Stopping NUC therapy in Piranga

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The Piranga Phase 2 Study

Piranga
Combination Therapies for Chronic Hepatitis B

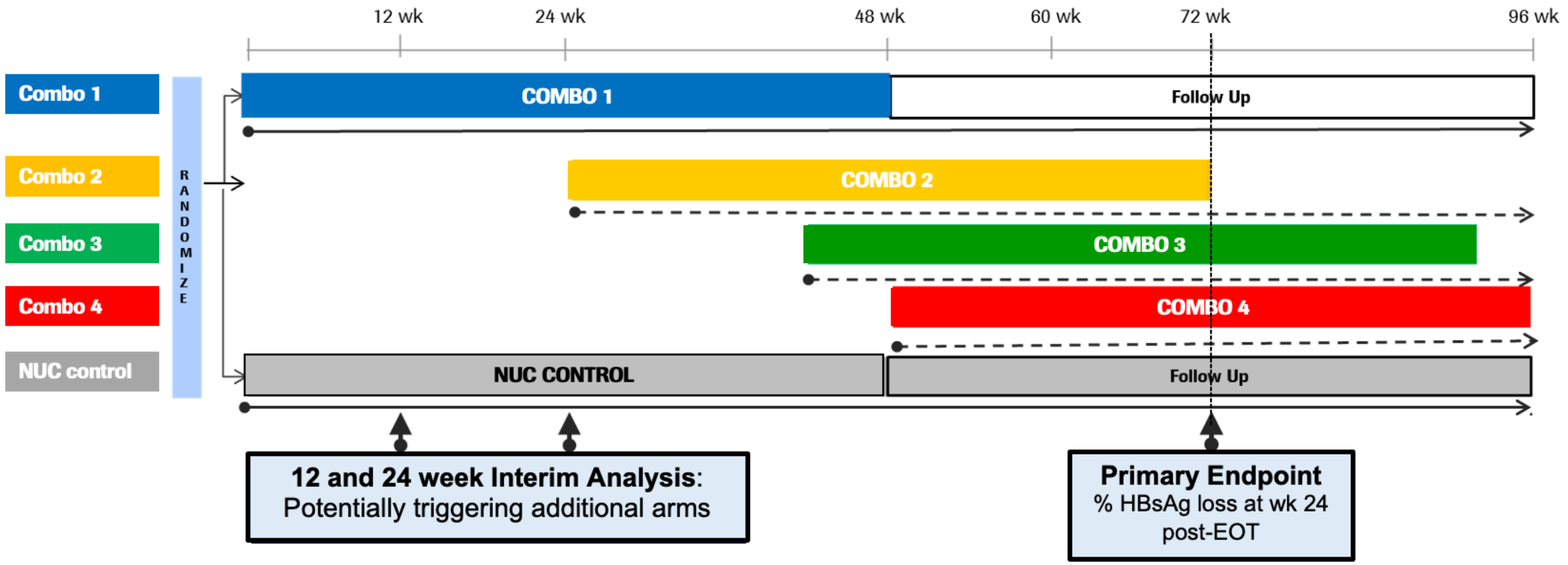
A phase 2, randomised, adaptive, open-label, platform trial to evaluate efficacy and safety of multiple combination therapies for the finite treatment of chronic hepatitis B

Current Population	• Virologically suppressed patients on NUC therapy for ≥12 months
Primary Endpoint	• Efficacy: % patients with HBsAg loss at 24 weeks post-end of treatment

Trial started in July 2020

Piranga schematic

Concept: To study multiple targeted finite therapies in an ongoing manner, with therapies allowed to enter or leave the platform on the basis of a decision algorithm



EOT=End-of-treatment

Piranga: Criteria for stopping NUCs

Participants will stop NUCs at any time during the follow-up period if samples taken at EoT (week 48) or at any of the follow-up visits show:

1. ALT <1.25 x baseline values, *AND*
2. HBV DNA <LLOQ or <20 IU/mL, *AND*
3. Negative HBeAg (if HBeAg positive at baseline), *AND*
4. HBsAg at EoT <100 IU/mL (or >1 log reduction from baseline, under review)

FDA's comments (2019) - Benchmarks that must be met for NUC discontinuation in combo arms: at a minimum, ALT <1.25 X ULN, HBV DNA <LLOQ, HBeAg negative. Also open to consider an absolute threshold in HBsAg level at EoT (in addition to a treatment-induced decrease)*

*noting that HBsAg decline to a certain plateau is currently not sufficiently validated as a surrogate endpoint for predicting HBsAg loss

EMA's comments (2019) – Same approach advised for discontinuation in NUC control arm as per other arms

LLOQ = lower limit of quantification

Piranga: Secondary efficacy endpoints

Current Population	• Virologically suppressed CHB patients on NUC therapy for ≥12 months
Primary Endpoint	• Efficacy: % patients with HBsAg loss at 24 weeks post-end of treatment
Secondary Efficacy Endpoints	• % patients with: i) HBsAg loss/seroconversion ii) HBeAg loss/seroconversion (for HBeAg-positive participants) iii) HBV DNA levels <2,000 IU/ml, <200 IU/ml and <LLOQ • Change from baseline in quantitative HBsAg, anti-HBs, HBeAg, anti-HBe, HBV DNA, **HBcrAg, HBV RNA***

*Roche Diagnostics investigational assay for use on the cobas® 6800/8800 Systems; LLOQ 10 copies/ml; linearity range 10 to 10^9 copies/ml on armoured RNA template

LLOQ=Lower limit of quantification