AZCQ IPTp Development Program
An Overview

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Development Team Head, Malaria

MMV Stakeholders Meeting
Daar-es-Salaam, June 1-3, 2011
AZCQ IPTp Program is Aligned with EM Vision & Mission

We will be recognized for meeting the diverse medical needs of patients in Emerging Markets around the world in an innovative, socially responsible and commercially viable manner.

We will develop bold and innovative partnerships.

We will reach patients we have never reached before.

We will provide medicines and services in an affordable manner.

We will maximize the value proposition for emerging markets inline and pipeline products in our current portfolio.

We will meet our financial commitments.

We will become the leading company in Emerging Markets.

We will provide medicines and services in an affordable manner.
We Are Working on Malaria Because…
Malaria is a Disease of Emerging Markets
IPTp is a High Unmet Medical Need

Malaria in Pregnancy is One of the Commonest *Preventable* Causes of Maternal and Infant Mortality & Morbidity in Sub-Saharan Africa

**36 Millions Pregnancies / Year in Africa**

**Key Factors**
- Malaria in Pregnancy causes
  - 10,000 maternal deaths per year
  - 200,000 infant deaths per year
- Resistance to SP (Sulfadoxine-pyrimethamine) in East and Southern Africa

**Adjacent Wins**
- Another demonstration of Pfizer’s supports of the UN Millennium Development Goals (Goal 3, 4 and 5)

**Sources:** Leerink Analysis, DHS reports, WHO, Roll Back Malaria
Strong Scientific Rationale
Azithromycin / Chloroquine (AZCQ) in IPTp

• AZ and CQ have demonstrated
  ▶ Synergistic activity against CQ resistant *P. falciparum* in vitro and in vivo
  ▶ Efficacy in two adult treatment clinical trials in sub-Saharan Africa irrespective of the level of CQ resistance

• High and sustained placental tissue levels of AZ

• AZ and CQ are marketed products, have extensive safety database and have been recommended and used in all trimesters of pregnancy
  ▶ AZ for Sexually Transmitted Infections (STI) as per CDC recommendation
  ▶ CQ for Malaria treatment and preventive treatment (weekly regimen – WHO)

• AZ and CQ combo has documented safety / tolerability in >1000 non-pregnant subjects in clinical trials

• Efficacy of AZ in treatment of STIs should provide additional benefit in preventing adverse pregnancy outcomes

• Scientific Advice from MHRA on regulatory and clinical program
  ▶ Non-clinical and clinical data allows proceeding with IPTp studies
IPTp Development Program
Goal & Strategy

● Goal

  • Develop an affordable fixed-dose combination of azithromycin (AZ) and chloroquine (CQ) for sub-Saharan Africa
    • Intermittent Preventive Treatment in Pregnancy (IPTp)
      – The combination is expected to improve pregnancy outcomes through clearance/prevention of falciparum infection and common sexually transmitted infections.

● Development Strategy

  • Develop an affordable and high quality fixed-dose formulation
  • Establish treatment efficacy in adults before evaluating for IPTp
    • Two adult falciparum malaria treatment trials completed in sub-Saharan Africa with efficacy of 98% and 100%
  • Seek stringent regulatory authority review prior to African approvals
  • Develop an access and delivery plan to enable affordability of AZCQ
  • Collaborate with Key stakeholders
Our Collaborators

- Share Development Cost
- Scientific Expertise
  - Expert Scientific Advisory Committee
- Access & Delivery Plan
- Stakeholder Engagement
- Scientific Expertise
- Stakeholder Engagement
  - WHO
  - Malaria in Pregnancy Consortium (MiP)
- Ethics Committee Review
A Win-Win Opportunity

TDR Clinical Research & Development Fellowships
supported by the Bill & Melinda Gates Foundation

Introduction

The Special Programme for Research and Training in Tropical Diseases (TDR) invites researchers from Disease Endemic Countries (DEC) to apply for a 12-month Career Development Fellowship on Clinical Research & Development (Clinical R&D). Successful candidates will be seconded to leading drug development institutions such as pharmaceutical companies and product development partnerships (PDPs) that are also taking part in this fellowship programme. The goal is to develop human resources to promote high quality clinical R&D in DEC. It is expected that qualified professionals will be able to enhance DEC product development capacity on diagnostics, drugs and vaccines for infectious diseases that disproportionately affect poor and marginalized populations.

The fellowship will train individuals in situ with relevant partners in order to develop specialized skills not readily taught in academic centres, including inter alia R&D project management, regulatory requirements and good practices. Upon
WHO/TDR Clinical R&D Fellows on IPTp Program (2010-2011)

Julius Atashili, MD, PhD, MPh
Cameroon

Edward Smith, MD
Peru

At the IPTp Investigator Meeting
WHO/TDR Clinical R&D Fellows on IPTp Program (2011-2012)

Steven Baveewo, MD
Uganda

Eric Some, MD
Burkina Faso
Affordability: A Driver for Innovation

Pfizer’s Capturing Global Advantage Initiative…

First Development Program in Pfizer to Collaborate with Generic Companies for Drug Substance and Drug Product

Drug Substance

- **Alembic**
- **Ipca Laboratories Ltd.**

Drug Product

- **Emcure**

  - Azithromycin
  - Chloroquine

  Azithromycin / Chloroquine Fixed-dose Combination

Cost of Goods Reduced Substantially
Affordability vs. Commercial Viability
A Tough Balancing Act…

Low COGs and Development Cost Sharing with MMV may be Insufficient for Making AZCQ Affordable for Women in Sub-Saharan Africa

Approached Global Funding Agencies

Over 70% Probability of Financial Mechanisms Being in Place so that African Countries Could Make AZCQ Affordable
Regulatory Challenges of Developing IPTp Drugs Specifically for Sub-Saharan Africa

- No review / approval by any stringent regulatory authority

- Inadequate regulatory infrastructure and experience in countries to review a new drug application for a new chemical entity

- IPTp is an unprecedented indication
  - Despite SP being recommended for IPTp in 33 African countries by National Malaria Control Programs
• Plan to submit IPTp dossier to EMA via Article 58 mechanism
  • For the evaluation of medicinal products intended exclusively for markets outside the Community in the context of cooperation with the Worldwide Health Organization (WHO)

• Scientific Opinion rendered by the Article 58 procedure should support and enable rapid registration of the product in Sub-Saharan Africa

• Article 58 is a novel mechanism
  • Pyramax is the first new drug being reviewed under this mechanism

• There are multiple WHO reviewers of Article 58 submission who may have varying perspectives: Global Malaria Program, TDR, Essential Medicines, Maternal and Child Health
IPTp is an Unprecedented Regulatory Indication
Multiple Regulatory Interactions Planned

- Scientific Advice Meeting with the MHRA was held on June 10, 2009
- Face-to-face meetings with African regulatory agencies were held prior to clinical trial application (CTA) submissions in 2 Q 2010
- WHO Article 58 Reviewers’ meeting planned in 4 Q 2011
- Scientific Advice meeting with another potential EMA (Article 58) rapporteur in 2011-2012
- EMEA Scientific Advice Meeting in 2012
- Plan to present IPTp program to newly being formed African Regulators Network
### Regulators vs. Policy Makers
#### Different Needs and Priorities

**An Example: IPTp Evaluation Guidance**

<table>
<thead>
<tr>
<th>Pivotal Study</th>
<th>WHO</th>
<th>EMA / MHRA</th>
</tr>
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<tbody>
<tr>
<td>Target Population</td>
<td>Per Protocol</td>
<td>ITT and MITT</td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>Low Birth Weight Neonates (LBW)</td>
<td>All Adverse Pregnancy Outcomes</td>
</tr>
<tr>
<td>All Adverse Pregnancy Outcomes Except LBW</td>
<td>Nonevaluable</td>
<td>Failures</td>
</tr>
<tr>
<td>Missing Data</td>
<td>Nonevaluable</td>
<td>Failures</td>
</tr>
<tr>
<td>Alpha Level</td>
<td>0.05</td>
<td>0.00125</td>
</tr>
<tr>
<td>MiP and Malaria Researchers Follow WHO Guidance</td>
<td>Yes</td>
<td>No</td>
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</table>

**Significant Impact on Sample Size and Data Acceptability**
Clinical Development Plan
Stakeholder Inputs

Ensuring Alignment of Policy Makers, Regulators and Collaborators
Pivotal IPTp Study Design
Incorporates the Inputs from Key Stakeholders

- Primary Objective
  - To establish superiority of AZCQ over SP in proportion of subjects with suboptimal pregnancy outcomes

- Study Design
  - Phase 3, randomized, open label, comparative, multi-center

- Subjects
  - Asymptomatic pregnant women at first ANC visit during 2nd trimester

- Sample size
  - ~ 2600-5200
  - ~ 50% primi- and secundi-gravidae
• Primary Endpoint
  - Occurrence of suboptimal pregnancy outcomes including abortions (spontaneous and induced), still births, premature births (<37 weeks), low birth weight (<2500g) live neonates, missing birth weight for any reason, and lost to follow up

• Key Secondary Endpoints
  - Occurrence of low birth-weight (<2,500 g) in live neonate
  - Occurrence of placental parasitemia
  - Occurrence of placental malaria
  - Occurrence of severe anemia (Hb < 8 g%) in mothers
  - Occurrence of anemia (Hb < 11 g%) in mothers
  - Occurrence of Sexually Transmitted Infections (STI)
  - Safety & tolerability including pregnancy outcomes and follow up through Day 28-42 post delivery
Primary Endpoint of Suboptimal Pregnancy Outcomes

• Loss to follow up rate in literature 20-30%
  - Women prefer to deliver at home
    • Estimated hospital delivery rate of 50%
  - Women may go to their mothers’ home/village to deliver

• Mitigation/Contingency
  - Stringent subject selection criteria
  - Field Workers for home visits, dose administration, AE reports and follow up
  - Hospital delivery at no cost to study participants
  - Separate/fully resourced facility for study participants in hospitals
  - Network with mid-wives in the communities

• Estimated increase in hospital delivery rate by about 10-15%
and to test for the presence of malaria parasite (germ). The woman will need to deliver the baby at the health centre/hospital. At delivery, or immediately after, a member of the study staff will visit her to collect information about her and the new baby’s health. Immediately following delivery, blood will be collected from the mother’s arm (approximately 1/2 teaspoon [2.5mL]) and from the placenta and from the portion of the umbilical cord connected to the placenta (that is, not from the portion still connected to the baby) to test for the presence of the malaria parasites. The umbilical cord, also called the birth cord, is the connection from the developing fetus (unborn baby) to the placenta. The placenta is the organ in the pregnant woman that connects the developing fetus to the uterine (womb) wall to allow nutrient uptake, waste elimination and gas exchange via the mother’s blood supply. If possible, a small sample of the placenta (the size of a stack of four Malawian 1-kwacha coins) will be collected to test for the presence of and/or damage caused by malaria. The mother and baby will have the following: (1) a physical exam; (2) the baby’s health will be checked including weighing and examining for any abnormalities or early signs of birth defects; (3) the baby’s eyes will be checked for any signs of infection and if an infection seems present a sample of eye discharge will be taken to determine the type of infection and treatment will be given per Malawi’s guidelines. The woman (and baby) will be in the study for about 7-8 months.

POSSIBLE SIDE EFFECTS, RISKS, AND DISCOMFORTS
All drugs including this study’s treatments can cause some side effects (bad effects) and may have some adverse reactions. The side effects observed in this study are common and usually mild and do not require medical intervention. However, some side effects can be more severe. If serious side effects are observed, they will be reported to the study staff. The following are some of the side effects that may occur:

- Headache
- Feeling sick
- Sleep problems
- Nausea
- Diarrhea
- Rash
- Itching
- Allergic reaction

If any of these side effects become severe or if you have any other concerns, please contact the study staff immediately.

Clinical Development
Drive • Develop • Engage
Adaptive IPTp Study Design

<table>
<thead>
<tr>
<th></th>
<th>IPTp Course 1</th>
<th>IPTp Course 2</th>
<th>IPTp Course 3</th>
<th>Follow ups</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZCQ: 1000 mg AZ + 620 mg CQ base QD for 3 days; 3 courses</td>
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<td></td>
<td></td>
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<tr>
<td>OR</td>
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<tr>
<td>SP: 1500 mg S and 75 mg P once; 3 courses</td>
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</table>

Day 0
(Screening, baseline, randomization)

Analysis time points as number or % evaluable subjects achieving primary endpoint:

<table>
<thead>
<tr>
<th></th>
<th>Sample size finalization</th>
<th>1st Interim Analysis</th>
<th>2nd Interim Analysis</th>
<th>Final Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=1000</td>
<td>50%</td>
<td>70%</td>
<td>100%</td>
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</table>

AZ=Azithromycin, CQ=chloroquine, S=Sulfadoxine, P=Pyrimethamine, QD=once daily, IA=interim analysis
IPTp Study Analysis Method

- Risk Ratio (RR) defined as:
  - \( \frac{\text{proportion events AZCQ}}{\text{proportion events SP}} \)

- Analysis adjusted for the randomization strata

- **Stringent Alpha level since only one pivotal study**
  - 0.00125 2-sided (equivalent to 0.000625 1-sided) for primary endpoint
  - 0.05 2-sided for all secondary endpoints
Internal Safety Surveillance Plan

- **Risk Management Committee (RMC)**
  - Multi-disciplinary Risk Management Committee (RMC) reviews clinical trial data, non-clinical information, and published literature on an ongoing basis

- **Product level Safety Review Plan**
  - Safety data across clinical and non-clinical studies, and published literature
  - Targeted Medical Events

- **Protocol specific safety monitoring**
  - Adverse event reporting including SAEs
  - Adverse pregnancy outcomes recorded as primary & secondary endpoints
  - Follow up visits by field workers
  - Weekly review of AE listing by the clinical study team
  - Monthly review of protocol deviations by the clinical study team

- **Bi-Monthly review of safety data**
  - Un-blinded cumulative safety data review by
    - Safety Risk Lead, and
    - A study independent clinician
  - Targeted medical events
External Data Monitoring Committee (E-DMC)

- **Membership: Regional Consideration**
  - Professor Rose Leke, Cameroon (Chair)
  - Dr. Harry Tagbor, Ghana
  - Dr. Zul Premji, Tanzania
  - Dr. Paul Milligan, UK

- **Safety and Efficacy data Review Plan**
  - First safety review after 400 subjects enrolled or 50 subjects completed last visit
    - on May 27, 2011 in Rome
  - Subsequent safety reviews every four months
  - Interim analysis safety and efficacy data at 50% and 70% completion
Robust Monitoring Plan and Capacity Building

- Stringent site selection process
- Pre-study audits by an independent audit team for all specialty laboratories
- Help build site infrastructure
- Intensive GCP, GLP and protocol training
- Site initiations for all sites
- Site Visits within 2 weeks of enrolling first subject
- Monitoring Visits at least once every 3 weeks
- Field Workers at each site for home visits, safety monitoring and ensuring compliance
- Plan to audit all sites early on by an independent audit team
Who Gives Informed Consent?

- Study Participant
- Family (Husband)
- Village Head
- Community

Community Advisory Boards
CLINICAL TRIAL
FOR PREVENTIVE TREATMENT
OF MALARIA IN PREGNANCY
MAJARIBIO YA DAWA
KWA TIBA YA KUZUIA MALARIA
KATIKA UJAUZITO

ENGLISH / SWAHILI
Prestigious UN Information & Communications Technology Award
Daar es Salaam, May 27, 2011
Welcome to the Steve Biko Centre for Bioethics

What is Bioethics?
Medical ethics traces its roots to several early ethical codes, the most famous of which is the Hippocratic Oath. Its primary concern was prescribing the ethics of the doctor-patient relationship.

Modern Bioethics began about fifteen years post World War Two in an attempt to ‘humanise’ medical education and practice. Medicine was considered a profession overly focused on scientific and technological advancements requiring specialized skills. As such, its “caring” nature seemed to have slipped. Bioethics aimed to reintroduce this care by invoking human values and the humanities into health sciences.

Today, the field of inquiry of bioethics has moved on to assume much broader proportions. Bioethics is about health, and thus it is also about life and death. It is about our bodies, procreation and birth, suffering and well-being. Importantly, it considers who controls decisions about our health and to what extent such control (if any) is morally justifiable.

Bioethics is the study of morality by careful and systematic reflection on, and analysis of moral decisions and behavior in the life sciences. There is a special emphasis on justice and fairness, sensitivity and empathy which addresses the human fears and concerns often experienced by patients.

Prominent issues facing bioethicists include those related to genetics, theories of human development, assisted reproductive technologies, dual loyalties, euthanasia and resource allocation in healthcare management.

The Steve Biko Centre for Bioethics

The Steve Biko Centre for Bioethics is a university-based centre committed to the values of justice, dignity, respect and freedom – both intellectual and academic.

Staff at the centre boast a wide range of expertise in ethics and they are deeply committed to furthering the discipline of bioethics in South Africa and internationally. Centre staff take pride in advising and consulting for policy makers at national and provincial level, as well as in programmes like Good Clinical Practice – and that is just the tip of the iceberg.
IPTp Program Study Sites

- Benin: Cotonou
- Cameroon: Buea
- Uganda: Kampala
- Kenya: Kisumu, Siaya
- Tanzania: Muheza, Mwanza
- Malawi: Blantyre

- In regions with high SP resistance
- Where SP continues as the SOC
First Subject Enrolled in Kampala on Oct 6, 2010
(N = 174)
Siaya Hospital Site Initiation Training Feb 7-11, 2011 (N = 40)
Recognition for IPTp Development Efforts
Looking Ahead in 2011

- Initiate all study sites
- Enroll first 1000 study participants
- Develop detailed regulatory plan
- Develop access and delivery strategy
  - A stakeholders meeting planned in September 2011
- Continue to engage stakeholders
### External Stakeholders

- African regulators
- African policy makers for malaria and for maternal & child health
- WHO: GMP, TDR, Essential Medicines, Making Pregnancy Safer
- Malaria experts & researchers
- Bioethicists
- Local communities

### Internal Stakeholders

- Legal
- Development Operations
- Regulatory
- Safety Risk Management
- Clinical Pharmacology
- Non-clinical Safety & PDM
- External Medical Affairs
- Country Medical Directors
Thank You!
## IPTp Study Sample Size Estimation

Protocol specified adaptive sample size based on the first 1000 subjects that achieve the primary endpoint, blinded to treatment group.

<table>
<thead>
<tr>
<th>Pooled Percent of Subjects observed to have Sub Optimal Pregnancy Outcome</th>
<th>Target Total Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pooled Percent ≤ 28%</td>
<td>5044</td>
</tr>
<tr>
<td>28% &lt; Pooled Percent ≤ 32%</td>
<td>4206</td>
</tr>
<tr>
<td>32% &lt; Pooled Percent ≤ 36%</td>
<td>3552</td>
</tr>
<tr>
<td>36% &lt; Pooled Percent ≤ 40%</td>
<td>3030</td>
</tr>
<tr>
<td>Pooled Percent &gt; 40%</td>
<td>2602</td>
</tr>
</tbody>
</table>
IPTp Study Interim Analyses

- Protocol specified ‘unblinded’ interim analyses at 50% and 70% of subject accrual (sequential analysis)

- Early stopping for both positive efficacy and futility

- Early stopping for positive efficacy only if statistical significance achieved in favor of AZCQ for both primary endpoint and LBW.
IPTp Study Power Considerations

- Simulation used to compute power & other trial metrics
- RR (AZCQ/SP)=0.80 assumed for primary endpoint, expect proportion with sub opt pregnancy in SP >=28%
- RR=0.77 assumed for LBW, expect proportion with LBW in SP>=12%
- Approx 90% power maintained for primary endpoint
- Approx 80% power maintained for LBW
- Early stop for efficacy, probability approx 40% to 50%
- Early stop for futility, probability approx 72% at first interim, 23% at second interim when RR=1
- Average sample size when LBW=15% is approx 3700