Commercialisation of R&D: Coartem®
Taking a TCM from Laboratory to Regulatory Approval

Heiner Grueninger
Hong Kong, September 5, 2013
Content of presentation

- Malaria – prevention and treatment
- Artemisia annua – the plant as source for a medication
- Artemisinin combination therapy (ACTs) – today’s standard malaria treatment
- Drug development of Artemether-Lumefantrine
- Development of a pediatric formulation
- Conclusions
Malaria

*Caused by parasites and transmitted by mosquitos*

- Caused by one-celled parasite *plasmodium*.
- Transmitted to people through the bites of infected mosquitoes.
- Mosquitoes pick up parasite when they bite a patient to obtain blood.
- When mosquito bites again, with its saliva parasites pass to healthy person being bitten.
Malaria

Preventable and curable

Prevention
- Insecticide-treated bed-nets for night-time prevention of mosquito bites
- Indoor residual spraying to kill mosquitoes that rest on walls and roofs of houses

Treatment
- Artemisinin-based combination therapy (ACTs) is currently most effective treatment
- 95% cure rate against *falciparum* malaria

Source: WHO Malaria Fact Sheet 2009
Artemisia annua

*From harvest to a medication for children*
What are artemisinins?

An overview

- Extracted from *Artemisia annua*
- Used as herbal remedy for fevers in China for thousands of years
- Artemisinin and derivatives extensively tested in China since late 1970s
- Used widely to treat malaria in Asia since 1980s
Artemisinin Combination Therapy (ACT)

The state-of-the-art anti-malaria treatment

Treatment of uncomplicated P.falciparum malaria:
‘To counter the threat of resistance of P.falciparum to monotherapies and to improve treatment outcome, WHO recommends that artemisinin-based combination therapies be used for the treatment of uncomplicated P.falciparum malaria.’

Preventing drug resistance:
‘WHO recommends oral artemisinin-based monotherapy should be removed from the market because their use will hasten the development of parasite resistance. Countries need to ensure that patients are diagnosed properly and take the full dose of ACTs to prevent the development of drug resistance.’
ACTs are combinations of two drugs

Separate mode of action and complementary PK

- To avoid emergence of resistance, and
- To achieve complete parasite clearance

‘Use of combinations of anti-malarials that do not share the same resistance mechanism will reduce the chance of selection because the chance of a resistant mutant surviving is the product of the per parasite mutation rates for the individual drugs, multiplied by the number of parasites in an infection that are exposed to the drugs.’ (N.White, 1999; Phil. Trans. R. Soc. Lond. B; 354, 739-749)

In ACTs the fast and extensive anti-parasitic effect of a short regimen of an artemisinin derivative is combined with a slower acting second drug that clears remaining parasites thus avoiding recrudescence (= reoccurrence of same infection) adapted from J.K. Baird, 2005; N. Eng. J. Med.; 352;15 1565-1577

<table>
<thead>
<tr>
<th>Drug</th>
<th>Parasite density</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumefantrine (half-life ~ 3-6 days)</td>
<td>[Drug]</td>
</tr>
<tr>
<td>Artemether (half-life ~2 hours)</td>
<td>Time</td>
</tr>
</tbody>
</table>

To avoid emergence of resistance, and
To achieve complete parasite clearance
Study A025: regimen selection

6-dose is preferable over 4-dose

- 4-dose (3-day) vs 6-dose (3-day) and 6-dose (5-day) regimens
  - Artemether 20 mg/lumefantrine 120 mg tablets given according to patient weight (1 tab/dose for <15kg/children, 4 tabs/dose for >35 kg/adults)

<table>
<thead>
<tr>
<th></th>
<th>28-day PCR-corrected cure rate (%)</th>
<th>Median time to fever clearance (h)</th>
<th>Median time to parasite clearance (h)</th>
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</thead>
<tbody>
<tr>
<td>4-AL/3-day</td>
<td>83</td>
<td>23</td>
<td>44</td>
</tr>
<tr>
<td>6-AL/3-day</td>
<td>97</td>
<td>35</td>
<td>44</td>
</tr>
<tr>
<td>6-AL/5-day</td>
<td>99</td>
<td>22</td>
<td>44</td>
</tr>
</tbody>
</table>

- Significantly improved cure rate with 6-dose vs 4-dose regimens (p<0.001)
- 6-dose regimens highly effective and very well tolerated
From molecule to medicine: MMV’s R&D process

1. Find hits
   (those compounds able to kill the parasite)

2. Test hits
   in vitro and in vivo
   in the laboratory, for drug-like qualities to produce a lead compound

3. Improve lead compound’s properties
   by re-engineering or optimizing it to remove any undesirable features until it can be considered a drug candidate

4. Test the safety of the drug candidate in the lab
   NB: All laboratory work is conducted to ISO Good Laboratory Practice standards

5. Phase I clinical trials
   to determine the safety and appropriate dose of the drug in humans – healthy volunteers without the disease (~100 people)
   NB: All clinical trials Phase I & II are conducted to ISO Good Clinical Practice standards

6. Phase II clinical trials
   to ascertain safety, and ability of the drug to cure malaria – also known as “proof-of-concept” (~100 – 600 patients)

7. Phase III clinical trials
   to compare the safety and efficacy of the drug, head-to-head, against the best currently available treatment (~3000 patients)

8. Registration
   by a stringent drug regulatory authority and/or WHO prequalification that thoroughly evaluates all aspects of the medicine in order to decide if it should be deemed a legitimate pharmaceutical product

For further information see www.mmv.org

Total 10–15 years

MMV
Medicines for Malaria Venture
Study A2401: adult non-immune travellers

Confirms high cure rate and rapid fever + parasite clearance

- 165 non-immune adult travellers with falciparum malaria treated at centers in non-endemic areas of the EU and Columbia
  - All patients received the 6-dose/3-day Coartem regimen (4 tablets per dose)

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<tbody>
<tr>
<td>AL: n=126&lt;sup&gt;a&lt;/sup&gt;</td>
<td>96</td>
<td>37</td>
<td>42</td>
</tr>
</tbody>
</table>

<sup>a</sup>per-protocol population

- High 28-day parasitologic cure rate, comparable with rates seen in trials in endemic countries (ranging from 94–97%)
  - Most common treatment-related AEs were insomnia (6.7%), vomiting, headache and vertigo (each 3.6%)

Sub-Saharan Africa bears highest burden

*Children are most vulnerable*

Spatial distribution of *Plasmodium falciparum* malaria stratified by endemicity (2010)

- Endemicity of *P. falciparum* malaria is highest in central and western areas of sub-Saharan Africa, Mozambique and Madagascar.
- *P. falciparum* species inflicts over 91% of malaria-related deaths in Africa, **86% of which were children under five**

Source: Malaria Atlas Project
Coartem® dispersible tablets

A tailor-made formulation for children

Coartem® standard tablet

- Difficult to administer for children (esp. in outpatient setting)
- Requires crushing for small children (can lead to under-dosing)
- Bitter taste (can lead to vomiting)

Coartem® dispersible tablets

- Rapidly dispersible in water < 3 min
- Suitable for all ages (5-35kg)
- Sweet tasting to mask bitter taste
Coartem® dispersible tablets

Reconstitution to a drinkable suspension
Coartem® dispersible tablets

*Developed in 3 steps*

- **Children**
  - Palatability
    - *Study B2101*

- **Adult healthy volunteers**
  - Pharmacokinetics Characteristics
    - *Study B2104*

- **Children with malaria**
  - Dispersible vs crushed tablets
    - *Study B2303*
Palatability study in children

Evaluating best formulation and flavor

Q1 Dispersible Taste
Q2 Crushed Taste
Q3 Convenience of Dispersible use vs Crushed

1 2 3 4 5

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Pharmacokinetic profile in healthy adults

Evaluating Artemether, DHA and Lumefantrine

Abdulla S et al. Malaria J 2010; 9:253
Phase III safety and efficacy study
Evaluating anti-malaria activity in patients (children)

- Randomized, multicenter, two-arm, investigator-blinded
- All patients received 6 doses at 0, 8, 24, 36, 48 and 60 hours
  - 5 to <15kg: 1 tablet b.i.d.
  - 15 to <25 kg: 2 tablets b.i.d.
  - 25 to <35kg: 3 tablets b.i.d.
- Male or female infants and children ≤12 years of age of body weight ≥5 kg and <35 kg
- *Uncomplicated* *P. falciparum* parasitaemia of > 2,000 and < 200,000 parasites/µL associated or not with other plasmodium species
- Fever with temperature ≥ 37.5°C or fever sensation within 24 hours
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Enrolling patients into phase III study

Slow start, rapid finish

899 patients, 8 sites in 5 countries: Benin, Kenya, Mali, Mozambique, Tanzania/Zanzibar; recruitment completed January 207
Phase III safety and efficacy study

Comparing crushed and dispersible tablets

- 6-dose regimen with dispersible formulation and crushed tablets were compared in 899 African children with uncomplicated Malaria in five countries
  - Doses were adjusted for body weight as follows:
    1 tablet (5 to <15 kg), 2 tablets (15 to <25 kg), 3 tablets (25 to <35 kg)

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<tbody>
<tr>
<td>Dispersible tablet</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(N=403)(^a)</td>
<td>98</td>
<td>8</td>
<td>34</td>
</tr>
<tr>
<td>Crushed tablet</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(N=409)(^a)</td>
<td>99</td>
<td>8</td>
<td>35</td>
</tr>
</tbody>
</table>

\(^a\)modified ITT population

- Cure rates were similar across three different body weight categories (doses were adjusted for body weight)
- Tolerability was good for both formulations, with no differences in the pattern and overall incidence of adverse events
Reducing the disease burden of malaria

Global efforts are yielding positive results

<table>
<thead>
<tr>
<th>2004</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria Cases</td>
<td>243 million</td>
</tr>
<tr>
<td>Malaria Deaths</td>
<td>947,000</td>
</tr>
<tr>
<td>Child mortality Every 30 seconds</td>
<td></td>
</tr>
<tr>
<td>Treatment guidelines Treat every fever case with an antimalarial</td>
<td>Use Rapid Diagnostic Tests</td>
</tr>
<tr>
<td>Number of ACT doses procured worldwide 5 million</td>
<td>216 million*</td>
</tr>
</tbody>
</table>

* 2010
Conclusion

Steps to a worldwide availability of the ACT

The leaves of *Artemisia annua*, the sweet wormwood plant, have been a Chinese herbal remedy for over 2,000 years.

1970s – Artemisinin identified by Chinese researchers as the active antimalarial constituent of *A. annua*

1980s – 1990s
Researchers at the Beijing Academy of Military Medical Sciences profiled the combination of artemether and lumefantrine

1990s – Novartis conducted the clinical development for the fixed-dose combination, Coartem®

1999 – First approval (Swiss Health Authorities)

2004 – First fixed-dose ACT to meet WHO’s pre-qualification criteria for efficacy, safety and quality

2008 – Availability of pediatric formulation
Thank you!