

Study Title: First-Line Dasatinib or Nilotinib Followed by Response Guided Switch to Imatinib in Newly Diagnosed Chronic Phase Chronic Myeloid Leukemia.

Study Phase: Phase 2

Study Site: Emory Healthcare (Winship Cancer Institute)
GA CORE approved centers across State of Georgia

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	Adverse event
AP	Accelerated phase
BCR-ABL	Fusion transcript or protein resulting from the 9;22 chromosomal translocation responsible for formation of the Philadelphia Chromosome
BP	Blast phase
CBC	Complete blood count
CCyR	Complete cytogenetic response
CHR	Complete hematologic response
CML	Chronic myelogenous leukemia
CMR	Complete molecular response
CNS	Central nervous system
CP	Chronic phase
ECG	Electrocardiogram
eCRF	Electronic case report form
ENESTnd (trial)	Evaluating Nilotinib Efficacy and Safety in Clinical Trials Newly Diagnosed Philadelphia Chromosome Positive (trial)
FDA	Food and Drug Administration
GCP	Good clinical practice
ICF	Informed consent form
ICH	International Conference on Harmonization
IDMC	Independent data monitoring committee
IRB/IEC	Institutional review board/Independent ethics committee
IRIS	International Randomized Study of Interferon versus STI571
IS	International scale
ITT	Intent-to-treat
MCyR	Major cytogenetic response
MMR	Major molecular response
NCCN	National Comprehensive Cancer Network
PCR	Polymerase chain reaction
Ph+	Philadelphia chromosome positive
PK	Pharmacokinetics
PPI	Proton pump inhibitors
QoL	Quality of life
qRT-PCR	Quantitative reverse transcriptase polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitor

PROTOCOL SYNOPSIS

Study drugs	Imatinib (IM), Nilotinib (NIL), Dasatinib (DAS)
Study Title	First-Line DAS or NIL Followed by Response Guided Switch to IM in Newly Diagnosed Chronic Phase Chronic Myeloid Leukemia (CP-CML)
Phase	Phase 2
Eligible Population	CP-CML
Summary and Study Rationale	IM, NIL and DAS are FDA-approved for upfront treatment in CP-CML. DAS and NIL are very potent agents and lead to fast molecular responses (MR), but have so far not shown survival benefits as compared to IM. The long term safety profile of IM compares favorably with DAS and NIL. A switch to IM in patients with optimal response to NIL or DAS can reduce long-term toxicities while maintaining the benefits of a faster initial response and possibly at a lower cost.
Study Design	Prospective open label, single-arm trial
Study Objectives	<p>Primary Objective: To assess incidence of major molecular response (MMR) at 12 months.</p> <p>Secondary: To assess</p> <ul style="list-style-type: none"> • Progression free survival (PFS) at 12 and 24 months. • Accelerated phase (AP) or blast phase (BP) transformation-free survival at 12 and 24 months • Incidence of deep MRs (\geqMR⁴) at 12 months and 24 months • Safety • Patient reported outcomes (PRO) <p>Exploratory : To assess</p> <ul style="list-style-type: none"> • Prognostic significance of detecting aberrant myeloid or lymphoid markers on diagnostic bone marrow • Ability to enroll subjects who maintain deep molecular remissions in TKIs discontinuation trials
Diagnosis and Main Inclusion Criteria	CP-CML
Number of Patients	100
Duration of Patient Participation	5 years
Approximate Duration of Study	7 years
Dosage and Administration	IM 400 mg/d, DAS 100 mg/d, NIL 300 mg bid
Concomitant Medications/treatment	No contraindicated drugs. Caution with drugs known to interact with each tyrosine kinase inhibitor (TKI)
Study Endpoints	<p>Primary Endpoint:</p> <p>The proportion of subjects who achieve MMR at 12 months will be determined. Only MMR at 12 months will be</p>

	<p>considered, MMR achieved before the 12 months and then subsequently lost will not be considered.</p> <p>Secondary Endpoints:</p> <ul style="list-style-type: none"> i. PFS will be measured from the time of CML diagnosis to the time of loss of MMR or loss of hematologic response ii. AP or BP free survival will be measured from the time of CML diagnosis to the time of transformation to AP or BP iii. The number of subjects with BCR-ABL1 transcript levels \leq MR⁴ at any time will be determined iv. Safety will be evaluated by the assessment of laboratory and clinical adverse events (AEs) using the CTCAE v4.03 criteria. Safety will be assessed by the frequency, duration, and severity of AEs and SAEs, and clinical evaluations and changes in clinical laboratory blood samples v. The PRO score extracted from the MDASI-CML will be determined and intra and inter subject changes will be compared at the different study-defined time points <p>Exploratory Endpoints:</p> <ul style="list-style-type: none"> i. Outcomes of subjects with and without detectable cells with aberrant lymphoid or myeloid markers at diagnosis will be compared ii. The proportion of subjects who achieve and maintain deep MR for 2 years and therefore qualify or enroll on a TKI discontinuation trial will be determined. Outcomes following TKI discontinuation will be collected
<p>Statistical Analysis</p>	<p>Primary end point is MMR at 12 months. Assuming that subjects able to switch from DAS or NIL to IM at 3-6 months will achieve at 12 months the same rate of MMR achieved with continuous DAS or NIL i.e. 55%(P1) but not less than 40% (P0) which is achieved with upfront IM, 85 subjects will be needed to achieve 80% power to detect a difference (P1-P0) of 0.1500 using a one-sided binomial test. The target significance level is 0.0500. The actual significance level achieved by this test is 0.0449. These results assume that the population proportion under the null hypothesis is 0.4000. With an assumption that up to 15% of subjects who start DAS or NIL will not be able to switch to IM and will not be included in the efficacy analysis, but will be included in the safety and outcome analysis at 5 years, the total sample size will be 100 subjects.</p>

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1. Background:

1.1 Chronic Myeloid Leukemia:

Chronic myeloid leukemia (CML) is a clonal myeloproliferative stem cell disorder characterized by the presence of a signature hybrid oncogene, the BCR-ABL1 [1] and a unique triphasic clinical course. The majority of patients (~80%) are diagnosed during the early phase, or chronic phase (CP), however, and without effective treatment, CML invariably progresses to the advanced phases of the disease: AP phase (AP) or blast phase (BP). The Philadelphia chromosome (Ph⁺), the driving leukemogenic mechanism in CML, is a reciprocal translocation between chromosome 9 and 22 that juxtaposes two genes involved in cell signaling, signal transduction, and cell proliferation: BCR and ABL1. The ABL1 gene encodes non-receptor tyrosine kinases which become deregulated and constitutively active by the juxtaposition of BCR. BCR-ABL1 is central in controlling downstream pathways involved in cell proliferation, regulation of cellular adhesion and apoptosis. The understanding of the pathophysiology of CML led to development of drugs that specifically target the tyrosine kinase activity in BCR-ABL1. These tyrosine kinase inhibitors (TKI) became the mainstay of modern therapy in CML [2] and have revolutionized patients outcomes. Indeed, treatment of patients with CML with TKIs is ranked as one of the great medical success stories of the past 30 years and for a new patient with CP-CML receiving IM, complete cytogenetic response (CCyR) are achieved in approximately 80% which translates into life spans indistinguishable from those of similar persons without leukemia. Imatinib (IM, Gleevec[®], Novartis), dasatinib (DAS, Sprycel[®], Bristol-Meyers Squibb) and nilotinib (NIL, Tasigna[®] Novartis) are approved by the FDA as first-line TKIs for the treatment of CML.

1.2 Measuring Response to therapy in CML: Molecular Response (MR):

Detection of BCR-ABL1 by quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) is feasible on blood as well as marrow samples and is now a widely accepted method for monitoring response to therapy. [3] An excellent correlation exists between blood qRT-PCR and marrow cytogenetics and qRT-PCR. Response is measured by a decrease in BCR-ABL1 levels on a logarithmic scale. A 1 log reduction is a drop to below 10%, while a major molecular response (MMR) is defined as a 3 log reduction (0.1%). Deep MR includes transcripts levels BCR-ABL1 < 0.01% (MR⁴), < 0.0032% (MR^{4.5}) and < 0.001% (MR⁵). [4] Transcripts levels < MR^{4.5} define complete MR (CMR). In the absence of universal standards or reagents for PCR assays, the International Scale (IS) was developed to harmonize MR across laboratories by applying a laboratory specific conversion factor. Practically, all laboratories are currently reporting PCR results using the IS, which permits the avoidance of regional variabilities. [5] **Therefore blood monitoring by qRT-PCR for BCR-ABL1 can be done reliably using the IS at local laboratories to assess response to therapy in CML.**

1.3 Efficacy of First Line Tyrosine Kinase Inhibitors in CP-CML:

1.3.1 Imatinib:

IM is the first TKI approved by the FDA as first-line therapy in CP- CML in 2002, and is very effective. Indeed, survival of CP-CML at 8 years is 85% (93% when only CML-related deaths are considered). Once a complete cytogenetic response (CcyR) is achieved, survival for CML patients treated with IM becomes indistinguishable from the general population. [6] **IM is therefore a very safe and effective treatment for CP-CML.**

1.3.2 Dasatinib:

DAS was approved in 2010 for use as first-line treatment for CP-CML following results from a phase 3 randomized trial (DASISION) that compared DAS 100 mg/d to IM 400 mg/d. At 12 months, higher rates of CcyR and MMR were observed with DAS as compared to IM (77 vs. 66% and 46 vs.28%).[7] Long term (5year) follow up has so far not shown a difference in progression-free survival (PFS, 85 vs 86%) or overall survival (OS,91 vs 90%).

1.3.3 Nilotinib:

NIL was approved for first-line treatment of CP-CML in 2010 following results from a phase 3 randomized trial (ENESTnd) that compared NIL 300 mg or 400 mg twice daily to IM 400 mg once daily. At 12 months, MMR was 44% for 300mg and 43% for 400 mg of NIL and 22% for IM. CcyR was also higher in the NIL arms 80% and 78% respectively, vs 65% with IM.[8] With 4 years of follow-up and despite the faster and deeper responses with NIL there was no survival advantage for NIL as compared to IM. OS at 4 years was 94.3% and 96.7% in the NIL arms as compared to 93.3% in the IM arm. [8]

1.4 Safety of First Line Tyrosine Kinase Inhibitors in First Line Use CP-CML:

TKI therapy is associated with both class-specific and drug-specific short term and long term side-effects.

1.4.1 Imatinib:

After short term exposure, the most common non-hematological adverse events (AEs) seen in more than 10% of patients were fluid retention (42%), gastrointestinal (GI) AEs (10-20%), myopathy (10%) and rash (10%). The majority of these AEs were grades 1-2 AEs. The discontinuation rate due to early AEs is <5%. [7]

Long term safety data with up to 9 years of follow-up is available for patients treated with IM.[6] IM appears well tolerated with no new AEs reported with long-term exposure.

1.4.2 Dasatinib:

After short term exposure, the most common non-hematological AEs occurring in more than 10% of patients included fluid retention (19%), pleural effusion (10%), GI AEs (17%), myopathy (11%) and rash (10%). The discontinuation rate was 5% with these short term AEs.[7]

Long term treatment with DAS is safe in the majority of patients, but reports of pulmonary AEs with prolonged use are emerging. Pleural effusions and fluid retention appear to be increasing with 5 year follow-up studies reporting up to 30% incidence of pleural effusions.[9] Reports of pulmonary hypertension are also emerging with more than 1 year of exposure to the drug. A French registry study reported an incidence of 0.45% in DAS-treated patients.[10]

1.4.3 Nilotinib:

After short term exposure to NIL, the most common non-hematological AEs occurring in more than 10% of patients include elevated liver enzymes (40-60%), hyperglycemia (35%), lipase (24%), skin rash(31%), headache (14%), myalgias (10%). Although QT interval prolongation occurs in less than 10%, FDA's approval of NIL includes a black box warning for possible life-threatening QT prolongation and possible sudden death. . The discontinuation rate was 5% with these short term AEs.[8]

Long term treatment with NIL has shown increased risks of peripheral arterial disease (PAD). Clinically evident PAD as measured by ankle brachial indices was observed in higher frequency in NIL than in IM-treated patients (~30 vs 6%)[11]. Other large studies also confirm an increased incidence of PAD in 3-7%[10, 12] NIL is administered twice daily, and therefore non-adherence is more commonly observed than with IM and DAS which are administered once daily.[12, 13]

Drug:	Non hematological Early AEs in > 10%	Early discontinuation due to AEs	Long-term AEs
Imatinib 400 mg/d	Fluid retention (43%) Myalgia (39%) Diarrhea (21%)[7]	4.3 %	None[6]
Dasatinib 100 mg/d	Fluid retention (25%) Diarrhea (19%) Myalgia (13%)[7]	5 %	Pleural effusion 30%[9] Pulmonary Hypertension 0.45% [10]5 years
Nilotinib 300 mg bid	Biochemical abnormalities (40%) Rash (30 %) Headache (10%) [8]	5 %	Peripheral vascular problems (6-30%) [12] 4 year

Table 1: Short-term and long-term AEs associated with IM, DAS and NIL.

1.5 Prognostic significance of MR

1.5.1 MMR at 3 month:

Early MR is predictive of progression free survival. The 3 month 1 log reduction can be predictive of MMR at 12 months as well with approximately 55% of patients on 2nd Generation(2G)-TKIs achieving MMR as compared to 40% on IM.[14] In another study, transcript levels below 10% by qRT-PCR at 3 months was associated with a 8-year OS of 93.3% as compared to 56.9% if qRT-PCR was > 10% (p < .001).[15] These results were independently confirmed and are widely accepted.[16, 17]

1.5.2 MR at 6 months:

In addition to patients who achieve the 1 log reduction in transcript levels at 3 months, patients achieving 2 log reduction at 6 months have excellent prognosis. A qRT-PCR level of less than 1% at 6 months predicts CcyR at 2 years and CMR at the same time point. In fact, European Leukemia Net (ELN) guidelines define treatment failure as a qRT-PCR greater than 10% at 6 months.[16]

1.5.3 Deep MR:

Attaining deep MR may increase the number of patients discontinuing TKIs.[4]. Indeed treatment free remission is now considered an important goal in CML therapy, and the success of TKI discontinuation is linked to the achievement of deep MR.

Drug	<u>1 log reduction in qRT-PCR at 3 month</u>	MMR at any time in 12 month	Deep MR at 4 years
Imatinib 400 mg	64%[8]	28%[8]	23% [18]
Dasatinib 100 mg	84%[17]	46%[7]	42 % [7]
Nilotinib 300 mg BID	91% [14]	51%[8]	40 %[14] [19]

Table 2: Early and deep MR achieved with IM, DAS and NIL.

1.6 Outcomes of Patients who switch from 2G-TKIs to IM:

We identified 12 patients with CP CML diagnosed between 08/2013 and 06/2015 who received first line therapy with DAS (9), NIL (2), and ponatinib (PON, 1) and subsequently switched to IM. Reasons for switching to IM included: TKI toxicity, physicians' preference, drug availability and closure of a clinical trial. Response to TKI was assessed by quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) for BCR-ABL1. Response to these ≥ 2 G-TKIs at 3 months was as follows: CHR (n=12), 1 log (<10%, n=12), 2 log (<1%, n=8), and 3 log (MMR, <0.1%, n=3) reductions of BCR-ABL1 transcripts. Median qRT-PCR at 3 months was 0.77% (range 0-7%).

Median time to discontinuation of ≥ 2 G-TKIs and initiation of IM was 106 days (range, 92 – 203) from diagnosis. IM was started at 400 mg/d and was well tolerated except in 2 patients who discontinued due to grade 2 skin rash (1) and grade 2 anxiety (1). Both patients switched back to DAS at 54 and 228 days after initiation of IM respectively. All patients that switched to IM were evaluable with a follow up of at least 3 months. These patients have shown a continuous response with 12/12(100%) achieving a 2 log reduction at 6 months, and 5/7(70%) achieving MMR at 12 months. With up to 30 months follow-up (median 12 months), all patients showed continuous decrease in their transcripts (Figure 1) and no losses of MMR or progression to BP were observed. With a median follow-up of 12 months (range 5-30 months), 5 patients achieved CMR.

This retrospective analysis shows that IM can be safely and effectively administered following optimal response to ≥ 2 G-TKIs.

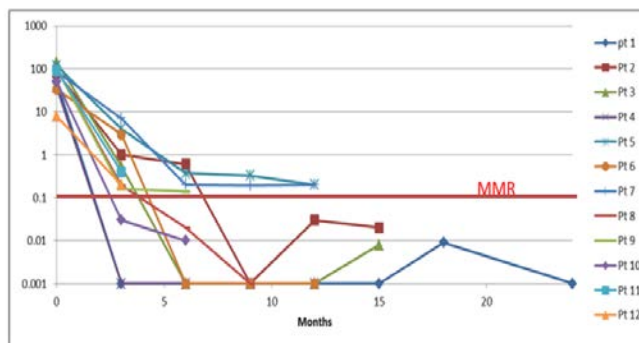


Figure 1: Molecular responses in patients who switched from > 2G-TKIs to IM

1.7 Rationale for the study:

Based on the short-term safety and high early MRs associated with front-line 2G-TKIs and our preliminary data showing continuous responses in patients who switch to IM following optimal responses, we propose a study testing the safety and efficacy of starting DAS or NIL in newly diagnosed CP-CML patients followed by a switch to IM after early MR. This strategy aims to combine the benefits of faster deep MR achieved with DAS or NIL and the safety of prolonged exposure to IM.

Given that the majority of CML patients are diagnosed and managed in private Oncology practices, this trial will be conducted both at Emory and through the Georgia Center for Oncology Research and Education (CORE).

Georgia CORE is a public private partnership dedicated to generating collaborative resources for cancer prevention, care, research and education. One of the goals of Georgia CORE is to expand access to cutting-edge therapies in Georgia through cancer clinical trials. Georgia CORE's network includes 24 academic or community oncology practices, with 9/10 of Georgia's oncologists belonging to this organization. Georgia CORE plays a role in facilitating regulatory requirements for sites that use a central IRB, and also monitors the IRB interactions for the sites using local IRBs. A partnership with the community through Georgia CORE will allow rapid accrual of CML patients on the proposed trial.

2. Study Objectives and Hypothesis

2.1 Objectives:

- Primary Objective: To assess incidence of MMR at 12 months.

- Secondary: To assess
 - PFS at 12 and 24 months.
 - AP or BP transformation-free survival at 12 and 24 months
 - Incidence of deep MR (\geq MR⁴) at 12 months and 24 months
 - Safety
 - Patient reported outcomes (PRO)

- Exploratory : to assess
 - The prognostic significance of detecting aberrant myeloid or lymphoid markers on diagnostic bone marrow
 - Ability to enroll subjects who maintain deep molecular remissions in TKI discontinuation trials

2.2 Hypothesis:

We hypothesize that patients with newly diagnosed CP-CML who achieve a 1 log reduction in BCR-ABL1 transcript level at 3 months or a 2 log reduction at 6 months following front-line treatment with DAS or NIL will show continuous MR following a switch to IM. . We also hypothesize that the TKIs DAS, NIL, and IM will be safe and well-tolerated, that the incidence of MMR at 12 months in subjects who switch to IM will be comparable to the incidence reported with continuous treatment with DAS or NIL (Table 2) [7, 8], and that subjects will achieve and maintain deep MR which will offer them the opportunity to enroll in TKI discontinuation trials. We also hypothesize that loss of response and progression to advanced phases CML following a switch to IM will be comparable to the incidence reported with continuous treatment with DAS or NIL.[7, 8] We also hypothesize that PRO using the MD Anderson Symptom Inventory (MDASI-CML, appendix D) assessed at study-specific time points will reflect a more favorable profile with IM as compared to DAS or NIL. We also hypothesize that marrow flow cytometry performed at diagnosis will predict early progression to advanced phases of the disease.

3. Investigational Plan

3.1. Overall Study Design and Plan:

This is an open-label multicentric phase 2 study that will enroll newly diagnosed previously untreated CP-CML patients. A standard of care diagnostic bone marrow aspirate will be required to confirm the diagnosis of CP-CML. Eligible patients who sign consent will start front-line DAS at 100 mg once a day or NIL at 300mg twice a

day at the discretion of the treating hematologist. Response will be assessed through measurements of BCR-ABL1 transcripts by qRT-PCR (IS) using local laboratories at time points recommended by the ELN guidelines (**Appendix B**). Drug compliance will be measured by obtaining prescription fill information from the pharmacy. These are drugs are being filled by specialty pharmacies and obtaining a prescription fill information at the end of one year is a much better way to assess compliance. A study-dedicated research coordinator or the investigator will contact subjects on predefined time points using telephone or video conferencing to provide education about CML and common side-effects of TKIs, provide reminders to complete MDASI-CML forms when due, assess compliance, and address questions related to CML response. Should subject report new AEs during these communications, the research nurse will ask subjects to contact the local hematologist, who may then consult with the investigator. Results of response monitoring done at local laboratory will be collected by research nurse and discussed with the investigator. A study-specific letter interpreting the qRT-PCR according to the ELN guidelines will then be generated and transmitted to both subjects and treating hematologist. Subjects with BCR-ABL1 levels < 10% at 3 months or < 1% at 6 months, will switch to IM at 400 mg once a day. Subjects not achieving these landmark responses will be taken off study but will continue treatment per standard of care guidelines. Patients and physicians may opt not to switch but the information regarding the reasons and follow up information will continue to be collected unless patient prefers to come off the study. The study primary endpoint (MMR) will be assessed by blood qRT-PCR at 12 months. Study duration is 2 years and all subjects will be offered to enroll in the long-term follow-up part of the study.

3.2 Endpoints:

Primary Endpoint:

The proportion of subjects who achieve MMR at 12 months will be determined. Only MMR at 12 months will be considered, MMR achieved before the 12 months and then subsequently lost will not be considered.

Secondary Endpoints:

- i. PFS will be measured from the time of CML diagnosis to the time of loss of MMR or loss of hematologic response
- ii. AP or BP free survival will be measured from the time of CML diagnosis to the time of transformation to AP or BP
- iii. The number of subjects with BCR-ABL1 transcript levels \leq MR⁴ at any time will be determined
- iv. Safety will be evaluated by the assessment of laboratory and clinical adverse events (AEs) using the CTCAE v4.03 criteria. Safety will be assessed by the frequency, duration, and severity of AEs and SAEs, and clinical evaluations and changes in clinical laboratory blood samples
- v. The PRO score extracted from the MDASI-CML will be determined and intra and inter subject changes will be compared at the different study-defined time points

Exploratory Endpoints:

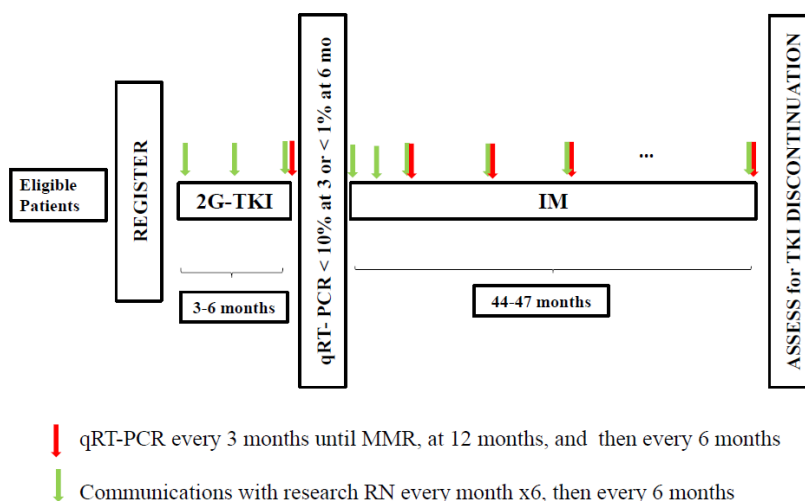
- i. Outcomes of subjects with and without detectable cells with aberrant lymphoid or myeloid markers at diagnosis will be compared
- ii. The proportion of subjects who achieve and maintain deep MR for 2 years and therefore qualify or enroll on a TKI discontinuation trial will be determined. Outcomes following TKI discontinuation will be collected

3.3 Description of Treatment:

All newly diagnosed CP-CML patients will be offered to participate in the study. The primary hematologist (co-investigator) will discuss the study and counsel both patient and care-giver. The objectives of the study, procedures, alternative therapies and potential risks and benefits of participation will be explained. Preliminary data suggesting that the detection of lymphoblasts by flow cytometry on the diagnostic marrow may be a marker for early blast transformation will be disclosed to the patient. Patient will be given the time to read the consent and the opportunity to ask questions before signing the consent form approved by the local or central Institutional Review Board (IRB). Within 48 hours of consenting, protocol registration procedures will be completed. Eligibility checklist form will be verified by the investigator prior to enrollment. Subjects will then start DAS at 100 mg once a day or NIL at 300 mg twice a day at the treating hematologist discretion. After initiation of TKI, subjects will be monitored by their local hematologists according to the standard of care. Response to therapy will be assessed through measurements of BCR-ABL1 transcripts by qRT-PCR (IS) using local laboratories at time points recommended by the ELN guidelines (**Appendix B**). Subjects who achieve either a 1 log reduction (<10%) at 3 months or a 2 log reduction (1%) at 6 months in their BCR-ABL1 transcript levels, will be offered to switch to IM at 400 mg once a day. Subjects with qRT-PCR above 10% at 6 months will be taken off study and managed according to standard of care, but will be followed for survival. Eligible subjects who decline to switch to IM will come off treatment and continue to be followed for safety and survival. All subjects will be followed for a total of 60 months from the time of last subject's enrollment on the study.

A study-dedicated research coordinator will contact subjects every 3 months in the first six months after initiating treatment, then every 6 months thereafter, using telephone or video conferencing to provide education about CML and common side-effects of TKIs, provide reminders to complete MDASI-CML forms when due, assess compliance, and address questions related to CML response. The nurse will also provide educational resources available on the internet.

Figure 2. Study schema



(<http://www.cmladvocates.net/education>, <http://www.nationalcmlsociety.org/side-effects>). Research nurse will also collect documentation of AEs and reports of qRT-PCR collected every 3 months from the treating hematologist. The nurse will also review results of the qRT-PCR with the investigator, generate and transmit a

standardized report that summarizes response to treatment using ELN guidelines. Study schema is shown in **Figure 2**.

Local hematologists will manage AEs and dose modifications according to the NCCN guidelines (**Appendix C**). AEs and dose modifications will be collected by the research nurse. Should the local hematologist decide to discontinue the first-line TKI due to intolerance, a switch the 2G-TKI to complete the first 3 months of therapy will be encouraged after discussion with the investigator. Subjects with intolerance or inadequate response to IM will be switched back to the 2G-TKI they received prior to initiating IM after discussion with the investigator.

4. Selection of Study Population

4.1 Inclusion Criteria:

1. Newly diagnosed, previously untreated CP-CML (by WHO definition) (hydroxyurea permitted up to 7 days prior to enrollment)
2. Age > 16 years
3. Able to give written informed consent and comply with all study visits and procedures.

4.2 Exclusion Criteria:

1. CML in AP or BP
2. Unable to receive TKI for insurance reasons (uninsurable)
3. Refuse or unable to perform telephone or video conferences with research nurse
4. Subjects who are pregnant, breast feeding or sexually active and unwilling to use effective birth control while on treatment with TKI
5. Clinically significant gastrointestinal disease, digestive dysfunction, or surgery that would compromise absorption of oral administration of medications
6. Any medical or psychological condition that, in the opinion of the Investigator, might interfere with the subject's participation in the trial, poses any additional risk for the subject, or confounds the assessment of the subject

5. Study Procedures

5.1 Schedule of Events: The required procedures for the study and data collection process are shown in **Table 3**.

Table 3. Schedule of Events: study requirements.	Screening ± 14days	Day1	Evaluations at 3 and 6 months ± 14 days	Evaluations at 3, 6, 9, and 12 months ± 2 days	Evaluations q 6 months ± 7 days after 12 months	End of Treatment
¹ Informed Consent	X					
² History and Demographics	X					
³ CML history	X					
⁴ Physical Examination	X			X	X	X
⁵ Concomitant medications	X			X	X	X
⁶ CBC, differential and Serum Chemistries,	X			X	X	X
⁷ Urine HCG	X					

⁸ Blood qRT-PCR for <i>BCR-ABL1</i>				X	X	X
⁹ Compliance			X	X	X	X
¹⁰ Adverse Events			X	X	X	X
¹¹ Nurse Telemonitoring		X		X	X	X
¹² PRO			X*	X**		

* between first and second month only

** between third and fourth month, (1 month after starting IM) and at 12 months only if switched to imatinib

¹*Informed Consent*: All subjects must take part in the informed consent process prior to any study related activity. During the consent process, the person obtaining consent must inform the subject of all elements of informed consent. Adequate time must be allowed for questions and for the subject to make a voluntary decision. No protocol-specific procedures are to be performed until the subject has signed and dated the IRB approved informed consent form. Each subject's participation in the trial begins with the signing and dating of the informed consent form.

²*Medical/Surgical History and Demographics*: Medical/surgical history that includes diagnoses and therapies as well as demographic information that consists of the subject's age, gender, race, and ethnicity will be recorded.

³*CML History*: The initial presentation history and pathology including date of first onset of leukocytosis, CBC with differential, serum chemistries and LDH, spleen size and extra-medullary disease, diagnostic bone marrow aspirate and biopsy (overall marrow cellularity, morphologic number of blasts, cytogenetic findings with number of metaphases, FISH for BCR-ABL1, qRT-PCR for BCR-ABL1, and percentage of aberrant cells if flow cytometry performed must be recorded

⁴*Vital signs and Physical Examination*: Vital signs including temperature, pulse, and blood pressure, and complete physical examination, including weight, must be performed at screening, every 3 months in the first year, then biannually as part of standard of care unless new AEs.

⁵*Concomitant medications*: All prescribed, over the counter, and supplemental/herbal medications, including route of administration (oral, topical, intravenous, rectal, subcutaneous, etc.), frequency, and duration will be recorded.

⁶*Complete Blood Count (CBC), differential and Serum Chemistries*: CBC with automated differential and serum chemistries will be obtained at screening, every 3 months in the first year, then biannually as part of standard of care unless new AEs.

⁷*Urine human chorionic gonadotropin (HCG)*: HCG will only be performed in pre-menopausal women of childbearing age with no history of hysterectomy or bilateral tubal ligation.

⁸*Blood qRT-PCR for BCR-ABL1*: Blood qRT-PCR for *BCR-ABL1* will be obtained every 3 months until MMR, at 12 months, and then bi-annually thereafter will be done as part of standard of care.

⁹*Compliance*: will be obtained by getting the prescription filling information from the specialty pharmacy that the patient used.

¹⁰*Adverse event assessments*: All AEs will be collected by research nurse quarterly regardless if the event is considered related to the treatment or not. The AEs documented on the diary card will also be collected.

¹¹*Nurse/Coordinator Telemonitoring:* Research nurse will communicate with subject on day1, monthly in the first 6 months, then biannually unless new AEs

¹² *PRO:* subjects will receive the MDASI-CML questionnaire at the referring hematologist's office. Questionnaire will be obtained between first and second month 1 month after starting TKI, and between third and fourth month(1 month after starting IM) and at 12 months. The nurse will educate and remind subjects to complete forms when due

End of Treatment or Early Termination Procedures: The End-of-Treatment (or early termination) Visit should be performed within 2 weeks (14 days) of the subject/investigator decision to end treatment. ABL1 domain mutation will be obtained as part of standard of care in case of progressive disease. Subjects will be followed for up to 60 months. Reasons for coming off treatment will be documented.

Long Term Follow-up:

- *Safety:* All AEs ongoing or starting within 30 days after the End-of-Treatment must be recorded on the case report form (CRF). After this time, ongoing AEs thought to be at least possibly study-drug related and all ongoing serious adverse events (SAE) should be followed at least every 4 weeks until they resolve to baseline (or CTCAE grade ≤ 1), stabilize, or are considered to be chronic or irreversible.
- *Relapse-free Survival:* After enrollment on a TKI discontinuation trial or if subjects withdraw from study for toxicity or any reason, information on disease status (qRT-PCRs) will be collected every 6 months for up to 60 months from the time the last subject is registered on study.

5.2 Description of Study Visits

5.2.1 Visit 1 (Day -14 to -1): Screening

- Obtain written informed consent
- Record demographic data including age, gender, and race
- Obtain and Review medical, surgical, and CML history as described above.
- Record prior and concomitant medications including start/stop dates, indication, dose and frequency taken within 7 days of Day 1.
- Record results of CBC with differential count and CP Comp which is part of standard of care
- Collect urine for pregnancy test for female patients who are not postmenopausal or surgically sterile which is part of standard of care. If positive, repeat and confirm results prior to Visit 2. A second positive test will result in exclusion of the patient from the study.
- Obtain and record height in cm, weight in kg, vital signs, body temperature, systolic/diastolic BP and pulse rate. Obtain and record physical examination with spleen size in cm below the costal margin, and any extra medullary disease, as a part of standard of care.

5.2.2 Visit 2 (Day 1): Initiation of Treatment

- Review and document all inclusion and exclusion criteria to ensure that subjects meet all inclusion criteria and none of the exclusion criteria.
- First nurse telemonitoring
- MDASI-CML questionnaire

5.2.3 Disease response evaluation Visits (Months 3, 6, 9 and 12 ±14 days)

- Collect and record results of blood qRT-PCR of *BCR-ABL1*
- remind subjects of dosing instructions, and obtain drug diary card
- Assess TKI compliance by collecting prescription fill information from the pharmacy at 6 and 12 month visit only.
- Collect AEs and SAEs
- MDASI-CML questionnaire between 3rd and 4th month (1 month after starting IM) and at 12 months.

5.2.4 Visits (once patient is in MMR, every 6 months ± 14 days)

- Collect and record blood qRT-PCR of *BCR-ABL1*
- Assess TKI compliance by completing MMAS-8 at each telecommunication

5.2.5 Unscheduled Visits:

Unscheduled visits may occur at any time at the investigator's discretion, and appropriate clinical and laboratory measurements performed based on AEs or other findings.

5.2.6 End of Treatment Visit (±14 days)

The end of treatment visit will be at the time of last study monitoring or visit coinciding with loss of response or disease progression visit and should be completed as soon as possible after an end of study event. Only information about AEs and SAEs will be collected at this visit.

5.3 Subject Registration and Identification:

Demographic information on all subjects who sign the Informed Consent Form will be recorded on the master subject log. Those subjects who complete screening procedures and meet all eligible criteria may be enrolled. At the time of enrollment, the subject will be assigned a unique identification number, consisting of a study site number and a unique consecutive number.

5.3.1 Screen Failure:

Subjects who have signed informed consent and subsequently fail to meet the inclusion and/or exclusion criteria are defined as screen failures. For all screen failures, the Investigator is to maintain a screening log that documents the subject initials and reason(s) for screen failure. A copy of the log will be retained in the Investigator's study files.

5.3.2 Early Discontinuation:

In the event that a subject is withdrawn from the study, every effort will be made by the Investigator to document and report the reasons for withdrawal as thoroughly as possible. The reason(s) for termination must be clearly reported in the subject's CRF. An End-of-Treatment reason for discontinuation must be recorded for any subject who is registered. In the event that the subject fails to return for the necessary visit(s), an effort must be made to contact the subject to determine the reason, and this information should be recorded in the appropriate source record and the end-of-treatment CRF.

5.4 Study Duration:

The total estimated duration of the study is 7 years, including 24 months to accrue subjects, with 5 year for follow up for the last subject. TKIs will not be supplied to subjects as this is standard of care treatments and all drugs are approved for first line use in CML.

5.5 Withdrawal Criteria:

Subjects will be discontinued from further study if any of the following occur:

- Blast phase transformation
- Loss of MR (>1%) after initial achievement of MMR
- Significant deviation from the protocol or eligibility criteria
- Noncompliance with study or follow-up procedures
- Pregnancy
- Subject withdrawal of consent and decision to discontinue participation
- Termination of the trial
- Any other reason that, in the opinion of the Investigator, would justify removal of the subject from the study

5.6 Study Termination:

If the investigator, Data Monitoring Committee, or regulatory agencies discover conditions during the study that indicate that the study should be terminated, this action may be taken after appropriate consultation between the investigator, and Data Monitoring Committee. Conditions that may warrant termination of the study include, but are not limited to:

- Incidence of MMR at 12 months <28% at the first interim analysis
- Submission of knowingly false information from the research facility to the regulatory authorities
- Insufficient adherence to protocol requirements

Study termination and follow-up will be performed in compliance with the conditions set forth in the guidelines for GCP, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

6. Safety Assessments:

Safety Assessments: Safety will be assessed by routine physical and laboratory evaluations according to the schedule (**Table 3**) and as medically indicated. AEs will be recorded and the severity will be graded according to the NCI CTCAE v.4.0.

Adverse Events: Type, incidence, severity (graded in accordance with the NCI CTCAE v.4.0), timing, seriousness and relatedness, outcome, action taken with drug, and treatment will be assessed and documented by the investigator continuously throughout the study. Baseline malignancy-related signs and symptoms will be recorded as AEs during the study if they worsen in severity or increase in frequency. Procedures for following AEs at the end of treatment and beyond are outlined in Section 5.1.

7. PRO Questionnaire:

PRO assessments will be obtained using the MDASI-CML questionnaire. PRO generally encompass symptoms, multi-dimensional quality of life and functional status. Collection of PRO data offers the most powerful method to understand the subject experience with treatments by offering a more holistic approach to clinical response because the subjects' response can provide a richer picture of the treatment effects, both good and bad. In addition, minimizing symptoms and improving quality of life are increasingly being recognized as important goals in clinical studies. Changes in a person's physical, emotional, social and functional well-being are best measured by directly asking subjects about these areas using validated questionnaires, interviews or subject diaries. Non-English speaking subjects require validated survey in their languages. Subjects are required to complete the questionnaire in either English or Spanish whichever is their preference. MDASI-CML is a validated questionnaire derived from the MD Anderson symptom inventory questionnaires and consists of 13 symptom related questions and 7 CML specific questions in part 1. The second part consists of 6 questions that address the effects on subjects' quality of life. This is the only validated questionnaire in CML. The estimated time to completion is 5 minutes and the ease of completion has been validated by patient groups.[20]

8. Study Treatment:

All drugs are standard of care and no experimental drug will be given to subjects. The choice of treatment will be at the discretion of the treating physician. IM, DAS and NIL are all approved for first line use in CML. Subjects will be started on DAS or NIL as first line treatment.

8.1 Dose Selection, Treatment Administration, Compliance, and Dose Modifications:

DAS will be started at 100 mg once a day and NIL at 300 mg twice a day. Any dose reductions and dose interruptions will be noted. Subjects will be managed by the local oncologist with help from the PI or Co-Pi if requested. Dose modifications will be per the treating hematologist and as suggested by guidelines provided in **Appendix C**. Once subjects achieve a 1 log reduction in BCR-ABL1 at 3 months or 2 logs at 6 months, DAS or NIL will be discontinued and IM 400 mg once a day will begin. Dose modification of TKI will be done at the treating physician's discretion and will be per standard of care guidelines.(**Appendix C**) These events will be captured by the research nurse .

8.2 Allocation of Treatment:

The results of screening assessments for each subject will be reviewed by the investigator, who will approve each subject's enrollment. The choice of DAS and NIL will be at the discretion of the treating physician based on subject's location and the physician's choice.

8.3 Concomitant Medications:

All concomitant medications administered will be reviewed and standard guidelines will be followed for any medications with known drug interactions.

8.4 Treatment Supply:

8.4.1 Formulation, Packaging and Labeling:

Subjects will obtain the medication as per practice patterns which would be from pharmacies after insurance approval or after subject assistance programs that are available.

8.4.2 Treatment Storage, Dispensing, and Accountability

Subjects will be taking the medication at home and they will be responsible for the storage of the drug. Subjects will be counselled on the importance of adhering to the treatments. RN will contact the subject at diagnosis, monthly in the first 6 months and every 6 months for 60 months from start of treatment (Table 3). RN will ensure education is provided to the subject regarding compliance and will also ensure subject is completing the compliance diary. Compliance will be assessed by getting the prescription fill information from the pharmacy at 12 month intervals

8.4.3 Disposition of used and unused supplies

N/A.

9. Adverse Event Reporting

9.1 Adverse Events

9.1.1 Adverse Event Definition

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product whether or not considered related to the medicinal product. Any worsening of a preexisting condition, which is temporally associated with the use of the drug (i.e., occurs after the first dose of drug), is also an AE. AEs include:

- Abnormal test findings
- Changes in physical exam findings
- Other untoward medical events, regardless of their relationship to the drug, such as injury, events that require surgery, accidents, or apparently unrelated illnesses, and hypersensitivity
- AEs may include signs or symptoms resulting from: drug overdose, drug withdrawal, drug abuse, drug misuse, drug interactions, drug dependency, and, in utero drug exposure

9.1.2 Abnormal Laboratory Tests

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms that are considered clinically significant in the opinion of the investigator
- Test result requires additional diagnostic testing (other than merely repeating an abnormal test) or medical/surgical intervention
- Test result leads to a change in drug dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy

- Test result is considered to be an AE by the investigator

9.1.3 Performing Adverse Event Assessment

All observed or volunteered AEs, regardless of treatment group or suspected causal relationship to the investigational product, will be reported as described in the following sections. For all AEs, the investigator must pursue and obtain information adequate to determine the outcome of the AE and to assess whether it meets the criteria for classification as a serious AE requiring immediate notification to the appropriate regulatory agencies.

9.1.4 Reporting Period

For all enrolled subjects, AEs (serious and non-serious) should be recorded on the CRF beginning on day 1 and concluding 30 days following the last dose of the assigned study treatment or the investigator/subject decision to discontinue treatment, whichever occurs later. Any ongoing AEs thought to be at least possibly study-drug related and all ongoing SAEs after this time should be followed at least every 4 weeks until they resolve to baseline (or CTCAE grade \leq 1), stabilize, or are considered to be chronic/irreversible.

9.1.5 Adverse Event Severity

The severity of AEs will be assessed according to the CTCAE, v.4.0. If the AE is not defined in the CTCAE, the investigator will determine the severity of the AE based on the following definitions:

- Mild (grade 1): The AE is noticeable to the subject but does not interfere with routine activity. The AE does not require discontinuing administration or reducing the dose of the drug
- Moderate (grade 2): The AE interferes with routine activity but responds to symptomatic therapy or rest. The AE may require reducing the dose, but not discontinuing administration of the drug
- Severe (grade 3): The AE significantly limits the subject's ability to perform routine activities despite symptomatic therapy. In addition, the AE leads to discontinuing administration or reducing the dose of the drug
- Life-Threatening (grade 4): The AE requires discontinuing administration of the drug. The subject is at immediate risk of death
- Death (grade 5): The subject dies as a direct result of the complication or condition induced by administration of the drug

9.1.6 Causality

The investigator's assessment of causality must be provided for all AEs (serious and non-serious). An investigator's causality assessment is the determination of whether exists a reasonable possibility that the investigational product caused or contributed to the AE. In addition, if the investigator determines an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and on the SAE form and report such an assessment in accordance with the SAE reporting requirements. The investigator will use medical consideration and use the following categories of causality to determine the relatedness of an AE with the drug based on the following definitions. Not all criteria in each category of relatedness must be present.

- Definitely Not Related (not drug related): The subject did not receive drug, OR the temporal sequence of the AE onset relative to the administration of the drug is not reasonable, OR there is another obvious cause of the AE
- Probably Not Related (not drug related): there is evidence of exposure to drug, there is another more likely cause of the AE, dechallenge (if performed) is negative or ambiguous, rechallenge (if performed) is negative or ambiguous
- Possibly Related (drug related): there is evidence of exposure to drug, the temporal sequence of the AE onset relative to administration of the drug is reasonable, the AE could have been due to another equally likely cause, dechallenge (if performed) is positive
- Probably Related (drug related): there is evidence of exposure to drug, the temporal sequence of the AE onset relative to administration of the drug is reasonable, the AE is more likely explained by the drug than by another cause
- Definitely Related (drug related): there is evidence of exposure to drug, the temporal sequence of the AE onset relative to administration of the drug is reasonable, dechallenge is positive, rechallenge (if feasible) is positive, the AE shows a pattern consistent with previous knowledge of the test drug or a test drug class

9.1.7 Expectedness

The expectedness of an SAE is assessed by the Investigator in the overall classification of SAEs for regulatory reportability. Side effect profile for all the drugs is well known and subjects will be counselled on the expected side effects from the drugs they are taking.

9.2 Serious Adverse Events

The definitions and reporting requirements of ICH Guidelines for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2A, will be adhered to.

9.2.1 Serious Adverse Event Definition

An AE is considered an SAE if at least one of the following conditions applies:

- Death: An AE that results in death is any subject death within 30 days of the last dose of drug administration. The cause of death or AE that resulted in a fatal outcome is the SAE
- Life-threatening AE: An AE that places the subject, in the view of the investigator or the sponsor, at immediate risk of death from the event as it occurred (i.e., this does not include an event that had it occurred in a more severe form might have caused death)
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions: Any substantial disruption of a person's ability to conduct normal life functions
- Inpatient hospitalization or prolongation of existing hospitalization: Hospitalization refers to admission of a subject into a hospital for any length of time
- A congenital anomaly/birth defect: A fixed, permanent impairment established at or before birth
- Cancer: Occurrence or diagnosis of a new cancer during the study is considered an SAE. A new cancer is a cancer that is histopathologically different than the cancer under study in the trial (i.e., does not include metastatic or progressive disease)
- Overdose: Occurrences of overdose must be reported as an SAE

- Important medical event: Medical and scientific judgment should be exercised in determining whether an event is an important medical event. An important medical event may not result in death, be life-threatening, or require hospitalization. However, if it is determined that the event may jeopardize the subject and/or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical events should be reported as serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization; or the development of drug dependency or drug abuse.

AEs (reported from clinical studies) that require hospitalization or prolongation of hospitalization are considered serious. Any initial admission (even if less than 24 hours) to a health care facility meets these criteria. Adverse events that require emergency room care that do not result in hospital admission are not SAEs unless assessed by the investigator to be an important medical event. Hospitalization does not include the following: Hospice facilities, Respite care, skilled nursing facilities, Nursing home, Routine emergency room admissions, and same day surgeries (as outpatient/same day/ambulatory procedure)

Hospitalization or prolongation of hospitalization in the absence of a precipitating AE is not in itself an SAE. Examples include: social admission (e.g., subject has no place to sleep), optional admission not associated with a precipitating AE (e.g., for elective cosmetic surgery that was planned prior to study enrollment [appropriate documentation is required for these cases]), hospitalization or prolongation of hospitalization for scheduled therapy of the target malignancy of the study is not considered an SAE

9.2.2 Reporting Serious Adverse Events

All SAEs will be reviewed and assessed by study investigators. SAEs will be reported to the IRB of record for each site according to their IRB's policies.

9.2.3 Follow-up Information of Serious Adverse Events

Appropriate diagnostic tests should be performed and therapeutic measures, as medically indicated, should be instituted. Appropriate consultation and follow-up evaluations should be carried out until the event has resolved or is otherwise explained by the investigator. For all SAEs, the investigator is obligated to pursue and provide information to the appropriate regulatory agencies. There should be routine follow-up through and including 30 days after the last administration of assigned study treatment or the investigator/subject decision to discontinue treatment, whichever occurs later, in all subjects in order to monitor for the occurrence of SAEs. If an SAE continues after the 30-day evaluation period, then the subject must be followed until the event resolves or returns to baseline. The medical monitor may specify a longer period of time if required to assure the safety of the subject.

9.3 Other Safety Issues

9.3.1 Pregnancy

Females of childbearing potential and fertile males will be informed as to the potential risk of conception while participating in this treatment and will be advised that they must use effective contraception as is the standard of care. If a subject is confirmed pregnant during the trial, appropriate counseling should be provided and the follow up will continue per standard of care recommendations.

9.3.2 Overdose

An overdose is defined as the accidental or intentional ingestion or infusing of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE. These adverse events will be monitored as instructed in the schedule of events and as clinically indicated.

10. Statistical Considerations

10.1 General Considerations

For the purposes of this protocol and all analyses, a month of treatment is defined as 30 days, and will be the same length as a cycle of treatment.

10.2 Analysis Population Intention to treat (ITT) population: The ITT population includes all subjects who are enrolled in the study.

Safety Population: The safety population includes all subjects who have received at least 1 dose of TKIs.

Per-protocol Population: The per-protocol population includes all subjects who are enrolled, receive at least one dose of drug, and have no major protocol violations that could be expected to impact response data, such as: failure to satisfy one or more eligibility criteria, administration of other anti-cancer therapy concurrent with drug, and administration of incorrect drug dose. Major protocol violations will be finalized and documented prior to final data analysis.

10.3 Study Endpoints

Primary Endpoint: The primary objective is to determine the proportion of subjects who achieve MMR at 12 months will be determined. Only MMR at 12 months will be considered, MMR achieved before the 12 months and then subsequently lost will not be considered.

Secondary Endpoints:

- i. PFS will be measured from the time of CML diagnosis to the time of loss of MMR or loss of hematologic response
- ii. AP or BP free survival will be measured from the time of CML diagnosis to the time of transformation to AP or BP
- iii. The number of subjects with BCR-ABL1 transcript levels \leq MR⁴ at any time will be determined
- iv. Safety will be evaluated by the assessment of laboratory and clinical adverse events (AEs) using the CTCAE v4.03 criteria. Safety will be assessed by the frequency, duration, and severity of AEs and SAEs, and clinical evaluations and changes in clinical laboratory blood samples
- v. The PRO score extracted from the MDASI-CML will be determined and intra and inter subject changes will be compared at the different study-defined time points.

Exploratory Endpoints:

- i. Outcomes of subjects with and without detectable cells with aberrant lymphoid or myeloid markers at diagnosis will be compared

- ii. The proportion of subjects who achieve and maintain deep MR for 2 years and therefore qualify or enroll on a TKI discontinuation trial will be determined. Outcomes following TKI discontinuation will be collected

10.4 Determination of Sample Size:

Subjects that switch to IM will only be included in the analysis to assess the number of subjects that achieve MMR at 12 months which is the primary end point for the study. We assume that 15% will not achieve a 1 log reduction at 3 months or 2 log reduction at 6 months and therefore will not switch to IM. Assuming that the subjects switched to IM will have the same rate of MMR of 55%(P1) [8,14] at 12 months but not less than 40%(P0) as obtained with IM alone, a sample size of 85 achieves 80% power to detect a difference (P1-P0) of 0.1500 using a one-sided binomial test. The target significance level is 0.0500. The actual significance level achieved by this test is 0.0449. These results assume that the population proportion under the null hypothesis is 0.4000. We estimate that up to 15% of subjects started on DAS or NIL will not be able to switch to IM and will not be included in the analysis but will be included in the safety and outcome analysis at 5 years. The total sample size required will be 100 subjects to achieve the 85 subjects required for analysis towards the primary end point.

10.5 Safety and Efficacy Analysis

All subjects receiving at least 1 dose of drug will be considered evaluable for safety. Listings of laboratory test results will also be generated, and descriptive statistics summarizing the changes in laboratory tests over time will be presented. Exposure to drug over time will also be summarized. The AE incidence rates, as well as the frequency of occurrence of overall toxicity, categorized by toxicity grades (severity) will be described as obtained from subject forms and subject communications. Descriptive statistics will summarize the changes in BCR-ABL1 testing over time will be presented. Loss of MMR is defined as an increase in BCR-ABL1 by qRT-PCR test above 0.1% that is both confirmed within a month and associated with a rise in the qRT-PCR on a confirmatory test obtained 4 weeks later (ELN definition). For the primary and secondary efficacy endpoints, subgroup analyses will be performed by baseline potential prognostic factors. Subgroups will include: age, gender, race, underlying diagnosis, and other disease-related prognostic factors (disease status).

10.6 Interim Analysis

Interim analysis will be done after 50% of subjects that are enrolled and switched to IM have a 12 month follow up. The estimated 12 month MMR for DAS and NIL is 55%. The study hypothesizes that the rate of MMR will be similar to that of first line DAS or NIL and better than that seen with IM. Hence an MMR of less than 40% seen with IM alone would be taken as grounds for stopping the trial.

10.7 Protocol Deviations and Violations

To be protocol-compliant, a subject must not have any major protocol deviations during the study period. Protocol deviations will be identified prior to final analysis and will be listed by treatment group in the clinical study report.

11. Quality Control and Quality Assurance and Study Monitoring

The investigator is responsible for performing quality control and assurance checks. Before enrolling any subjects into this study, the investigator will review the protocol, the CRFs and instructions for their completion, the procedure for obtaining informed consent, and the procedure for reporting AEs with all personnel listed on the delegation of authority. All the regulatory documents will be collected by Emory study PI with the assistance of Georgia CORE. The investigator will perform monthly evaluation of the conduct of the trial and perform the following:

- Review information recorded in the CRFs and verify against source documents
- Review data for safety information and to identify missing data
- Review protocol violations, out-of-range data, and other data inconsistencies

Emory PI will set up monthly teleconference with GA CORE study sites investigators who have enrolled patients to provide oversight to the study. Data source documents (in the forms of patient medical records) from all consented subjects will be sent to and stored at Emory University from Georgia Core approved outside facilities. The data source documents will be used to complete case report forms by the Emory PI and his designee. The Emory PI and his designee will also be responsible for collecting all the study visits telecommunications to complete study case report forms.

Data gathered after the subjects sign the consent forms will be uploaded onto Oncore and information maintained in a database that will be accessible only by the Emory IRB approved personnel.

The Multi-Site Coordinator from Winship Cancer Institute of Emory University will be responsible for conducting remote monitoring visits annually.

This study will also be monitored by the DSMB Winship Committee.

12. Ethical Conduct of the Study

This study will be conducted in accordance with the ethical standards that have their origin in the Declaration of Helsinki and that are consistent with GCP guidelines and the applicable regulatory requirements.

12.1 Institutional Review Boards Approval

The protocol and the informed consent document must have the initial and at least annual approvals of the IRB. The signed IRB approval letter must identify the documents approved (i.e., list the investigator's name, the protocol number and title, the date of the protocol and informed consent document, and the date of approval of the protocol and the informed consent document). Any advertisements used to recruit subjects should also be reviewed by the IRB. Approval will be obtained from Emory IRB initially and the protocol will be submitted to GA CORE IRB to run this trial across the state of Georgia. Any amendments will need to be approved by both the IRBs once the trial is active.

Per Georgia Core SOP: [Interactions with the Institutional Review Board \(IRB\)](#), Georgia CORE communicates with the central IRB on behalf of the Georgia CORE network sites who use a central IRB throughout the research process in order to ensure compliance with the regulations and to protect the safety and well-being of study subjects. Georgia CORE network sites that use a local IRB are responsible for following their standard operating

procedures for interacting with the IRB. Georgia CORE will monitor the IRB interactions of the sites using local IRBs. In addition, Georgia CORE will be providing the study sponsor with a periodic investigator trial report for sponsor to review.

12.2 Subject Information and Consent

The study informed consent form will follow regulations that provide protection for human subjects in clinical investigations and to describe the general requirements for informed consent. The informed consent document will contain all of the elements of the informed consent specified in the regulations. Nothing in this protocol or the regulations is intended to limit the authority of a physician to provide emergency medical care under applicable regulations. In addition, regulatory agencies will be granted permit to conduct inspections and review records pertaining to this clinical investigation.

12.3 Subject Confidentiality

Throughout the course of the study, all PHI record will be kept securely using password protected computer terminals. Access to the data will be on a need to know basis, therefore, only those investigators listed in the protocol will have access to the data. A high premium will be placed on ensuring that identifying information is not made available to staff engaged in routine care of the subject unless if necessary for the safe performance of their duties. For this reason, all research-related samples and clinical data will be de-identified using assigned study-specific registration numbers for such non-standard of care procedures as much as possible.

The investigator agrees to keep all information in strict confidence and to request similar confidentiality from his/her staff and the IRB. Study documents (investigators' brochures and other material) will be stored appropriately to ensure their confidentiality. The information provided to the investigator may not be disclosed to others without direct written authorization, except to the extent necessary to obtain informed consent from subjects who wish to participate in the trial.

12.4 Data Safety Monitoring Committee

Subject safety, study efficacy and compliance will be reviewed on a quarterly basis. The Data and Safety Monitoring Committee (DSMC) of the Winship Cancer Institute will also oversee the conduct of this study. This committee will review pertinent aspects of study conduct including subject safety, compliance with protocol, data collection and efficacy. Initial study monitoring will occur within 1 year from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. Subsequent monitoring will occur in routine intervals per the Winship Data and Safety Monitoring Plan (DSMP) version 1-16-2015.

The DSMC will review pertinent aspects of the study to assess subject safety, compliance with the protocol, data collection, and risk-benefit ratio. Specifically, the Winship Cancer Institute Internal Monitors assigned to the DSMC may verify informed consent, eligibility, data entry, accuracy and availability of source documents, AEs/SAEs, and essential regulatory documents. Following the monitoring review, monitors will provide a preliminary report of monitoring findings to the Emory PI and other pertinent individuals involved in the conduct of the study. The Emory PI is required to address and respond to all the deficiencies noted in the preliminary report. Prior to the completion of the final summary report, monitors will discuss the preliminary report responses with the Emory sponsor and other team members (when appropriate). A final monitoring summary report will then be prepared by the monitor. Final DSMC review will include the final monitoring summary report with

corresponding Emory PI response, submitted CAPA (when applicable), Emory PI Summary statement, and available aggregate toxicity and safety data.

The DSMC will render a recommendation and rating based on the overall trial conduct. The Emory PI is responsible for ensuring that instances of egregious data insufficiencies are reported to the IRB. Continuing Review submissions will include the DSMC recommendation letter. Should any revisions be made to the protocol-specific monitoring plan after initial DSMC approval, the PI will be responsible for notifying the DSMC of such changes. The Committee reserves the right to conduct additional audits if necessary.

13. Data Handling and Record Keeping

13.1 Case Report Forms and Study Records

Study-specific CRFs will be made available for the conduct of this study. Study data, contained in source documentation, will be entered into the CRFs for all subjects enrolled in the study. All pertinent data records will be maintained for 5 years after completion or termination of the study.

13.2 Source Documents

The investigator agrees that qualified representatives of the sponsor and regulatory agencies will have the right, both during and after this study, to conduct inspections and to audit and review medical records pertinent to the clinical study as permitted by the regulations. Subjects will not be identified by name in any reports stemming from the study, and confidentiality of information in medical records will be preserved. The confidentiality of the subject will be maintained unless disclosure is required by regulations.

13.3 Retention of Data

Trial documents (including correspondence related to this clinical study, subject records, source documents, CRFs, drug inventory records and IRB and sponsor correspondence pertaining to the study, original subject, laboratory, and drug inventory records relating to the study) will be retained until 5 years after completion or termination of the study and according to the Clinical Trial Office policies. Thereafter, records will not be destroyed but stored at an offsite location.

13.4 Study Termination

The study will be terminated at any time for any of the following reasons:

- Failure to enroll subjects
- Protocol violations
- Inaccurate or incomplete data
- Unsafe or unethical practices
- Questionable safety of the drug
- Administrative decision

In the event of the termination of the Study, a written statement describing why the study was terminated prematurely will be made available by the investigator.

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Appendices:

Appendix A: Definition of Response in CP-CML:

a. Hematological Response:

Hematologic Response	Definition
Complete Hematological Response	<ul style="list-style-type: none"> • WBC < 10 x 10⁹/L • Basophils < 5% in blood • No myelocytes, promyelocytes, myeloblasts in the differential in blood • Platelet count < 450 x 10⁹/L • Spleen not palpable

b. Cytogenetic Response:

Cytogenetic Response (based on analysis of at least 20 metaphases)	% Philadelphia Chromosome Positive Cells
None	>95%
Minimal	66-95%
Minor	36-65%
Partial	1-35%
Complete	0%
Major	Complete + Partial responses

c. Molecular Responses:

Molecular response	qRT-PCR BCR-ABL1/ABL ratio
MR ¹	≤ 10% , 1 Log reduction
MR2	≤1%, 2 Log reduction
MR3, MMR or Major	≤ 0.1%, 3 Log reduction
MR4	< 0.01% 4 log reduction
Deep Molecular response	< 0.0032% or undetectable

Appendix B: Timing of molecular monitoring: ELN guidelines:

Time Point	
At diagnosis	Chromosomal analysis FISH for t (9:22) qRT-PCR
During treatment	qRT-PCR every 3 months till MMR then every 3-6 months <i>and/or</i> Chromosomal analysis at 3,6 and 12 months till Ccyr then every 12 months
Failure/progression	qRT-PCR, chromosomal analysis, immunophenotype and mutation analysis

Appendix C: Management of Adverse events

Imatinib:

Hematologic Toxicities

- Chronic phase, absolute neutrophil count (ANC) $<1.0 \times 10^9/L$, and/or platelets $<50 \times 10^9/L$: Hold imatinib until ANC $\geq 1.5 \times 10^9/L$ and platelets $\geq 75 \times 10^9/L$, then resume imatinib at the starting dose of 400 mg. If recurrence of ANC $<1.0 \times 10^9/L$ and/or platelets $<50 \times 10^9/L$, hold drug until ANC $\geq 1.5 \times 10^9/L$ and platelets $\geq 75 \times 10^9/L$, then resume imatinib at reduced dose of 300 mg.
- Growth factors can be used in combination with imatinib for patients with resistant neutropenia.
- Grade 3-4 anemia: Check reticulocyte count, ferritin, iron saturation, B12, folate, and correct nutritional deficiencies if present. Transfusion support should be used if patient is symptomatic.

Non-Hematologic Toxicities

- Bilirubin $>3 \times$ institutional upper limit of normal (IULN) or liver transaminases $>5 \times$ IULN: hold imatinib until bilirubin $<1.5 \times$ IULN and transaminase levels $<2.5 \times$ IULN. Resume imatinib at a reduced daily dose (400 mg to 300 mg, 600 mg to 400 mg, or 800 mg to 600 mg).
- Severe hepatotoxicity or severe fluid retention: hold imatinib until the event has resolved. Treatment can be resumed as appropriate depending on the severity of the event.
- Patients with moderate renal impairment (CrCL = 20–39 mL/min) should receive 50% decrease in the recommended starting dose and future doses can be increased as tolerated. Doses greater than 600 mg are not recommended in patients with mild renal impairment (CrCL = 40–59 mL/min). For patients with moderate renal impairment, doses greater than 400 mg are not recommended. Imatinib should be used with caution in patients with severe renal impairment.

Specific Interventions

- Fluid retention (pleural effusion, pericardial effusion, edema, and ascites): diuretics, supportive care, dose reduction, interruption, or discontinuation. Consider echocardiogram to check LVEF.
- GI upset: Take medication with a meal and large glass of water.
- Muscle cramps: calcium supplement, tonic water
- Rash: topical or systemic steroids, dose reduction, interruption, or discontinuation

Dasatinib:

Hematologic Toxicities

- ANC $<0.5 \times 10^9/L$ or platelets $<50 \times 10^9/L$: Hold dasatinib until ANC $\geq 1.0 \times 10^9/L$ and platelets $\geq 50 \times 10^9/L$, then resume dasatinib at the starting dose if recovery occurs in ≤ 7 days. If platelets $<25 \times 10^9/L$ or recurrence of ANC $<0.5 \times 10^9/L$ for >7 days, hold drug until ANC $\geq 1.0 \times 10^9/L$ and platelets $\geq 50 \times 10^9/L$, then resume dasatinib at reduced dose of 80 mg once daily for second episode. For third episode, further reduce dose to 50 mg once daily.
- Growth factors can be used in combination with dasatinib for patients with resistant neutropenia and thrombocytopenia.
- Grade 3-4 anemia: Check reticulocyte count, ferritin, iron saturation, B12, folate, and correct nutritional deficiencies if present. Transfusion support should be used if patient is symptomatic.

Non-Hematologic Toxicities

- If a severe, non-hematologic, adverse reaction develops with dasatinib, treatment must be held until the event has resolved or improved.

Thereafter, treatment can be resumed as appropriate at a reduced dose depending on the initial severity of the event.

Specific Interventions

- Fluid retention events (ascites, edema, pleural and pericardial effusion): diuretics, supportive care.
- Pleural/pericardial effusion: diuretics, dose interruption. If patient has significant symptoms, consider short course of steroids (prednisone 20-50 mg/day x 3-4 days, may taper with 20 mg/day x 3-4 days); when resolved, reduce one dose level.
- GI upset: Take medication with a meal and large glass of water.
- Rash: topical or systemic steroids, dose reduction, interruption, or discontinuation

Nilotinib:

Hematologic Toxicities

- ANC $<1.0 \times 10^9/L$, and/or platelets $<50 \times 10^9/L$: Hold nilotinib and monitor blood counts. Resume within 2 weeks at prior dose if ANC $>1.0 \times 10^9/L$ and platelets $>50 \times 10^9/L$. If blood counts remain low for >2 weeks, reduce dose to 400 mg once daily.

Non-Hematologic Toxicities

- Elevated serum lipase, amylase, bilirubin, or hepatic transaminases grade ≥ 3 : hold nilotinib and monitor serum levels. Resume nilotinib at 400 mg once daily if serum levels return to grade ≤ 1 .

Specific Interventions

- Rash: topical or systemic steroids, dose reduction, interruption, or discontinuation.
- Growth factors can be used in combination with nilotinib for patients with resistant neutropenia and thrombocytopenia.
- Grade 3–4 anemia: Check reticulocyte count, ferritin, iron saturation, B12, folate, and correct nutritional deficiencies if present. Transfusion support should be used if patient is symptomatic.

M. D. Anderson Symptom Inventory (MDASI - CML)

Part I. How severe are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been *in the last 24 hours*. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	NOT PRESENT										AS BAD AS YOU CAN IMAGINE
	0	1	2	3	4	5	6	7	8	9	10
1. Your pain at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
2. Your fatigue (tiredness) at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
3. Your nausea at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
4. Your disturbed sleep at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
5. Your feeling of being distressed (upset) at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
6. Your shortness of breath at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
7. Your problem with remembering things at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
8. Your problem with lack of appetite at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
9. Your feeling drowsy (sleepy) at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
10. Your having a dry mouth at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
11. Your feeling sad at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
12. Your vomiting at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
13. Your numbness or tingling at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Date: _____
 Participant Initials: _____
 Participant Number: _____

Institution: _____
 Hospital Chart #: _____

	NOT PRESENT										AS BAD AS YOU CAN IMAGINE
	0	1	2	3	4	5	6	7	8	9	10
14. Your diarrhea at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
15. Your swelling of your hands, legs, feet, abdomen, or around your eyes at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
16. Your rash or skin change at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
17. Your muscle soreness or cramping at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
18. Your bruising easily or bleeding at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
19. Your feeling of malaise (not feeling well) at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
20. Your headache at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Part II. How have your symptoms interfered with your life?

Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items in the last 24 hours:

	DID NOT INTERFERE									INTERFERED COMPLETELY	
	0	1	2	3	4	5	6	7	8	9	10
21. General activity?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
22. Mood?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
23. Work (including work around the house)?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
24. Relations with other people?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
25. Walking?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
26. Enjoyment of life?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>