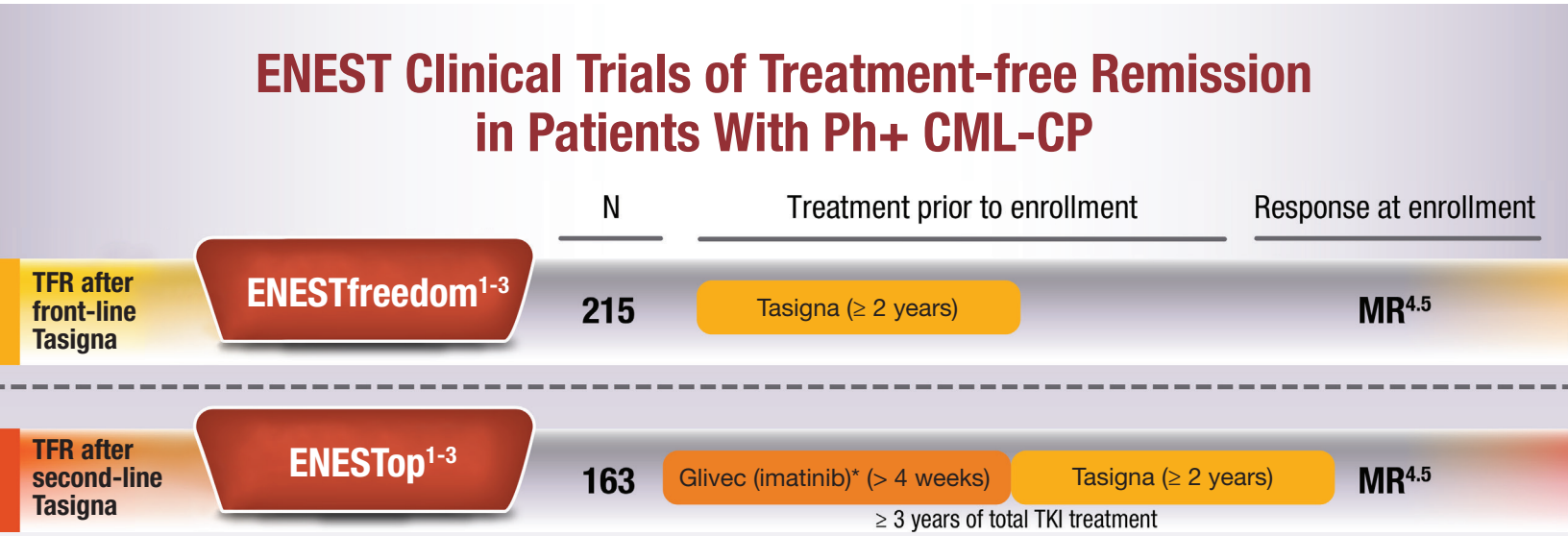
Novartis Treatment-free Remission Clinical Trial Program: Overview of ENESTfreedom and ENESTop

The **Novartis Treatment-free Remission (TFR) clinical trial program** is designed to evaluate the potential for adult patients with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in the chronic phase to achieve a sustained deep level of molecular response and maintain a major molecular response (MMR) after stopping Tasigna® (nilotinib) therapy – a concept called TFR.

As part of this initiative, Novartis is sponsoring four studies: **ENESTfreedom, ENESTop, ENESTpath and ENESTgoal.** ENESTfreedom and ENESTop are the first of the four studies to have TFR results presented.

The graphical representation of the clinical study design is provided for ease of understanding the unique structure of these trials. Stopping tyrosine kinase inhibitor (TKI) treatment for CML treatment is currently not a clinical recommendation and should only be attempted in the context of a clinical study.

ENEST Clinical Trials of Treatment-free Remission in Patients With Ph+ CML-CP



CML-CP, chronic myeloid leukemia in chronic phase; **ENEST**, Evaluating Nilotinib Efficacy and Safety in Clinical Trials; **MR⁴**, *BCR-ABL1* ≤ 0.01% on the International Scale (IS); **MR$^{4.5}$**, *BCR-ABL1*^{IS} ≤ 0.0032%; **MMR**, major molecular response (*BCR-ABL1*^{IS} ≤ 0.1%);

1. Mahon FX, et al. Presented poster: 2014 ASCO Annual Meeting; May 30-June 3, 2014; Chicago, IL [abstract TPS7124]; 2. https://www.clinicaltrials.gov. Accessed January 5, 2016; 3. Data on file

The safety and efficacy of stopping nilotinib treatment has not been demonstrated and should only be attempted as part of a controlled clinical study.

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May 2016
G-CML-1137880
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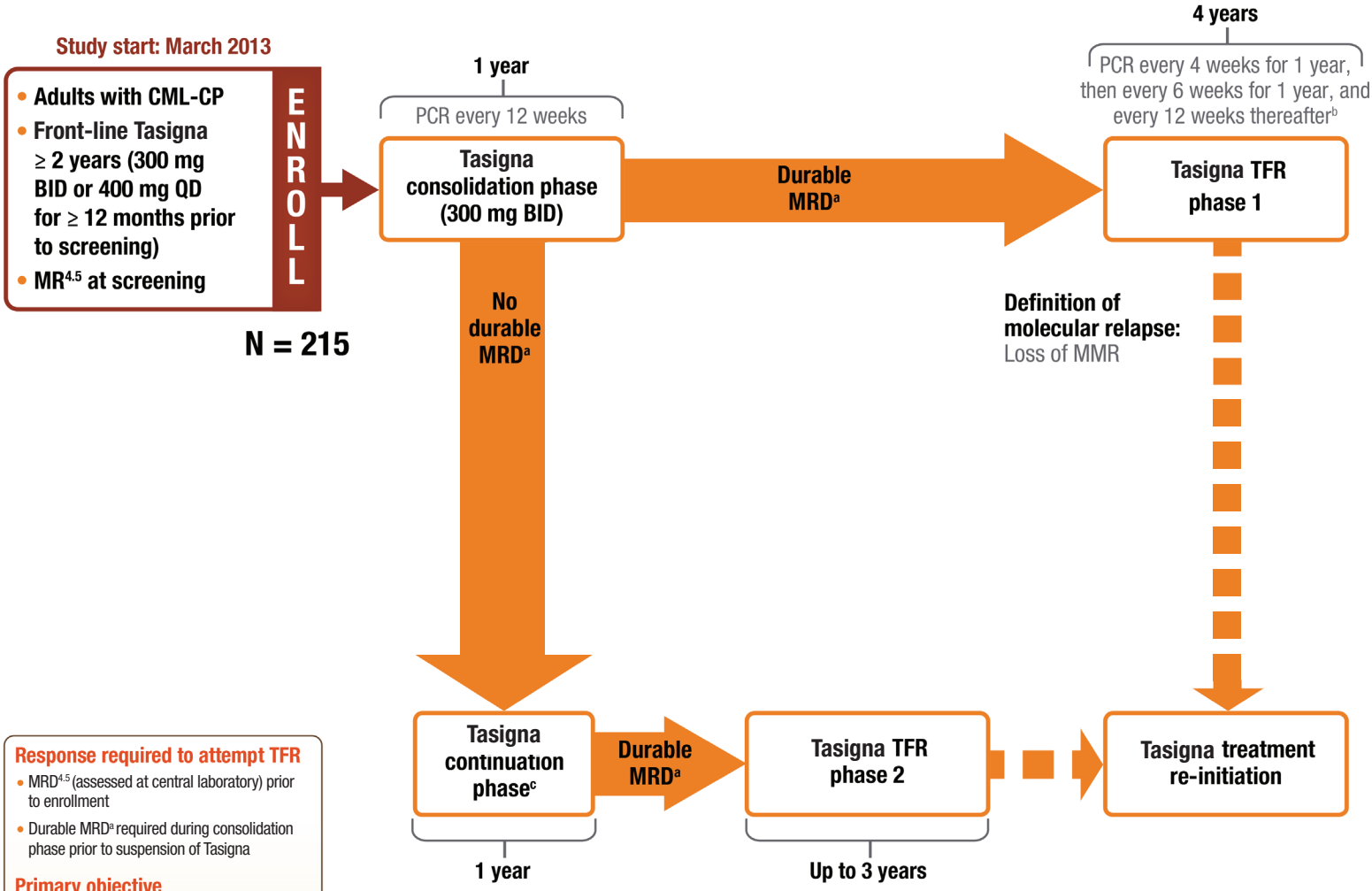
ENESTfreedom Study Design



Response required to attempt TFR

- MRD[4.5] (assessed at central laboratory) prior to enrollment
- Durable MRD[a] required during consolidation phase prior to suspension of Tasigna

Primary objective

Rate of TFR (no loss of MMR and no re-initiation of Tasigna treatment at 48 weeks from start of the TFR phase)

Estimated study completion: January 2019

BID, twice daily; **MRD**, minimal residual disease; **PCR**, polymerase chain reaction; **QD**, once daily.

[a] Durable MRD is defined as the following results from the last 4 quarterly PCR assessments: $MR^{4.5}$ in the last assessment, no assessment worse than MR^4, and ≤ 2 assessments between MR^4 and $MR^{4.5}$. [b] Patients with a loss of MR^4 during the TFR phase will undergo PCR monitoring every 2 weeks. [c] If no durable MRD after this point, patients may continue to receive nilotinib in the prolonged nilotinib continuation phase until the end of the study.

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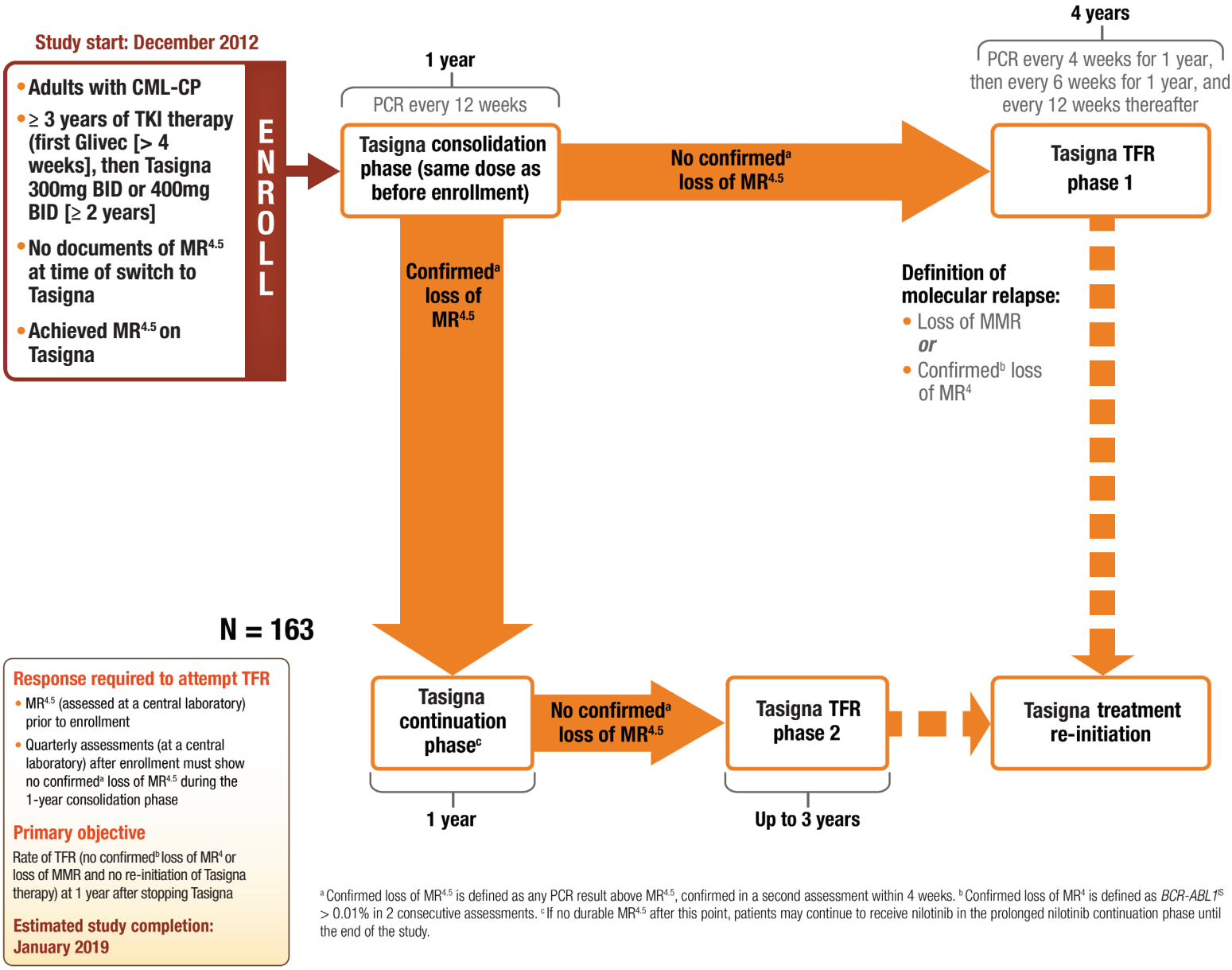
ENESTop Study Design



[a] Confirmed loss of MR4.5 is defined as any PCR result above MR4.5, confirmed in a second assessment within 4 weeks. [b] Confirmed loss of MR4 is defined as *BCR-ABL1*IS > 0.01% in 2 consecutive assessments. [c] If no durable MR4.5 after this point, patients may continue to receive nilotinib in the prolonged nilotinib continuation phase until the end of the study.

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About Tasigna (nilotinib)

Tasigna® (nilotinib) is approved in more than 122 countries for the treatment of chronic phase and accelerated phase Philadelphia chromosome-positive chronic myelogenous leukemia (Ph+ CML) in adult patients resistant or intolerant to at least one prior therapy, including Glivec® (imatinib), and in more than 120 countries for the treatment of adult patients with newly diagnosed Ph+ CML in chronic phase.

IMPORTANT SAFETY INFORMATION for TASIGNA® (nilotinib) Capsules

Use with caution in patients with uncontrolled or significant cardiac disease and in patients who have or may develop prolongation of QTc. Low levels of potassium or magnesium must be corrected prior to Tasigna administration. Monitor closely for an effect on the QTc interval. Baseline ECG is recommended prior to initiating therapy and as clinically indicated. Cases of sudden death have been reported in clinical studies in patients with significant risk factors. Avoid use of concomitant drugs known to prolong the QT interval and strong CYP3A4 inhibitors. Avoid food 2 hours before and 1 hour after taking dose. Reactivation of hepatitis B can occur in patients who are chronic carriers of this virus after receiving TKI treatment.

Use with caution in patients with liver impairment, with a history of pancreatitis and with total gastrectomy. Patients with rare hereditary problems of galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption should not use Tasigna. Tasigna may cause fetal harm in pregnant women. Women taking Tasigna should not breastfeed.

Cases of cardiovascular events included ischemic heart disease-related events, peripheral arterial occlusive disease, and ischemic cerebrovascular events have been reported. Serious cases of hemorrhage from various sites including gastrointestinal were reported in patients receiving Tasigna. Grade 3 or 4 fluid retention including pleural effusion, pericardial effusion, ascites and pulmonary edema have been reported. Cases of tumor lysis syndrome have been reported in Tasigna-treated patients who were resistant or intolerant to prior
CML therapy.

The most frequent Grade 3 or 4 adverse events are hematological (neutropenia, thrombocytopenia, anemia) which are generally reversible and usually managed by withholding Tasigna temporarily or dose reduction. Chemistry panels, including electrolytes, lipid profile, liver enzymes, and glucose should be checked prior to therapy and periodically. Tasigna can cause increases in serum lipase. The most frequent non-hematologic adverse events were rash, pruritus, nausea, fatigue, headache, alopecia, myalgia, constipation and diarrhea.

Please see full Prescribing Information including Boxed WARNING at www.tasigna.com.

TFR is an investigational use for Tasigna. There is no guarantee Tasigna will become commercially available for this use.

Stopping CML treatment is currently not a clinical recommendation and should only be attempted in the context of a clinical study.

An important part of the Novartis TFR studies is the inclusion of regular molecular monitoring using the International Scale Real-Time Quantitative Polymerase Chain Reaction Test to determine if a patient's level of disease remains in remission or if the reintroduction of treatment is needed.

*Known as Gleevec® (imatinib mesylate) tablets in the US, Canada and Israel.

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