Doris Shank on 6/2/2020.

23. **<Section 10.0. Adverse Event Reporting, Page Number 28>**
Changed Text: For the Phase I portion, all ~~non-hematologic AEs and hematologic~~ AEs ~~such as persistent cytopenias~~ that are not related to the underlying disease, will be assessed and entered in the study database. ~~AE also includes abnormal laboratory values or test results, even when they do not induce clinical signs or symptoms or require therapy.~~ **Lab and test abnormalities that are >/= grade 2 or higher regardless of clinical significance will be assessed and entered into the study database.** The period of time for AE collection will be from the time of initiation of the study medication to 30 days after last dose of study medication. ~~Following this time period, subjects will be followed for relapse and overall survival.~~

Rationale for change: Clarification from the discussion with PSCI CTO Clinical Research Nurse Educator Doris Shank on 6/2/2020.

24. **<Section 10.0. Adverse Event Reporting, Page Number 28>**
Changed Text: In the Phase II portion, ~~AE includes hematologic AEs such as persistent cytopenias that are not related to the underlying disease, abnormal laboratory values or test results, even when they do not induce clinical signs or symptoms or require therapy. Abnormal non-hematologic laboratory values will constitute AEs only if they induce adverse > Grade II clinical signs or symptoms or do not improve with treatment~~… ~~Unanticipated~~ SAEs will be followed until resolution or until an off study criterion is met (whichever occurs first).

Rationale for change: Clarification from the discussion with PSCI CTO Clinical Research Nurse Educator Doris Shank on 6/2/2020. Redundant information. FDA does not delineate between anticipated or unanticipated SAEs. All SAEs are to be reported to the FDA and followed until resolution.

25. **<Section 10.0. Adverse Event Reporting, Page Number 28>**
Changed Text: ~~Signs and symptoms~~ Adverse events will be recorded and entered into the database individually, except when considered manifestations of a medical condition or disease state.

Rationale for change: Clarification from the discussion with PSCI CTO Clinical Research

Nurse Educator Doris Shank on 6/2/2020. Signs and symptoms are not typically used in research.

26. **<Section 10.1 AE Characteristics, Page Number 29>**
Deleted Text: AEs will be identified in the database as 'unexpected' or 'expected' ~~for those AEs requiring expedited reporting only.~~

Rationale for change: Clarification from the discussion with PSCI CTO Clinical Research Nurse Educator Doris Shank on 6/2/2020. All AEs need to be assessed for expectedness. That determines whether they meeting reporting requirements or not.

27. **<Section 10.1 AE Characteristics, Page Number 29>**
Changed Text: The clinical research staff and Regulatory Associates of PSCI CTO will coordinate the reporting process between the **sponsor-**investigator and IRB ~~as well as other applicable reporting agencies (e.g. FDA, Solutex).~~ **The SAEs must report to the sponsor-investigator within 24 hours of knowledge SAEs.**

Rationale for change: Clarification from the discussion with PSCI CTO Clinical Research Nurse Educator Doris Shank on 6/2/2020.

28. **<Section 10.3.1 Reporting Adverse Reactions and Unanticipated Problems to the IRB, Page Number 30>**
Changed Text: AEs **of this nature as well as SAEs** will be ~~submitted~~ **reported** to the IRB **within 5 business days** in accordance with the IRB policies and procedures as noted in the Investigators Manual.

Rationale for change: Clarification from the discussion with PSCI CTO Clinical Research Nurse Educator Doris Shank on 6/2/2020. To define the time frame reporting to IRB.

29. **<Section 10.3.3 Reporting SAEs to Solutex, Inc., Page Number 30>**
Changed Text: A copy of **MedWatch 3500A** ~~the SAE report submitted to the Penn State IRB or FDA when applicable~~ will be provided to Solutex, Inc. representative Julio Boza, General Manager Azur Global Nutrition, email: jboza@azur-gn.com.

Rationale for change: Clarification from the discussion with PSCI CTO Clinical Research Nurse Educator Doris Shank on 6/2/2020.

30. **<Section 11.6 Data Safety Monitoring Plan, Page Number 32>**
Changed Text: The DSMC will review all data prior to each DLT review for dose escalation. The DSMC will determine if the next cohort will be opened, expanded, de-escalated or the protocol be placed on hold. Additionally all exception and/or prospective deviations must be approved by the DSMC prior to execution. On an annual basis ~~(increased frequency if determined by SRC)~~,

Rationale for change: Per discussion with PSCI CTO Clinical Research Nurse Educator Doris Shank on 6/2/2020, clarification required for reviewing DLT's for dose escalation and protocol exemption/deviations; and the inaccurate information was removed.

31. <Section 12.0 Statistical Consideration, Page Number 32>

Changed Text: ~~Simon's optimal two-~~ **Single** stage design will be used for the Phase II portion of the study based on the assumption that the complete molecular response rate is 25% for subjects on TKI alone **vs. 50% for TKI + GoldAID EPA**. The design ~~described in below table~~ involves a maximum of n = ~~24~~ **30** subjects, has a type I error rate (α) of 0.05, and provides statistical power ≥ 80% when the response rate for subjects on the combination therapy of TKI and GoldAID EPA is at least 50%. Assuming a 10% drop-out rate, a total of n = ~~27~~ **34** subjects will be enrolled. ~~If ≤ 2 successes, defining as either stable disease stable MMR or CMR, are observed in these subjects, then the Phase II portion of the trial will be stopped early for futility.~~ **An interim analysis for excess toxicity will be performed based on the presence of DLTs and their grades. In brief, once half of the phase II cohort has been accrued (n = 17), the proportion of patients exhibiting DLTs greater than grade 2 will be computed. We will suspend the trial (pending the DSMB's investigation) if n = 3 or more patients exhibit a DLT of grade greater than 2 in the interim analysis. This stopping threshold corresponds to approximately 18% of the number of accrued patients at the time of the interim analysis and is within the FDA's suggested range (15% - 25%).**

	~~**Description**~~
~~Stage 1~~	~~Enroll 9 patients. If ≤ 2 successes (i.e. has response following the proposed treatment) are observed in these 9 patients, then the Phase II portion of the trial will be stopped early for futility. If at least 3 successes are observed, then the trial will proceed to Stage 2.~~
~~Stage 2~~	~~Enroll an additional 15 patients (for a total of 24). If ≤ 9 successes are observed in these 24 patients, then the treatment will be considered insufficiently effective for the study population. If at least 10 successes are observed, then the treatment will be considered sufficiently effective and recommended for further investigation in larger studies.~~

Rationale for change: Clarification from the discussion with the study team and Dr. Vonn Walter on 6/4/2020. The Simon's optimal two-stage design will be changed to single stage design. There will be 7 more subjects than the current protocol. All the Simon's optimal two-stage design related languages were removed.

32. <Section 14.0 Subject Stipend (compensation) and/or Travel Reimbursements, Page Number 32>

Deleted Text: ~~Subjects may receive travel reimbursement only with approval from the IRB on a case by case basis. Funding for any travel reimbursement will be provided by the PSCI.~~

Rationale for change: Clarification from PI, this was a mistaken statement so it is removed.

33. Administrative changes: Minor changes involving grammar, punctuation, wordsmithing, and other editorial changes have been made throughout the document. All are clearly identified in the track-changes version of the amendment.

	Version Date
FDA Approved Protocol	7-6-2020
Amended Protocol	7-28-2020

Section and page numbers are references to the (17-085 protocol VERSION dated 7-28-2020) amended protocol.

34. <Title Page, Page Number 1>
Old Text: dated 7/6/2020

New Text: dated 7/28/2020

Rationale for change: Updating document version date

35. <Section 3.2 Exclusion Criteria, Page Number 14>
Old Text: 3. Known previously documented HIV, Hepatitis B, or Hepatitis C infection.

New Text: 3. Medical documented or self-reported history of HIV, Hepatitis B, or Hepatitis C infection.

Rationale for change: To be consistent with the exclusion criteria #3 in the synoposis, per IRB request on 7/27/2020.

36. <Section 3.2 Exclusion Criteria, Page Number 14>
Old Text: 3. Known previously documented HIV, Hepatitis B, or Hepatitis C infection.

New Text: 3. Medical documented or self-reported history of HIV, Hepatitis B, or Hepatitis C infection.

Rationale for change: To be consistent with the exclusion criteria #3 in the synopsis, per IRB request on 7/27/2020.

37. <Section 9.0 Correlative Studies, Page Number 29>
Added Text: •The research blood processing refers to the **PSCI-17-085** lab manual.

Rationale for change: "PSCI-17-085" was added to specify the lab manual, per IRB request on 7/27/2020.

	Version Date
FDA Approved Protocol	7-28-2020

Amended Protocol	9-22-2020

Section and page numbers are references to the (17-085 protocol VERSION dated 9-22-2020) amended protocol.

38. **<Title Page, Page Number 1>**
Old Text: dated 7/28/2020

New Text: dated 9/22/2020

Rationale for change: Updating document version date

39. **<Protocol Synopsis, Page Number 5; Section 3.1 Inclusion Criteria, Page Number 12; Section 3.3 Definitions of Therapeutic Response, Page Number 14>**
Changed Text: Stable molecular response defined as 2 sequential BCR-ABL p210 levels done in the same lab with less than ½ log ~~reduction~~ **variation** of BCR-ABL p210 3-6 months apart.

Rationale for change: Clarifications per PI, the "variation" is a more accurate term than "reduction" to describe stable molecular response of CML to TKIs (Renault I, et al. Rev Bras Hematol Hemoter. 2011; 33(6): 455-60).

40. **<Appendix D, Page Number 44>**

Rationale for change: Added table as Appendix D 1 (Criteria for Evaluation of Subject Eligibility), the original appendix D became appendix D2. Per PI's suggestion, a new table (appendix D1) was created to clarify definitions for stable molecular response (1 log and ½ log variations), MR and PR, and help evaluate the eligibility of subjects.

	Version Date
FDA Approved Protocol	9-22-2020
Amended Protocol	10-26-2020

Section and page numbers are references to the (17-085 protocol VERSION dated 10-26-2020) amended protocol.

41. **<Title Page, Page Number 1>**
Old Text: dated 9/22/2020

New Text: dated 10/26/2020

Rationale for change: Updating document version date

42. <Protocol Synopsis, Exclusion Criteria, Page Number 6; Section 3.2, Exclusion Criteria, Page 13>

Old Text: Medical documented or self-reported history of HIV, Hepatitis B, or Hepatitis C infection.

New Text: Documented history of HIV, Hepatitis C, or known active Hepatitis B on therapy (HIV, Hepatitis B or C testing is not required for eligibility assessment).

Rationale for change: Clarifications per PI and Doris Shank, the interim administrative director of PSCI CTO on 10/26/2020, this is a more accurate statement.

43. <Section 4.0 Registration Procedures, Page Number 14>

Deleted Text: Subject begins treatment within 2 days of registration.

Rationale for change: Clarification from study team on 10/6/2020, this statement was not accurate, the screening period in the study calendar is Day -28 to 0.

44. <Section 7.0 Study Procedures, Page Number 19>

Changed Text: "X" was added to the 2nd column of BCR-ABL test, "X" was deleted in the 1st column of correlative studies.

Rationale for change: Clarification from PI on 10/6/2020 and sub-I Dr. Prabhu, *BCR-ABL* p210 PCR test and correlative study (baseline) are required in Day 0 visit while correlative research blood is not necessary for screening visit.

45. <Section 7.0 Study Procedures, Page Number 19>

Added Text: Footnote 7. CBC with differential, chemistry testing and *BCR-ABL* p210 PCR to be performed only once if day 0 is within one week from screening visit.

Rationale for change: Clarification from PI on 10/6/2020, CBC with differential, chemistry testing and *BCR-ABL* p210 PCR to be performed only once if day 0 is within one week from screening visit.

46. <Section 7.2 Day 0 (first day of investigational medication administration), Page Number 20>

Changed Text: add bullet point "*BCR-ABL* p210 PCR", delete bullet point "correlative studies".

Added Text: add "performed only once if day 0 is within one week from screening visit" to CBC with differential, chemistry test and *BCR-ABL* p210 PCR.

Rationale for change: Clarification from PI on 10/6/2020 and sub-I Dr. Prabhu, BCR-ABL p210 PCR test and correlative study (baseline) are required in Day 0 visit while correlative research blood is not necessary for screening visit, and to be consistent with the section 7.0

study calendar.

47. <Section 7.9 Off Treatment Criteria, Page Number 21>

Deleted Text: Participants unable to receive GoldAID EPA for 28 days~~/weeks~~.

Rationale for change: Typographical error.

48. <Section 9.0, Correlative Studies, Page Number 1>

Old Text: Section 9.0 Correlative Studies. The following correlative studies listed below will be completed at time points specified in Section 7.0. Objective response versus stable disease will be monitored on/about Month 3, 6, 9 and 12 time period during Year 1 and Month 15, 18, 21 and 24 time periods during the Year 2.

- We will use *BCR-ABL* p210 gene rearrangement assay by quantitative PCR at screening visit, on/about Month 3, 6, 9 and 12 during Year 1 and Month 15, 18, 21 and 24 during Year 2. This is a standard of care assay and will be executed through available laboratories at HMC.
  The following correlative studies will be studied through the laboratories of Drs. Prabhu and Paulson at University Park at Penn State University at screening visit, on/about Month 3, 6, 9 and 12 during Year 1 and Month 15 and 24 during Year 2:
  - The research blood processing refers to the PSCI-17-085 lab manual. Differential expression of genes and modulated pathways in CML leukemic progenitors will be studied. Specifically, *in vivo* correlation by measurement of PG isoforms, omega-3 index and SPMs will be studied.

Changed Text: Section 9.0 **Laboratory** Studies. The following **Laboratory** studies listed below will be completed at time points specified in Section 7.0.

9.1. BCR-ABL p210 PCR test.

Objective response versus stable disease will be monitored on/about Month 3, 6, 9 and 12 time period during Year 1 and Month 15, 18, 21 and 24 time periods during the Year 2. We will use *BCR-ABL* p210 gene rearrangement assay by quantitative PCR at screening visit, on/about Month 3, 6, 9 and 12 during Year 1 and Month 15, 18, 21 and 24 during Year 2. This is a standard of care assay and will be executed through available laboratories at HMC.

9.2. Correlative Studies.

The following correlative studies will be studied through the laboratories of Drs. Prabhu and Paulson at University Park at Penn State University at screening visit, on/about Month 3, 6, 9 and 12 during Year 1 and Month ~~15~~ **18** and 24 during Year 2:

- The research blood processing refers to the PSCI-17-085 lab manual. Differential expression of genes and modulated pathways in CML leukemic progenitors will be studied. Specifically, *in vivo* correlation by measurement of PG isoforms, omega-3 index and SPMs will be studied.

Rationale for change: Clarification from the study team on 10/6/2020, section 9.0 sub-title was changed from "Correlative studies" to "Laboratory studies" to be accurate. Section 9.0 was also broken into two sections: section 9.1 to describe BCR-ABL p210 PCR test while section 9.2 to describe the correlative studies in collaboration with Dr. Prabhu and Dr. Paulson at University Park Penn State. There was a typo error in section 9.2 the correlative study should be done in month 18 not month 15.

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Section and page numbers are references to the (17-085 protocol VERSION dated 11-25-2020) amended protocol.

49. <Title Page, Page Number 1>
Old Text: dated 10/26/2020

New Text: dated 11/25/2020

Rationale for change: Updating document version date

50. <Protocol Synopsis, Exclusion Criteria, Page Number 6; Section 3.2, Exclusion Criteria, Page 13>
Changed Text: Documented history of HIV, Hepatitis C, or known active Hepatitis B on therapy (HIV, Hepatitis B or C testing ~~is not required for eligibility assessment~~ are part of usual care testing absent a trial).

Rationale for change: Per IRB request in response to MOD00025526 submission, and per Kimberly Perkins, the coverage analyst at Penn State College of Medicine Clinical Trial Office, HIV and hepatitis serology labs are part of usual care testing absent a trial.