Statistical Analysis Plan

TRIAL FULL TITLE	Multi-Drug Combination-Therapies to Prevent the Development of Drug Resistance *Phase II Controlled Clinical Trial Assessing Candidate Regimens of Multiple-Antimalarial Combinations for the Treatment of Uncomplicated Malaria in Africa*
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1 SAP Signatures

I give my approval for the attached SAP entitled MultiMal_SAP03032020

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3 Abbreviations and Definitions

3.1 Definitions

qPCR

A polymerase chain reaction procedure is used to quantify the amount of P falciparum-specific DNA present and is transformed into number of parasites/µL. Where the presence of gametocytes is suspected the sample can be tested for the presence of Psf25 transcripts using an RT-PCR method or the sample can be concentrated for detection by microscopy.

Re-emergence/Recurrence

Re-emergence (recrudescence and re-infection) is defined as the appearance of asexual parasites after clearance of initial infection irrespective of genotype. Recrudescence or re-infection must be confirmed by microscopy (positive blood smear) and PCR analysis.

Recrudescence

Recrudescence is defined as the appearance of asexual parasites after clearance of initial infection with a genotype identical to that of parasites present at baseline. Recrudescence must be confirmed by microscopy (positive blood smear) and PCR analysis.

Re-infection

Re-infection is defined as the appearance of asexual parasites after clearance of initial infection with a genotype that differs from that of parasites present at baseline. Re-infection must be confirmed by microscopy (positive blood smear) and PCR analysis. Confirmed new infection will not be regarded as treatment failure or recrudescence.

3.2 Abbreviations

Ab	Antibody
ACPR	Adequate clinical and parasitological response
ACT	Artemisinin combination therapy
AE	Adverse Event
AFC	Oral artesunate-fosmidomycin-clindamycin
ALT	Alanin transaminase

AP	Oral artesunate/pyronaridin standard treatment
APAP	Oral artesunate-pyronaridine-atovaquone/proguanil
AST	Aspartate transaminase
AUC	Area under curve
BMI	Body Mass Index
CI	Confidence interval
CRF	Case Report Form
CSR	Clinical Study Report
ETF	Early treatment failure
FCT	Fever clearance time
HAV	Hepatitis A virus
Hb	Haemoglobin
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
LAR	Legally acceptable representative
LCF	Late clinical failure
LFT	Liver function tests
LPF	Late parasitological failure
MedDRA	Medical Dictionary for Regulatory Activities
MedDRA SOC	MedDRA System Organ Class
PCR	Polymerase chain reaction
PCT	Parasite clearance time
PRR	Parasite reduction rate
RCT	Randomised controlled clinical trial
SAP	Statistical Analysis Plan
SD	Standard deviation
SEA	South East Asia
TEAE	Treatment related adverse event
TESAE	Treatment related severe adverse event
ULN	Upper limit of normal
WHO	World Health Organization

4 Introduction

Antimalarial drug resistance is one of the most important challenges in the control and elimination of malaria. Artemisinin combination therapy (ACT) as bi-therapy is the standard of care in all malaria endemic countries (World Health Organization, 2018). However, the efficacy of ACTs as bi-therapy declined in the past decade in the Greater Mekong Region of South East Asia (SEA). Subsequently, epidemiological genomic studies confirmed that in fact artemisinin resistance developed much earlier in numerous foci, resulting in resistant parasites. Importantly, drug resistance against the partner drugs evolved simultaneously leading to decreasing cure rates of first line antimalarial treatments in SEA (Amato et al., 2017; 2018; Miotto et al., 2015). Multi-drug combination therapy is an appealing approach to increase the barriers for resistance if partner drugs with matched half-lives are combined. Specific drugs were carefully considered during the design of this study. The outcome of this consideration was that the specific multi-therapeutic ACT combinations, discussed below, were decided on based on the following aspects: efficacy, potential for drug interactions, modes-of-action, half-life of the individual drugs, parasitological stages the drug acts on, dosing, availability of a paediatric formulation and cost.

The two drug combinations envisaged to investigate during this study address two particular aspects of treatment of uncomplicated malaria in the sub-Saharan African region. Firstly, **artesunate-pyronaridine-atovaquone/proguanil** uses a quadruple drug treatment with combinations of different modes of action to protect each other from the parasite developing resistance to either during the treatment. Secondly, the combination of **artesunate-fosmidomycin-clindamycin** as a matched-short-half-life combination additionally addresses the issue of bacterial co-infections which frequently occur in sub-Saharan Africa.

5 Study Design

A **randomised-controlled clinical trial** (RCT) will be conducted comprising three treatment arms:

Group A: Oral artesunate/pyronaridin standard treatment **(AP)**
Group B: Oral artesunate-pyronaridine-atovaquone/proguanil **(APAP)**
Group C: Oral artesunate-fosmidomycin-clindamycin **(AFC)**

There are 3 age groups in the step-down procedure:
18-65y --> 11-17y --> 6 months - 10 y

For **Group A**: It will be **0 patients** for 18-65y, **10 patients** for 11-17y and **10 patients** for 6 months - 10y

For **Group B**: It will be **10 patients** for 18-65y, **10 patients** for 11-17y and **20 patients** for 6 months - 10y

For **Group C:** It will be **10 patients** for 18-65y, **10 patients** for 11-17y and **20 patients** for 6 months - 10y

Randomization and group allocation

A 1:2:2 randomization will be performed for each age group using computer generated random permuted blocks stratified by country of recruitment. Block sizes will be variable between 4 and 9 to ensure allocation concealment will be maintained throughout the conduct of this open-label trial. Allocation will be concealed until the randomization is performed by the investigator. No blinding/masking will be performed for clinical investigations in this open label clinical trial. Genotyping of reappearing parasitaemia will be performed in a single-blinded way by concealing treatment groups to the molecular biologist.

Treatment schedules for treatment groups are summarized below:

Group A (AP):

Artesunate-pyronaridine (Pyramax): Once daily oral dosing for three days independent of food:

Paediatric dosing regimen:
5 <-8 kg: 1 sachet daily
8 -<15 kg: 2 sachets daily
15-20 kg: 3 sachets daily
1 sachet contains 20 mg artesunate and 60 mg pyronaridine
Adult dosing regimen:
20-<24 kg: 1 tablet daily
24-45 kg: 2 tablets daily
45-<65 kg: 3 tablets daily
>65 kg: 4 tablets daily
1 tablet contains 60 mg artesunate and 180 mg pyronaridine

Group B (APAP):

Atovaquone-proguanil (Malarone or generic): Once daily oral dosing for three days with food/milk:
5-8 kg: Atovaquone/proguanil 125 mg/50 mg

9-10 kg: Atovaquone/proguanil 187.5 mg/75 mg
11-20 kg: Atovaquone/proguanil 250 mg/100 mg
21-30 kg: Atovaquone/proguanil 500 mg/200 mg
31-40 kg: Atovaquone/proguanil 750 mg/300 mg
>40 kg: Atovaquone/proguanil 1000 mg/400 mg

Group C (AFC):
Artesunate: 2 mg/kg twice daily oral dosing for 3 days independent of food as calculated closest to the capsule strength
Fosmidomycin: 30 mg/kg twice daily oral dosing for 3 days independent of food as calculated closest to the capsule strength
Clindamycin hydrochloride: 10 mg/kg twice daily oral dosing for 3 days independent of food as calculated closest to the capsule strength (150 mg, 300 mg, 600 mg)
Include a brief statement of the purpose of the analyses. For example:
These analyses will assess the efficacy and safety of [IMP] in comparison with the [standard] and will be included in the clinical study report

5.1 Study Objectives and Outcomes

5.1.1 Study Objectives

5.1.1.1 Primary objective

To describe the pharmacokinetic properties of each partner drug and their principal active metabolites in the two antimalarial combination treatments artesunate-pyronaridine-atovaquone/proguanil (APAP) and artesunate-fosmidomycin-clindamycin (AFC), respectively in patients with uncomplicated malaria.

5.1.1.2 Secondary objective

- To determine the PCR corrected adequate clinical and parasitological response (ACPR=cure rate) on Day 42 in per protocol population
- To determine the PCR corrected cure rate on day 28 in per protocol population
- To determine the PCR uncorrected cure rates on days 28 and 42 in intention to treat population
- To determine the safety and tolerability of combination therapies in intention to treat population
- To determine the parasite clearance dynamics of combination therapies
- To determine the proportion of patients with sexual stage parasitaemia during follow up

5.1.2 Outcomes (i.e. Study endpoints)

5.1.2.1 Primary outcome

Descriptive analysis of pharmacokinetics of each partner drug and their principal active metabolites

5.1.2.2 Secondary outcomes

- PCR corrected adequate clinical and parasitological response on Day 42 in per protocol population
- PCR corrected adequate clinical and parasitological response on day 28 in per protocol population
- PCR uncorrected adequate clinical and parasitological responses on days 28 and 42 in intention to treat population
- Safety and tolerability of combination therapies in intention to treat population
- Parasite clearance dynamics of combination therapies
- Proportion of patients with sexual stage parasitaemia during follow up

5.1.2.3 Safety outcomes

5.1.2.3.1 Adverse events

Adverse events are reported at each study visit.

5.1.2.3.2 Concomitant medication

Usage of medications during study period will be recorded.

5.2 Inclusion-Exclusion Criteria

Inclusion Criteria

1. Male or female patient age >6 months <66 years.
2. Body weight >5 kg <90 kg
3. Presence of mono-infection of P. falciparum with:

a. Fever, as defined by axillary temperature ≥ 37.5°C or oral/rectal/tympanic temperature ≥ 38°C, or history of fever in the previous 24 hours

b. Microscopically confirmed parasite infection, in range 1,000 to 100,000 asexual parasites /µL of blood.

4. Written informed consent provided by the adult patient, or parent or legally acceptable representative (LAR) of the minor patient or by an impartial witness (if the patient or patient's LAR is illiterate), stating that the information has been read and/or is understood, and

by the medically qualified Investigator. Children will be asked to provide assent where appropriate. The age from which this will be sought will be defined by local legislation.

Exclusion Criteria

1. Presence of severe malaria (according to WHO definition – WHO 2013)
2. Anti-malarial treatment in the last 6 weeks.
3. Known history or evidence of clinically significant disorders such as, cardiovascular, respiratory (including active tuberculosis), hepatic, renal, gastrointestinal, immunological (including active HIV-AIDS), neurological (including auditory), endocrine, infectious, malignancy, psychiatric, history of convulsions or other abnormality (including head trauma).
4. Mixed Plasmodium infection
5. Severe vomiting, defined as more than three times in the 24 hours prior to enrolment in the study or inability to tolerate oral treatment, or severe diarrhoea defined as 3 or more watery stools per day
6. Severe malnutrition (defined for subjects aged ten years or less as the weight-for- height being below -3 standard deviation or less than 70% of median of the NCHS/WHO normalised reference values, and for subjects aged greater than ten years, a body mass index (BMI) of less than 16 (WFP Manual, Chapter 1)).
7. Known history of hypersensitivity, allergic or adverse reactions to any of the study drugs
8. Known active Hepatitis A IgM (HAV-IgM), Hepatitis B surface antigen (HBsAg) or Hepatitis C antibody (HCV Ab).
9. Haemoglobin level below 8 g/dL.
10. Serum creatinine levels $\geq$2 x ULN
11. Female patients of child bearing potential must be neither pregnant (as demonstrated by a negative pregnancy test) nor lactating, and must be willing to take measures not to become pregnant during the study period and safety follow-up period.
12. Have received an investigational drug within the past 4 weeks.
13. Previous participation in any malaria vaccine study or received malaria vaccine in any other circumstance.
14. Refusal to participate and to provide written or witnessed informed consent or assent.

6 Sample Size

Each group will consist of 20 evaluable patients (with 10 patients in the semi-immune sub-group allocated to the age groups 18-65 years and 11-17 years, respectively) and a consecutive group of 20 patients aged 6 months to 10 years, to allow for adequate pharmacokinetic characterization of study drugs. The total number of evaluable participants will be 100. The sample size was corroborated by a clinical trial simulation using NONMEM® (version 7.4, ICON development solutions, Hanover, USA). Simulation of 'virtual' clinical trials using the present trial design and literature information on the PK of the drugs indicated that the design supports estimation of structural pharmacokinetic parameters with high precision and accuracy (mean absolute bias: 5.9%, mean rRMSE: 12.1%).

The design is suitable to detect differences in drug clearance of 20% (e.g. mediated by PK drug-drug interactions) between the groups B (i.e. oral artesunate-pyronaridine-atovaquone-proguanil) or C (i.e. oral artesunate-fosmidomycin-clindamycin) vs. A (i.e. oral artesunate-pyronaridine) with adequate statistical power (> 81.8%).

7 General considerations

All relevant data obtained in this study and documented in the eCRF will be listed individually and, tabulated. All statistical analyses will be performed using STATA (version 15 or version 16; StataCorp, USA) and NONMEM® (version 7.4, ICON development solutions, Hanover, USA)

Data will be summarised as follows: Continuous variables by descriptive statistics (number of patients [n], mean, standard deviation [SD], minimum, median and maximum, and categorical variables by absolute and relative frequencies (n and %) or contingency tables.
Descriptive statistics will also be provided for subgroups such as country of recruitment, age group (adult, child) and gender.

Unless indicated otherwise, summary statistics will be reported for observed data only, by treatment arm, and missing data will not be imputed. If a baseline value is missing, no change from baseline will be calculated.

Unless otherwise specified, baseline is defined as the last available assessment (scheduled/unscheduled) prior to the administration of the study treatment. The

only exceptions are temperature, electrolytes (sodium, potassium) and glucose where the first Screening assessment is to be regarded as baseline.

7.1 Common Calculations

For quantitative measurements, change from baseline will be calculated as: (Test value at Visit X – baseline value).

For numerical values > 0 where the logarithmic transformation is required, the logarithm value will be calculated as: $\log_{10}$(Value).

7.2 Analysis Populations

7.2.1 Full Analysis Population

- All subjects who received any study drug

7.2.2 Per Protocol Population

All participants who received a full 3-day course of study drugs

AND

All participants having successfully completed sufficient study visits to calculate:

- PCR corrected adequate clinical and parasitological response on Day 42

OR

- PCR corrected cure rate on day 28

7.2.3 Safety Population

- All subjects who received any study treatment (including control) but excluding subjects who drop out prior to receiving any treatment.

7.3 Covariates and Subgroups

Each study arm will consist of 20 evaluable patients (with 10 patients in the semi-immune sub-group allocated to the age groups 18-65 years and 11-17 years, respectively) and a consecutive group of 20 patients aged 6 months to 10 years, to allow for adequate pharmacokinetic characterization of study drugs.

Covariate effects will be tested on the pharmacokinetic parameters using non-linear mixed effects modelling in the NONMEM® software. Covariates to be evaluated which are expected to have an impact on PK are body size descriptors such as

(ideal) body weight, body height, demographic data as well as laboratory parameters relevant to drug-eliminating organs.

Covariates will be tested using stepwise covariate modelling (SCM) using a standard forward-inclusion – backward-elimination procedure with an alpha of 5% in the forward-inclusion step, and an alpha of 0.5% in the backward elimination step. Actual significance levels of the SCM procedure will be elucidated by stochastic simulation and estimation using the final datasets.

7.4 Missing Data

For covariate testing in the PK analysis, missing covariates will be set to the population median or any other used centre point of the covariate relationship so the missing data are not influential for estimation of parameter-covariate relationships.

8 Analyses

8.1 Primary analysis (= Pharmacokinetic analysis)

Pharmacokinetic analyses will be performed using peripheral blood samples. Pharmacokinetic sampling will be performed following a predefined sampling schedule.

Pharmacokinetic modelling will be performed for all individual drugs using non-linear mixed effects modelling in NONMEM®. Patient characteristics (e.g. body composition, organ function, maturation) will be assessed as covariates of the pharmacokinetics of each drug (see section 9.3 Covariates). Potential drug-drug interactions of atovaquone-proguanil on artesunate-pyronaridine pharmacokinetics will be evaluated. The time-courses of the pharmacodynamic markers (PCR corrected antimalarial efficacy) will be modelled by multi-state pharmacometric modelling. The pharmacokinetics will be linked to pharmacodynamic models to derive the exposure-response relationships of each regimen. Patient covariates correlating with treatment success and/or failure will be evaluated. Time-to-event modelling will be employed on the recrudescence data from the follow-up period together with the linked pharmacokinetic-pharmacodynamic model to potentially identify predictive factors for treatment failure.

Pharmacokinetic variables that will be summarised will include the Clearance of each drug, distribution volumes and absorption rate constants. Pharmacokinetic-pharmacodynamic variables that will be summarized will comprise regimen-specific exposure-response variables describing the decline of the pharmacodynamic markers over time under treatment.

8.2 Secondary analyses

Secondary efficacy variables will be summarised descriptively with incidence rates or standard descriptive methods, including 95% confidence intervals, as appropriate and stratified by taken study medication. Time to event variables will be summarised with Kaplan-Meier estimates of the survival function and Cox regression analysis.

8.2.1 Outcome Classification

Treatment outcome is established according to a modified standard WHO classification:

- Early treatment failure (ETF)
    - danger signs or severe malaria on day 1, 2 or 3, in the presence of parasitaemia;
    - parasitaemia on day 2 higher than on day 0, irrespective of axillary temperature;
    - parasitaemia on day 3 with axillary temperature $\geq$ 37.5 °C; and
    - parasitaemia on day 3 $\geq$ 25% of count on day 0.
- Late clinical failure (LCF)
    - danger signs or severe malaria in the presence of parasitaemia on any day between day 4 and day 28 (day 42) in patients who did not previously meet any of the criteria of early treatment failure; and
    - presence of parasitaemia on any day between day 4 and day 28 (day 42) with axillary temperature $\geq$ 37.5 °C (or history of fever) in patients who did not previously meet any of the criteria of early treatment failure.
    - At 96 hours (day 4) post dose: failure to achieve parasite clearance irrespective of axillary temperature in patients who did not previously meet any of the criteria of ETF.
- Late parasitological failure (LPF)
    - presence of parasitaemia on any day between day 7 and day 28 (day 42) with axillary temperature $<$ 37.5 °C in patients who did not previously meet any of the criteria of early treatment failure or late clinical failure.
- Adequate clinical and parasitological response (ACPR)

- absence of parasitaemia on day 28 (day 42), irrespective of axillary temperature, in patients who did not previously meet any of the criteria of early treatment failure, late clinical failure or late parasitological failure

8.2.2 PCR corrected adequate clinical and parasitological response (ACPR) on Day 42 in per protocol population

On a specified Day, the PCR-adjusted ACPR is the proportion of patients that have no evidence of recrudescence as determined microscopically and genotypically as an absence of the same asexual parasitaemia (clone) as the original infection.

The proportion of individuals with PCR-corrected ACPR will be summarised descriptively on day 42 (=ACPR42) in the per-protocol population by treatment arm. Standard descriptive statistics as well as 95% confidence intervals will be provided.

8.2.3 PCR corrected adequate clinical and parasitological response (ACPR) day 28 in per protocol population

The proportion of individuals with PCR-corrected ACPR will be summarised descriptively on day 28 (=ACPR28) in the per-protocol population by treatment arm. Standard descriptive statistics as well as 95% confidence intervals will be provided.

8.2.4 PCR uncorrected adequate clinical and parasitological response (ACPR) on days 28 and 42 in intention to treat population

The PCR-uncorrected ACPR is the proportion of patients that have no evidence of asexual parasitaemia as detected microscopically, independent of whether any parasitaemia is due to re-infection or recrudescence.

The proportion of individuals with PCR-uncorrected ACPR28 and ACPR42 will be summarised descriptively in the intention to treat population. Standard descriptive statistics as well as 95% confidence intervals will be provided.

8.2.5 Kaplan Meier presentation for incidence rate of re-emergence, recrudescence and re-infection at Day 28 and 42

The risk of re-emergence, recrudescence and re-infection over 28 and 42 days will be estimated by the Kaplan-Meier method. Time to re-emergence, recrudescence and re-infection will be censored at the time of the last recorded visit, if re-emergence, recrudescence and re-infection respectively have not been observed by that time.

8.2.6 Parasite clearance dynamics of combination therapies

Parasite clearance time (PCT): It is defined as the time defined from dosing of the study medication until the first time that parasite could not be detected in a blood smear (i.e. negative). The first negative measurement needs to be followed by one consecutive negative parasitological assessment 6 to 12 hours afterwards.

Kaplan-Meier estimates will be used to evaluate parasite clearance time of baseline parasitaemia

Parasite reduction rate (PRR):
The parasite reduction rate is calculated as the slope of the linear portion of the regression fit of natural log parasitaemia (per mL) versus time (in hours).

There is an online tool by the WWARN network (https://www.wwarn.org/), which will be used to calculate the PRRs per study arm.

8.2.7 Fever clearance dynamics of combination therapies

Fever clearance time (FCT): Concerns only study patients with fever (≥37.5°C axillary temperature; or (≥38°C in alternative measurement routes) at dosing. It is defined as the time defined from dosing of the study medication until the first time that fever was not present anymore (<37.5°C axillary temperature; or <38°C in alternative measurement routes). The first negative measurement needs to be followed by one consecutive negative fever assessment taken 6 to 12 hours afterwards.

Kaplan-Meier estimates will be used to evaluate fever clearance time.

8.2.8 Proportion of patients with sexual stage parasitaemia during follow up

- Kaplan-Meier presentation of the risk of having gametocytes for:
    - Patients with gametocytes at baseline to time to clearance of gametocytes
    - Patients with no gametocytes at baseline to time to appearance of gametocytes

- Integrated number of gametocytes (AUC) at 28 and 42 days for (pre-specified endpoints calculated and reported outside of CSR):
    - Patients with gametocytes at baseline.
    - Patients with no gametocytes at baseline that develop gametocytes during the study.

8.3 Safety Analyses

Safety and tolerability of combination therapies will be assessed in intention to treat population.

8.3.1 General

8.3.1.1 Concurrent Illnesses and Medical Conditions

Coding system for medical history, diseases, symptoms and adverse events will be MedDRA. Medical history will be summarised for the Safety analysis set, and presented in data listings for all patients enrolled.

8.3.1.2 Prior and Concurrent Medications

Prior medication is defined as any medication that has been regularly been taken by a study participant prior to inclusion in the study. Concurrent medication is defined as any medication that was taken during the study that has not been regularly been taken prior to participation in the study. The active ingredient, including way of delivery and dosage will be documented. Concomitant medications will be summarised for the Safety analysis set, and presented in data listings for all patients enrolled.

8.3.2 Adverse events

All adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be presented by Preferred Term within each MedDRA System Organ Class (SOC).

Treatment-emergent adverse events (TEAEs) are defined as AEs which started at or after the administration of IMP (study treatment) and includes those events started prior to the first administration of IMP but which worsened after the dose intake, until the last scheduled assessment will be regarded as treatment-emergent, but before established anti-malarial treatment is administered, if required.

Treatment-related AEs are those rated by the Investigator as 'definite', 'probable' or 'possible'. In case relationship is unknown or missing the worst case will be assumed and the AE will be considered to be treatment-related.
All AEs will be listed, and will include the Investigator term, the preferred term, start and end date of AE, duration (days), severity, drug relationship, action taken and outcome.

An overview of the following TEAEs will be presented:

- TEAEs.
- Severe or life-threatening TEAEs (TESAEs)
- TESAEs leading to death.
- TESAEs of drug induced liver toxicity (Hy's law).
- TEAEs leading to premature study discontinuation.
- TEAEs leading to study drug discontinuation.
- TEAEs related to study drug.

Summaries will consist of the number of patients with at least one TEAE in each category (patients with multiple TEAEs in each category are counted only once in each category) presented by treatment arm for the Safety analysis set. The percentage of patients with at least one TEAE in each category will be calculated relative to the total number of patients in the Safety analysis set.

8.3.3 Laboratory Data

Summary statistics of absolute values and change from baseline over time for quantitative measurements and frequencies and percentages for qualitative data will be presented for all safety laboratory variables.
Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges and categorised as low, normal and high, and presented in data listings.

The shifts of quantitative ("low", "normal" and "high") safety laboratory assessments from baseline to each relevant post-baseline scheduled visit will be presented.
The proportion of patients with clinically significant abnormal values and patients meeting the Hy's law definition will be provided by laboratory variable and treatment arm.

Possible Hy's law case is defined as a patient with any value of ALT or AST above 3x upper limit of normal (ULN) together with an increase in bilirubin to a value higher than 2xULN (>35% direct) and NOT associated to an ALP value higher than 2xULN (FDA, 2009).

8.3.4 Vital Signs

Supine blood pressure and heart rate (absolute values and change from baseline) will be summarised by treatment arm and scheduled visit.

8.3.5 Safety outcomes

- Incidence of adverse events.

- Laboratory variables including change from baseline.
    - Haemoglobin drop
    - Hb drop > 2 g/dL from baseline
    - Hb < 5g/dL
- Absolute Neutrophil count < 1000/µL
- Proportion of patients meeting the Hy's law definition (see study protocol).
- LFT changes:
    - Any ALT or AST ≥5x ULN
    - Any AST or ALT ≥3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (eosinophil percent or count above the ULN)
    - ALT ≥3x ULN persisted for >4 weeks

9 Reporting Conventions

P-values ≥0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001". The mean, standard deviation, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Parameter estimates of the PK analysis in NONMEM® will be reported to the number of significant digits as quantified by the respective estimation algorithm. Quantiles, such as median, or minimum and maximum will use the same number of decimal places as the original data. Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures.

10 References

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