14th Stakeholders’ Meeting
Steady progress towards malaria elimination: Interventions for today and tomorrow
Denpasar, Bali | 11 – 12 October 2017

WONJUNE CHANG (CEO, Shin Poong Pharm.)
Pyronaridine Artesunate: Building the evidence base to expand access for the most recently approved ACT

- History of development for PYRAMAX
- Regulatory status and normative guideline
- Commitment to ongoing safety monitoring
Shin Poong: High Quality Global Manufacturer

Major worldwide supplier of API & Drug products for
• Mebendazole(1975) and Albendazole for soil-transmitted helminthiasis(1984)
• Praziquantel(1983) a treatment for schistosomiasis

We, Shin Poong, have walked the single path of promoting health and happiness of human beings

1962 Neglected Tropical Disease Treatments 2017

2011 Pyramax Plant, EU-GMP

2017
• 7 Manufacturing sites world-wide
• 5 overseas branches
• Intl' partnership w/ 59 companies
• Highly R&D focused company
• Antibiotic, CV, OS, OB/GY

2009. Osong plant dedicated to Cephalosporin

1996 Plant in Vietnam

1988, GMC Plant in Sudan

1990’s Major schistosomiasis eradication campaigns

2001 Partnership to develop Pyramax

2003, Schistosomiasis Control Initiative, UK

PYRAMAX Launch

1988, World Health Organization

The Carter Center

MMV Medicines for Malaria Venture
PYRAMAX: Public-Private Partnership As a Model

PYRAMAX development programme:
A prime example of a collaborative Public & Private partnership

For a Pharma Partner, collaborative R&D in unmet need requires:

- Long term and sustained commitment
- Commitment by the top of the organisation
- Ability to see the big picture
- Respect for partnership and full transparency
- Learning from setbacks
- Defining the product target to meet Regulatory Agencies, Funders, Medical communities and patients’ needs
From Pyronaridine and Artesunate to PYRAMAX

Pyronaridine + Artesunate

PYRAMAX
Fixed-Dose Combination to fulfil WHO recommendation

Film Coated Tablets 180 mg/60 mg

Granules for oral suspension 60 mg/20 mg
PYRAMAX is only ACT approved from SRA for safety and efficacy on treatment *P. vivax* (blood stage) patients

- PYRAMAX plus primaquine was well tolerated when administered concurrently in healthy volunteers *(Antimicrob Agents Chemother. 2015 Jan; 59(1):505-13)*
- PYRAMAX showed good tolerability and efficacy against *P. vivax* in Phase III *(Poravuth Y et. al., PLoS One. 2011 Jan 18;6(1):e14501)*
- When PYRAMAX is administered concurrently with primaquine, there is evidence of good tolerability and efficacy against *P. vivax* relapse *(Erni J. Nelwan et., al., BMC Medicine. 2015 13:294)*
For Shin Poong, obtaining a positive scientific opinion from EMA for PYRAMAX under Article 58 was just the beginning …

**2001-2003**
CMC and non-clinical

- Application of in-house technology for novel formulation for adults and paediatrics
- GLP non-clinical to describe fully profile
- Broad pharmacology profiling

**2003-2008**
Development clinical trials

- 2830 *P. falciparum* and *P. vivax* malaria patients treated:
  4 Phase III trials
  2 Phase II trials
  7 Phase I trials
- Demonstration of high and sustained efficacy and safety profile

**2009-2012**
EMA and MFDS Registrations

- First NCE to receive positive Opinion by new EMA process of Article 58 [Feb. 2012]
- Regulatory approval by MFDS [Aug. 2011]
- Prequalification by WHO [May, 2012]
- EMA commitments for PV and line extension

**2012-2017**
National Registrations; WHO PQ, EML/EMLc and STG/NTG

- Endemic country submissions to 7 SE Asia and 24 African countries
- Participation in WHO Pilot programme for registration in 10 countries in Africa and 5 countries in Asia
- Submission for WHO EML/EMLc → EML/EMLc listed WHO [June, 2017]
- Under review of WHO Guideline Review Committee for STG

**2012-2017**
Post Approval Clinical Trial Commitments, Pharmacovigilance

- WANECAM Trial completed for label broadening to include repeated dosing and paediatrics plus removal of certain restrictions
- CANTAM Trial ongoing to address gaps in label (malnourishment, HIV etc)
- WHO TES Programme
- PYRAMAX EXPLORE phase IV studies

**2003-2008**
PYRAMAX: the Long Path to Success

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**PYRAMAX: the Long Path to Success**
PYRAMAX Registration Status

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<th>WHO Collaborative Program (10)</th>
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Reg. Status Granules

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PYRAMAX Clinical Trial Phase II, III, IV in the World

### Phase II (7)
- Senegal, Gambia, Gabon, Uganda, Thailand, Cambodia, Indonesia

### Phase III (18)
- Senegal, Gambia, Mali, Ghana, Burkina Faso, Cote d'Ivoire, Gabon, DRC, Mozambique, Kenya, Tanzania, India, Thailand, Vietnam, Korea, Cambodia, Philippines, Indonesia

### Country Phase IV
- WANECAM (Burkina Faso, Mali, Guinea)
- CANTAM (Cote d'Ivoire, Cameroon, Congo, DRC, Gabon)
- INESS (Burkina Faso)
- TES (Vietnam, Myanmar, Cambodia)
Safety and efficacy of retreatments with pyronaridine-artesunate in African patients with malaria: a substudy of the WANECAM randomised trial


«Pyramax safety evaluated in 1015 patients receiving first treatment versus 316 (31.1%) patients retreated within 28–452 days (median 64 days). No evidence that Pyramax retreatment increased safety risk based on laboratory values, reported AEs, or ECGs»

Lancet Infectious Diseases, 2015
CANTAM: Phase IIIb/IV Cohort Event Monitoring study to evaluate, in real life setting, the safety and tolerability in malaria patients of the fixed-dose Artemisinin-based Combination Therapy Pyramax® (pyronaridine-artesunate)

The study to address gaps in the PYRAMAX current label (LFT on entry, HIV, malnourished) will be performed in public health facilities of the CANTAM network where Pyramax will be used in treatment of 8572 uncomplicated malaria episodes:

- Cameroon
- Republic of Congo
- DRC
- Gabon
- Côte d’Ivoire

Involves additionally African Coordinating Centre for Pharmacovigilance (PV) in Kinshasa, DRC and reporting PV to WHO Central Monitoring group in Uppsalla as well as EMA
Routine PharmacoVigilance

- Patients/Hospital
- Country distributor PV
- Shin Poong PV
- Central PV/QPPV

- Data entry of AE information (Cording of AE/Drug Info)
- Medical review / Writing of Case Narratives
- Safety Data Reconciliation
- Regulatory Reporting / PSUR
- RMP/RA Update

Education/Audit
**Pyronaridine tetraphosphate**
- Sustained schizonticidal effect, reducing drug resistance

**Artesunate**
- The most potent and rapidly acting agent with high parasite kill rate and spectrum activity

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**Indications & Dosage**

**Acute, uncomplicated malaria caused by P. falciparum or by P. vivax**
- Tablet form for adults and children over 20 kg and child-friendly Granules for infants and children from 5-20 kg

- 180/60 mg Film-coated Tablet and 60/20 mg Granules for oral suspension
- PY/AS once daily for 3 days

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**Why PYRAMAX**

- Only ACT approved by SRA for the treatment of both *P. falciparum* and *P. vivax* (blood stage) malaria
- Proven efficacy & safety from 7 randomized clinical trials with over 4,000 patients
- Better compliance due to once-daily regimen and no food effect
- Lower recrudescence rate and risk of resistance
- Easier stock management with neutral package

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**Approved**
- In 22 countries for Tablet
- In 7 countries for Granules

**Approved In 22 countries for Tablet**

**Approved In 7 countries for Granules**

**PYRAMAX: Designed to Succeed Against Malaria**
Safety and efficacy of re-treatments with pyronaridine-arketunate in African patients with malaria: a substudy of the WANECAM randomised trial

Insoo Seoara, Abdul Waheed Breeso, Insoo Zongo, Insoo Soojae, Isabelle Borgehi-Fuerer, Bakary Fofana, Daoua Camara, Amadou Sam, Aboubacar S. Cissokho, Omar B. Fofana, Nana de la O, Marie-J. Kamine, Issoo Thienn, Yves D. Camara, Mokhtir Minzak, Yell, Fideli, N'Kam, Montadoso, Salick Diallo, Alassane Diko, Jose Pedro G., Steffen Runzmann, Stephen Duparc, Robert M. Miller, Aliou S. Dibango, Jorn J. Van, Asef, J. Gomina, Jean-Rene Ouattara, Sandrine E. Simon, Abdoulaye Dioprat

“For the Health of the People”

Thank you for your attention

www.shinpoong.co.kr