Tafenoquine & G6PD

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HCMC 28th November 2011
Tafenoquine

- Discovered at WRAIR, development co-sponsored by GSK and Medicines for Malaria Venture (MMV)
- Oral primaquine analogue
- Active at all stages of malaria lifecycle (anti-hypnozoite)
- Anti-\textit{falciparum} activity
- No \textit{in vitro} cross-resistance
- Long half-life in man (2–3 weeks)
- >3,000 Subjects exposed
- Causes haemolysis in G6PD deficient subjects
Relapse Prevention
Chloroquine followed by Tafenoquine

Study 047 –
Efficacy over a broad range of Tafenoquine dose regimens

<table>
<thead>
<tr>
<th>Dose Regimen</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>300 mg×7d</td>
<td>7/7</td>
</tr>
<tr>
<td>500 mg×3d</td>
<td>8/9</td>
</tr>
<tr>
<td>500 mg×1d</td>
<td>6/7</td>
</tr>
<tr>
<td>CQ only</td>
<td>3/7</td>
</tr>
<tr>
<td>300 mg×7d</td>
<td>15/15</td>
</tr>
<tr>
<td>600 mg×3d</td>
<td>15/15</td>
</tr>
<tr>
<td>600 mg×1d</td>
<td>15/16</td>
</tr>
<tr>
<td>CQ only</td>
<td>2/10</td>
</tr>
<tr>
<td>CQ+PQ (15 mg×14d)</td>
<td>9/12</td>
</tr>
</tbody>
</table>
Relapse Prevention – Rationale for low dose Tafenoquine

No clear PK/PD relationship or trend between TQ concentrations and relapse
Tafenoquine Clinical Study Codes

- TAF106491 – Chloroquine interaction study
  - TAF114577 PGx companion protocol
- TAF110027 – G6PD Study
  - TAF115016 Enzyme assay validation companion protocol
- TAF112582 – Phase 2b/3 seamless study
  - TAF115226 Enzyme assay validation companion protocol
- TAF114582 – Thorough QTc study
- TAF115263 – Bioavailability/Dose Proportionality
- TAF113577 – Paediatric Treatment
Tafenoquine: overview of safety

TQ Exposure
- > 3000 subjects in variety ph 1-3 studies
- Malaria prophylaxis
- *P. vivax* treatment studies (n=182)

Expected Events
- Blood and lymphatic system disorders:
  - Haemolytic anaemia *(only in patients with Glucose-6-phosphate dehydrogenase deficiency)*
  - Methaemoglobinemia
- Eye disorders:
  - Corneal deposits (vortex keratopathy)
- Gastrointestinal disorders:
  - Nausea and Vomiting, Abdominal pain, Diarrhoea
  - Improved when administered with food
Tafenoquine: overview of safety

Areas of special safety interest – supportive data required

- **Haematology:**
  - Safety in G6PD deficient subjects (TAF 110027)
  - Haemoglobin changes
  - MetHb

- **Ophthalmology:**
  - Keratopathy
  - Retinopathy

- **QTc**
  - FDA requirements
  - Data important to provide treatment population vs Healthy Volunteers.
A Seamless Phase 2/3 ‘Super-study’ Design
Superiority versus chloroquine

Conventional program for *P. vivax* malaria:

**Phase 2 study – dose ranging**
3 TQ arms, 1 PQ arm
N=280
12 months

**Phase 3 study – pivotal study 1**
1 TQ arm, 1 PQ arm
Non-inferiority N = 1300

**Phase 3 study – pivotal study 2**
1 TQ arm, 1 PQ arm
Non-inferiority N = 1300

Seamless program for Tafenoquine:

**Part 1 : Phase 2**
4 TQ arms, 1 CQ arm, 1 PQ arm
N=270

Dose selection
FDA end of Ph2 mtg
CtP3 decision
Keep Part 1 sites open during dose selection phase
3-4 months
Patients recruited to part 1 are not used in pivotal phase 3 part (part 2)

**Part 2 : Phase 3**
1 TQ arm, 1 CQ arm, 1 PQ arm
Superiority vs CQ N = 600

Allocation of sites to Phase 3 replicate analyses 1 and 2

Studies run separately – submission time dependent on the last study to complete
DETECTIVE (TAF112582)

- Seamless phase 2b/3 study incorporating dose ranging and two replicate confirmatory analyses in one protocol

Part 1 (phase 2b) key objective:
  - Select one dose of TQ for part 2 which meets efficacy and safety requirements

Part 2 (phase 3) key objective:
  - Perform two replicate confirmatory analyses to fulfil registration requirements (US FDA and local regulatory agencies)
  - Each centre will be randomly allocated to 1 of 2 analyses prior to unblinding
  - Each centre will contribute data to only 1 of the 2 analyses
Part 1: Dose Ranging Phase

Double-blind Randomisation

N=324

Chloroquine# + 50mg Tafenoquine Day 1 or 2 (n=54)

Chloroquine# + 100mg Tafenoquine Day 1 or 2 (n=54)

Chloroquine# + 300mg Tafenoquine Day 1 or 2 (n=54)

Chloroquine# + 600mg Tafenoquine Day 1 or 2 (n=54)

Chloroquine# + 15mg Primaquine* Days 2-15 (n=54)

Chloroquine# Days 1-3 (n=54)

6 months follow-up

#CQ doses 600mg, 600mg and 300mg on days 1-3 given to all patients

*PQ given DOT for first 3 days only
Part 2: Confirmatory Phase 3

Double-blind Randomisation 2:1:1

- Chloroquine# + xxmg* Tafenoquine Day 1 or 2 (n=300)
- Chloroquine# + 15mg Primaquine† Days 2-15 (n=150)
- Chloroquine# Days 1-3 (n=150)

6 months follow-up

#CQ doses 600mg, 600mg and 300mg on days 1-3 given to all patients

* TQ dose selected after an interim analysis at the end of part 1

+ PQ given DOT for first 3 days only

600 new subjects will be enrolled to Part 2
Study Assessments

Critical Baseline Assessments (After Informed Consent)

- Demography, Medical History, Physical exam and Vital Signs
  - Temperature
  - G6PD quantitative & qualitative assays

Safety Assessment - Laboratory tests (Refer T&E)

- Haematology:
  - Hb, HCT, RBC, MCV, Differentiated WBC, platelets and reticulocytes.
  - Methaemoglobin

- Clinical Chemistry
  - LFTs (including total and indirect bilirubin), Renal Function (creatinine & BUN) and CPK.

- QTc

- Eyes
  - selected sites (retinal and corneal assessments anatomical and functional)

- SERUM pregnancy testing at baseline, urine thereafter
TAF115226

G6PD NORMAL RANGE STUDY

Justin Green
Project Physician Lead
Expression of G6PD deficiency phenotype influenced by:

- Severity class of mutation (I>II>III>IV>V)
- G6PD expression levels
- Environmental factors such as medication, diet or infection
- Exacerbated by co-inherited genetic erythrocyte alterations

G6PD deficiency, a recessive X-linked condition
Study rationale

- Need a normal range to support DETECTIVE study entry criteria
- Local laboratory SOPs differ around the world
- Differences in G6PD gene function may exist
- Influence of external factors on phenotype
  - Retics
  - Hb’opathy
  - Age of RBCs – transfusion
  - WC removal in SOP
Set up for TAF115226

- Spectrophotometer, cuvettes & pipettes
- Training from Shimadzu representative
- Commercial kits from Pointe Scientific or Trinity
- “How to” video

- Local “practice” runs, including e.g. reproducibility & stability at 4°C

- Triplicate assessment in duplicate of each sample = 6 readings per patient
  - Inter and intra-sample run variability
Entry Criteria

- Males 18-45 years old
- Hb > 12g/dL, abs retics <2.5%
- No evidence of haemoglobinopathy
- Re-Screens x2 only
Output from spectrophotometer
Worked example from Thailand

- Screened 45 males, tested 39 patients, excluded 5 subjects:

- Triplicate assessment of post-lysed samples gave CV 0.6-5.2%, mean CV 2.3%

- Enzyme activity 9.5 – 18.4 IU/gHb
  - Mean (SD) 12.1 (±2.2)
  - 95% CI 11.4 – 12.9

- Median 11.5 IU/gHb
Glucose 6 phosphate dehydrogenase deficiency, assessed by a quantitative spectrophotometric phenotype assay:

**Males:** Any subject with an enzyme level <70% of the site median value for G6PD normals will be excluded.

**Females:**
- (i) Those females with a screening Hb ≥ 10g/dL will only be excluded if their enzyme level is <70% of the site median value for G6PD normals.
- (ii) Those females with Hb ≥7 but < 10g/dL will be excluded if an enzyme level is not >90% of the site median value for G6PD normals.
G6PD exclusion criteria - DETECTIVE

Excluded if [G6PD]:

Male

Female

Hb

≥ 10 g/dl

≥ 7 but <10 g/dl

< 10.4

< 8.1

≥ 10 g/dl

< 8.1

< 10.4

e.g. Site median value = 11.5, 70% cut off = 8.1 IU/gHb, 90% cut off = 10.4 IU/gHb

Companion Validation Protocol = 016, 226
How do we complete the G6PD toxicity profile?

- **Ongoing studies** – Phase 2 evaluation of efficacy (TRaC study part 1) and G6PD safety evaluation (TAF110027 study) in parallel
- **Completed studies** – TAF114577 & Kenyan 043 prophylaxis studies
G6PD Study TAF110027

**Part A**
Investigate TQ-induced hemolysis in G6PDd heterozygous females (HVs)

**Part B**
Confirm Part A result in G6PDd heterozygous females with *P. vivax* malaria

**Part C**
Confirm Part B result in G6PDd hemi/homozygous subjects with *P. vivax* malaria

- TQ only
- CQ Days 1-3, TQ on Day 4+
- CQ Days 1-3, TQ on Day 4+

**Abbreviations:**
- HV=healthy volunteer
- TQ=tafenoquine
- CQ=chloroquine
Dose Escalation

Part A: Healthy Volunteers
HND (Highest non haemolytic dose)
- Defined as the dose of TQ at which no more than 2/6 subjects experiences a DLT (Dose limiting toxicity).

- DLT: Haemoglobin decline ≥25 g/L (or Haematocrit decline of 7.5%) or any clinically significant signs or symptoms of haemolysis.

- Dose escalation will be stopped if:
  - If ≥ 2/3 subjects or 3/6 subjects experience a DLT.
# G6PD and Haemoglobin decline: 100 mg

<table>
<thead>
<tr>
<th>Subject ID</th>
<th>Age (y)</th>
<th>G6PD Status</th>
<th>Mutation</th>
<th>% Stained cells</th>
<th>Enzyme activity (IU/gHB)</th>
<th>Max HB decline (g/L)</th>
<th>Max HB decline (day)</th>
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<tbody>
<tr>
<td>6</td>
<td>22</td>
<td>Normal</td>
<td></td>
<td>100</td>
<td>14.3</td>
<td>-21</td>
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<tr>
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<td></td>
<td>95</td>
<td>6.47</td>
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<tr>
<td>17</td>
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<td>32</td>
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<td>Mahidol</td>
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<td>2.19</td>
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<td>2.74</td>
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</table>
How do we complete the G6PD toxicity profile?

- **Ongoing studies** – Phase 2 evaluation of efficacy (TRaC study part 1) and G6PD safety evaluation (TAF110027 study) in parallel
- **Completed studies** – TAF114577 & Kenyan 043 prophylaxis studies
PGx approach

- Sequence G6PD gene in all female subjects in TRaC Pt 1 (Total n=324, expect ~100 females)
- Conduct a genotype-phenotype (Δ Hb) analysis in female subjects treated with TQ (+CQ), PQ (+CQ) and CQ alone (as comparator)

Rationale for a sequencing approach:

1. Five countries involved: India, Bangladesh, Thailand, Peru, Brazil – allelic heterogeneity
2. 400 allelic variants/160 G6PD functional mutations
3. Sequencing will enable accurate identification of known, novel and rare SNVs + small indels
This study: Investigate relationship between G6PD variants and Δ Hb in females treated with TQ+CQ, PQ+CQ and CQ alone in TRaC Pt 1*

On the basis of observations made in PGx study of TRaC Pt 1, design follow up study in confirmatory Phase III study (TRaC Part 2 - see back up)

*Prioritise sequencing of G6PD in any subjects with a study-defined SAE (Hb decline >2.5 g/dL)
**Timelines, reporting and resourcing**

- **Pt 1; FSFV= 3Q2011, LSLV= 2Q2012**
- **For results to be included in CSR, PGx SAC needs to be ≤ 6 months from LSLV**
- **Expected window for sequencing/analysis = 2Q2012-3Q2012**

<table>
<thead>
<tr>
<th>Resource</th>
<th>Timelines</th>
<th>Project tracking/reporting</th>
</tr>
</thead>
</table>
| Gx scientist=1 FTE x 8weeks (data collation) | ➢ Sequencing/Analysis: 2Q2012-3Q2012            | ➢ CSR
| StatGen=0.5FTE x 3wks     |                                                | ➢ RAP
| OP Gx=?                  |                                                |                            |