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

Heiner Grueninger

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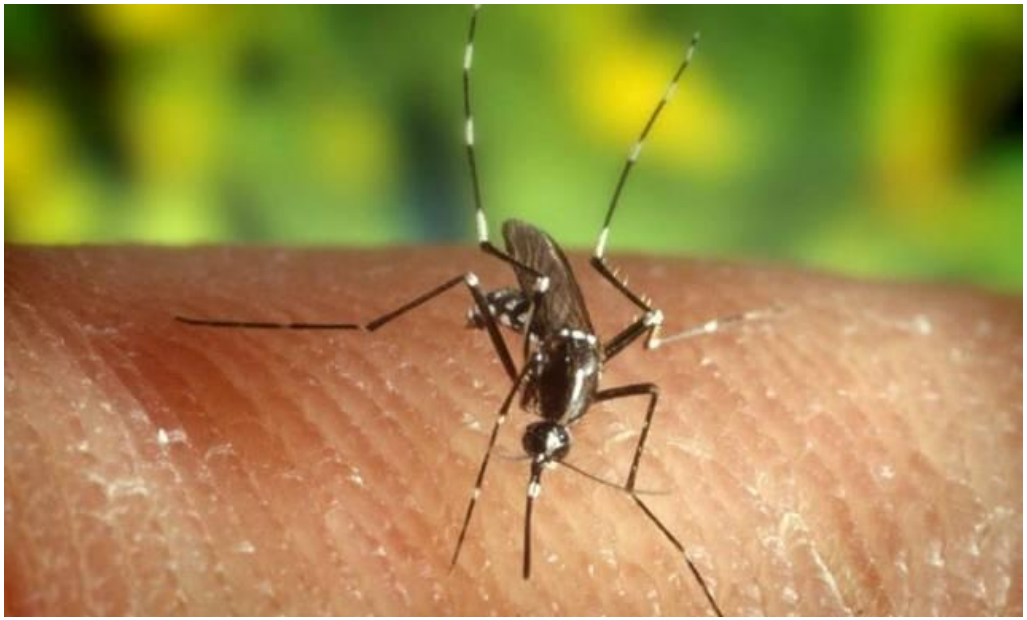
Content of presentation

- 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 mosquitos that rest on walls and roofs of houses

Treatment

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

Source: WHO Malaria Fact Sheet 2009

Artemisia annua

From harvest to a medication for children

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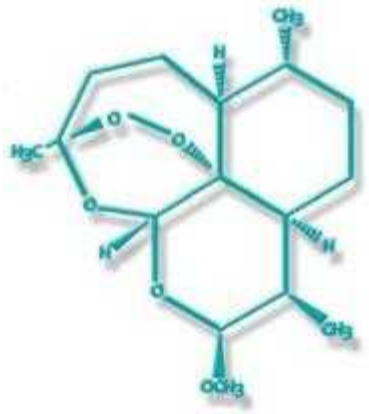
What are artemisinins?

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

Artemisia annua



Artemisinin

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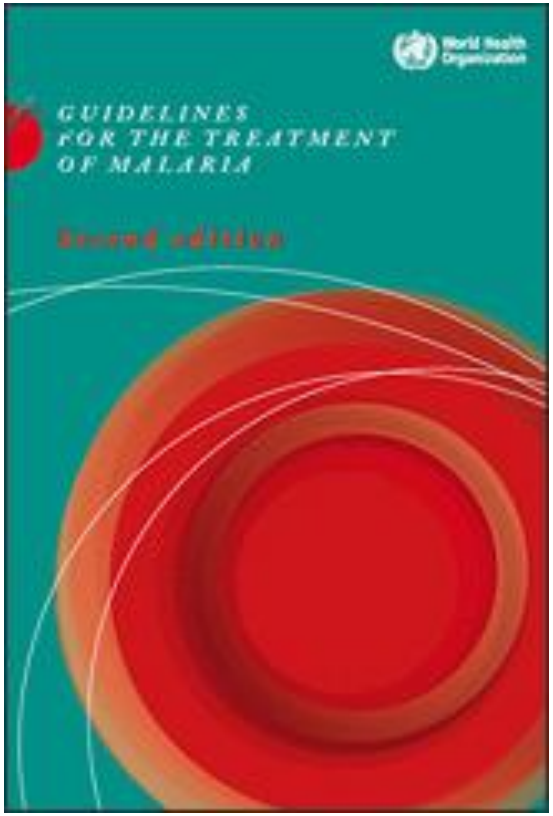
Artemisinin Combination Therapy (ACT)

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

WHO Malaria Tratment Guidelines



Treatment of uncomplicated P.falciparum malaria:
'To counter the threat of resistance of *P.falciparum* to monotherpies 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.'

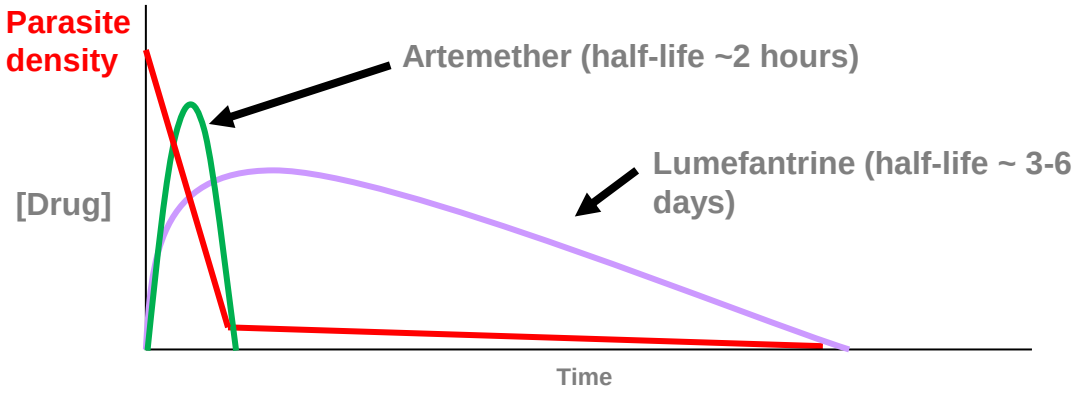
ACTs are combinations of two drugs

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 (= reoccurance of same infection)
adapted from J.K. Baird, 2005; N. Eng. J. Med.; **352;15** 1565-1577



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Study A025: regimen selection

6-dose is preferable over 4-dose

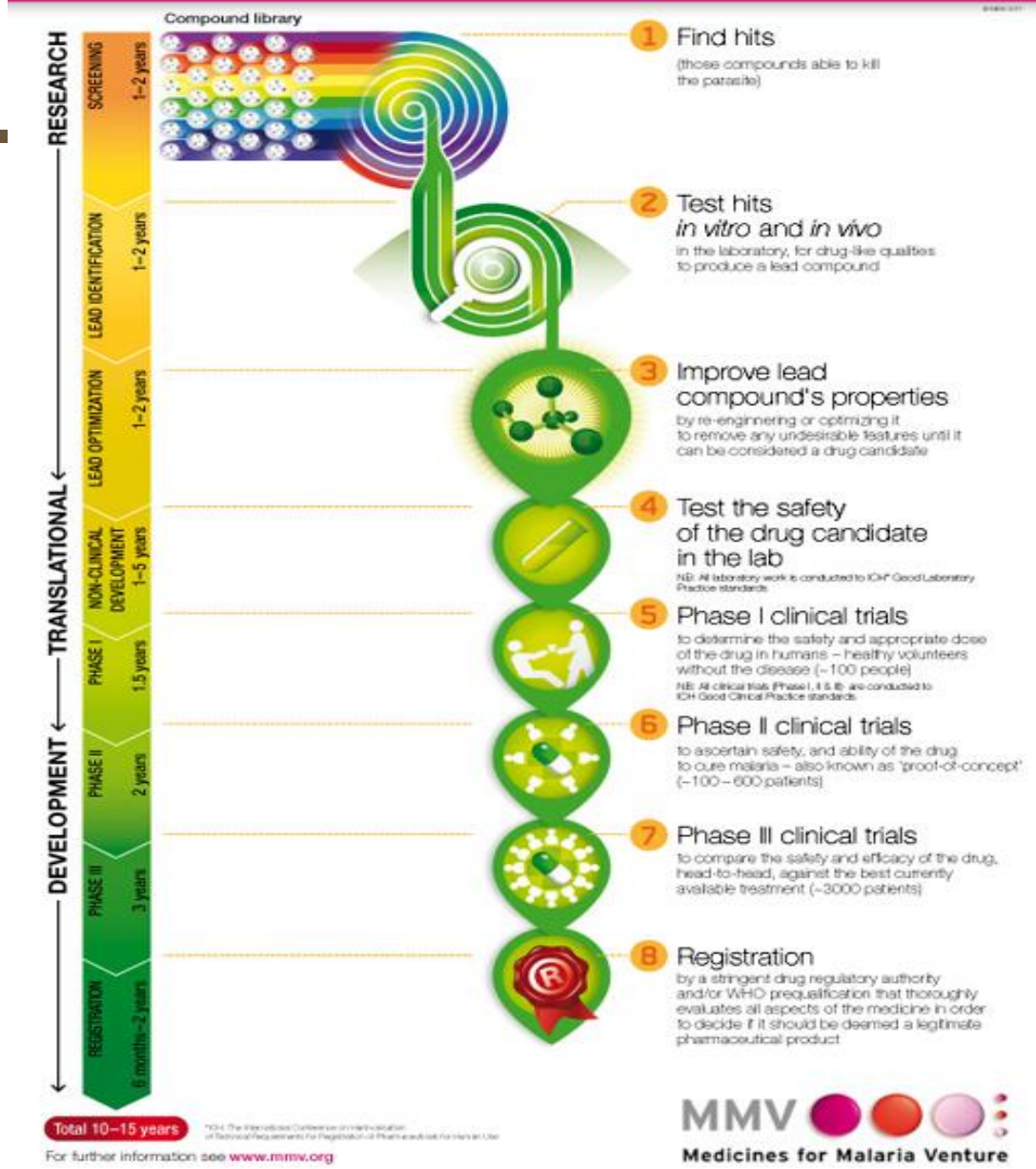
- 4-dose (3-day) vs 6-dose (3-day) and 6-dose (5-day) regimens
  - Artemether 20 mg/lumefantrine 120 mg tablets given according to patient weight (1 tab/dose for <15kg/children, 4 tabs/dose for >35 kg/adults)

	28-day PCR-corrected cure rate (%)	Median time to fever clearance (h)	Median time to parasite clearance (h)
4-AL/3-day	83	23	44
6-AL/3-day	97	35	44
6-AL/5-day	99	22	44

- Significantly improved cure rate with 6-dose vs 4-dose regimens ($p<0.001$)
- 6-dose regimens highly effective and very well tolerated

Vugt MV et al. Am J Trop Med Hyg 1999; 60(6): 936–942

From molecule to medicine: MMV's R&D process



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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)

	28-day PCR-corrected cure rate (%)	Median time to fever clearance (h)	Median time to parasite clearance (h)
AL: n=126[a]	96	37	42

[a]per-protocol population

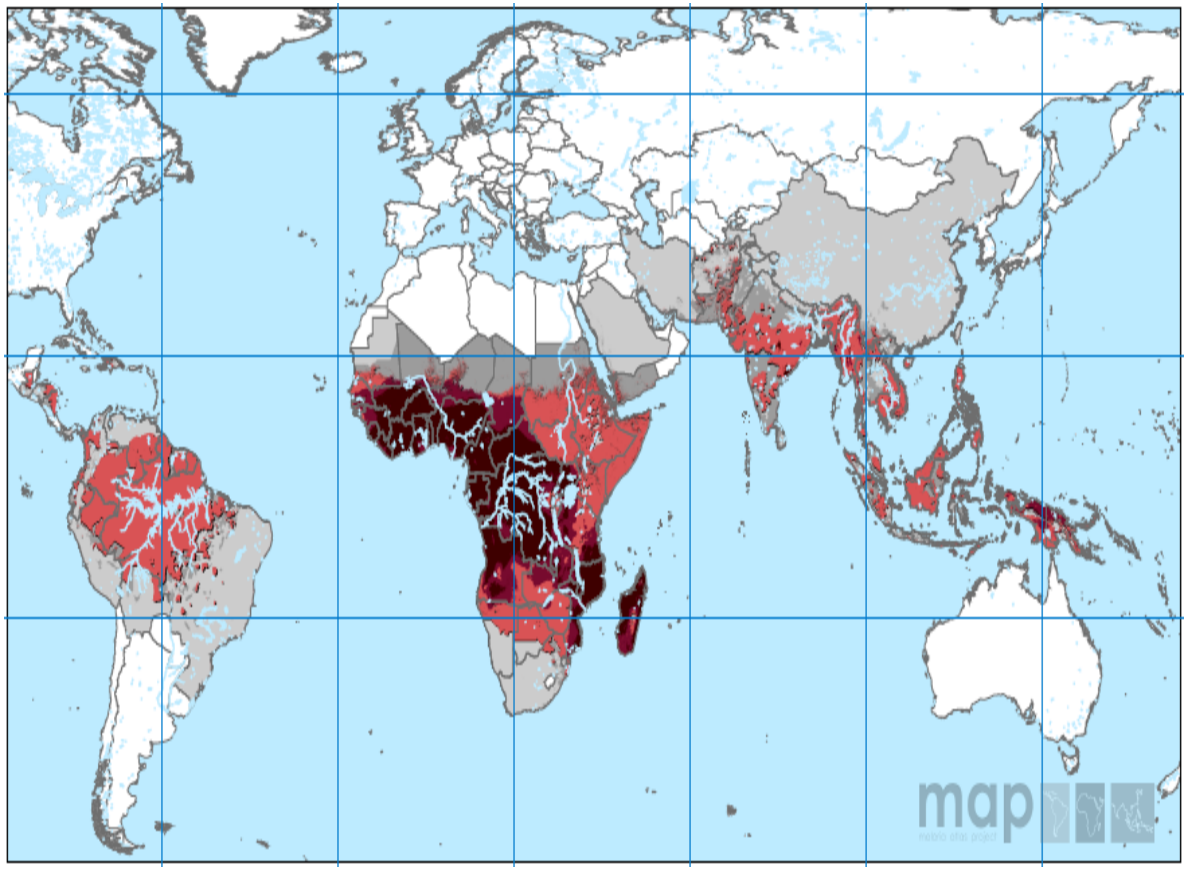
- High 28-day parasitologic cure rate, comparable with rates seen in trials in endemic countries (ranging from 94–97%)
  - Most common treatment-related AEs were insomnia (6.7%), vomiting, headache and vertigo (each 3.6%)

Hatz C et al. Am J Trop Med Hyg 2008; 78(2): 241–247

Sub-Saharan Africa bears highest burden

Children are most vulnerable

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



Source: Malaria Atlas Project

- 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**

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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

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Coartem® dispersible tablets

Reconstitution to a drinkable suspension

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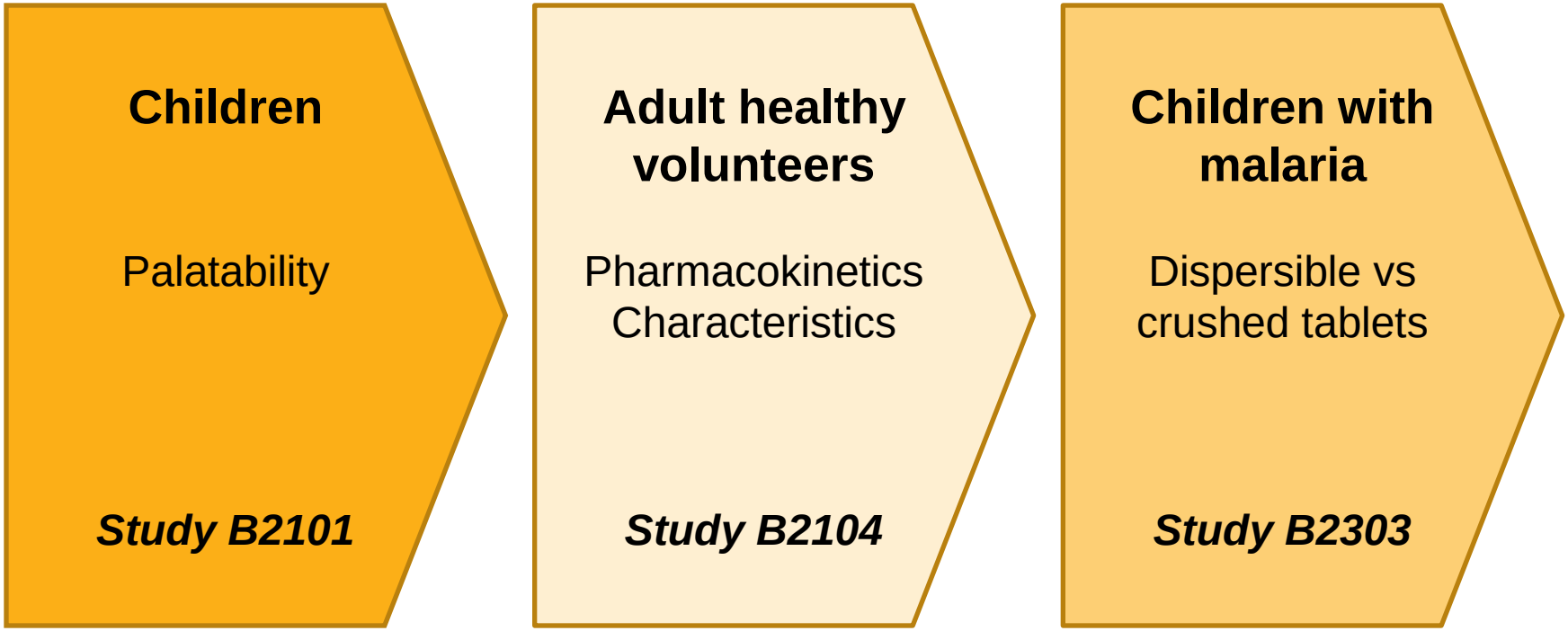
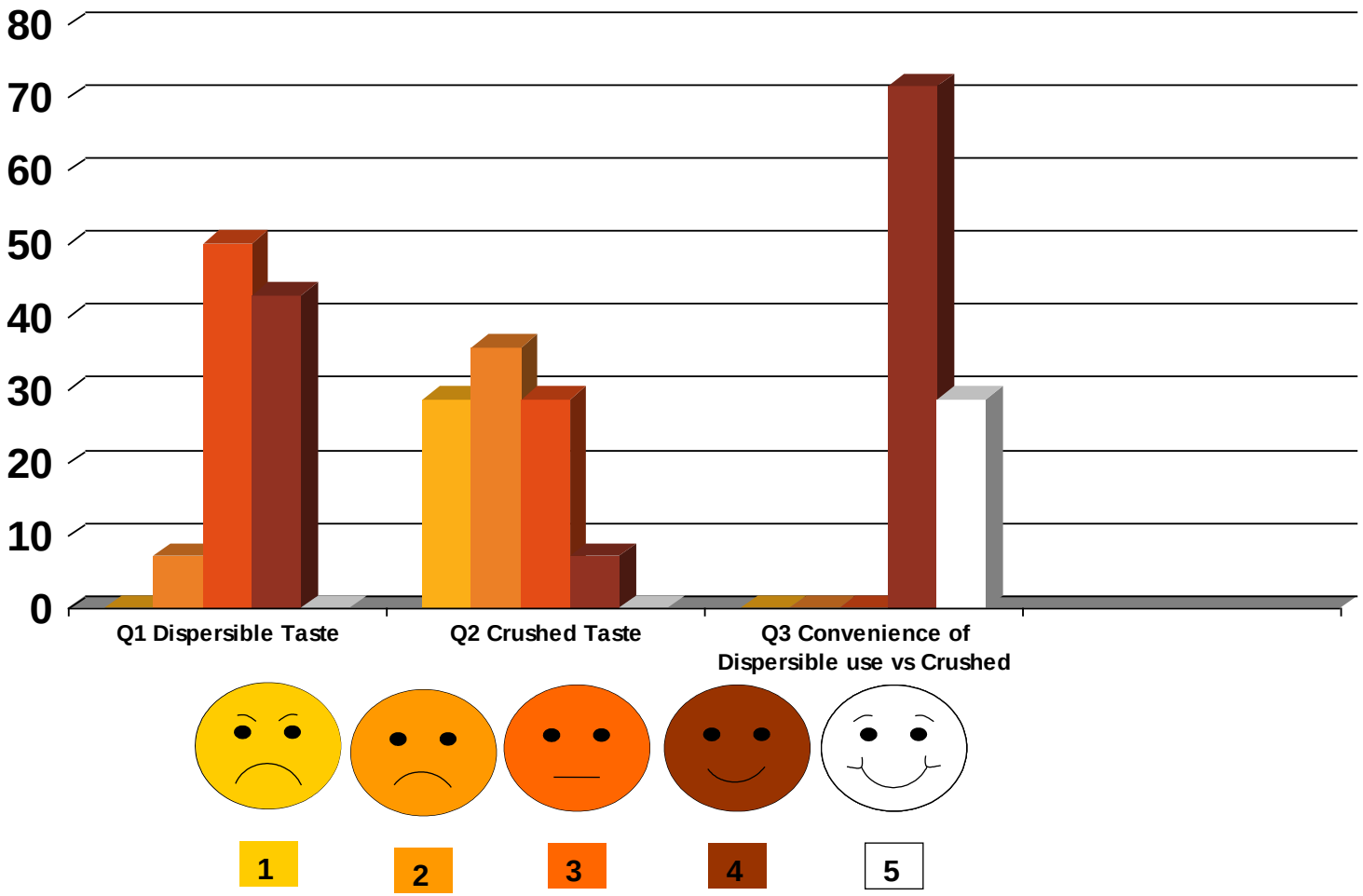
Coartem® dispersible tablets

Developed in 3 steps



Palatability study in children

Evaluating best formulation and flavor



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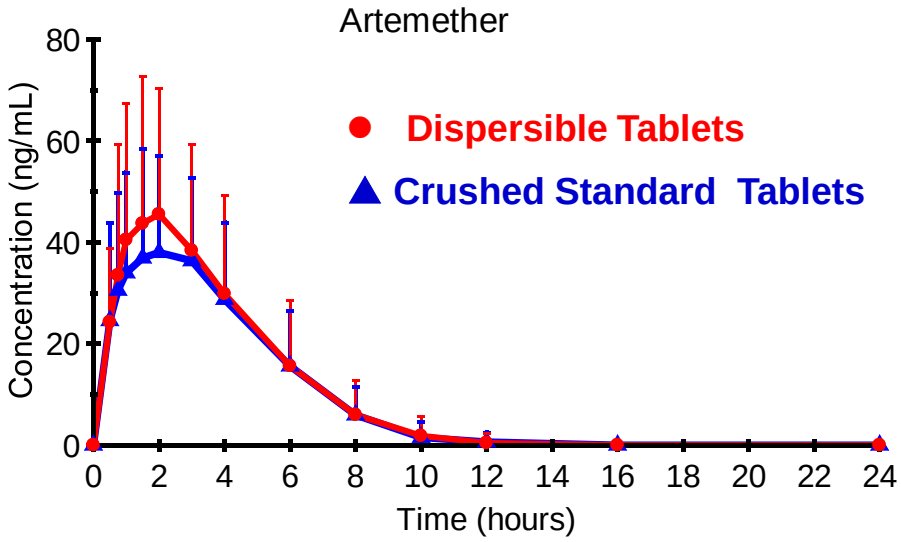
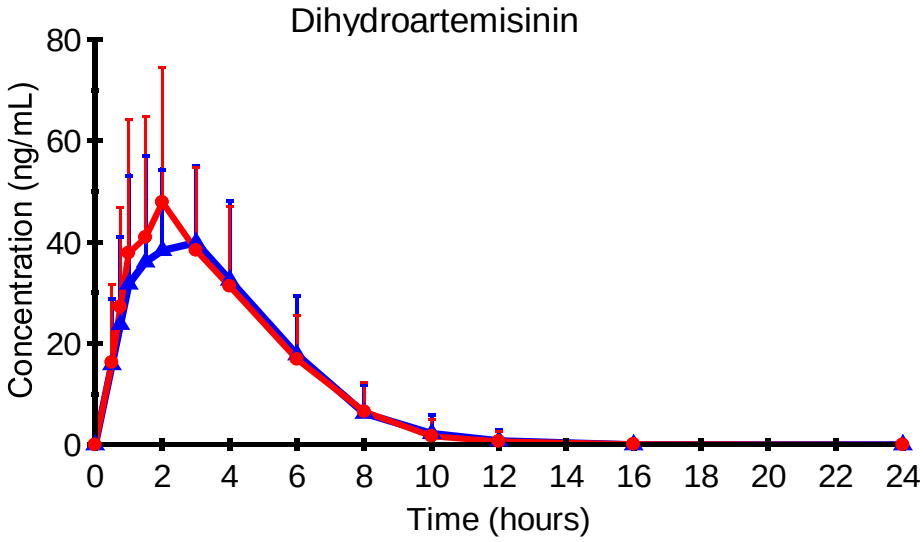
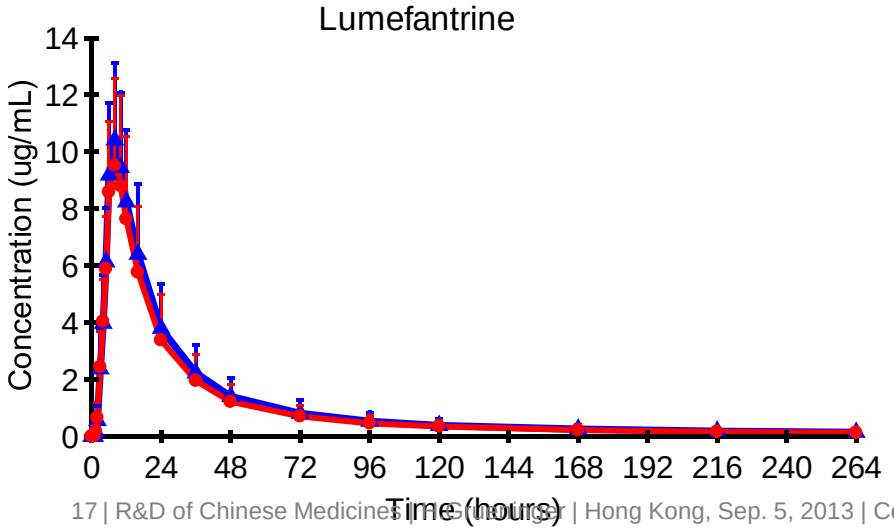
Pharmacokinetic profile in healthy adults

Evaluating Artemether, DHA and Lumefantrine







48 healthy adults

Abdulla S et al. Malaria J 2010; 9:253

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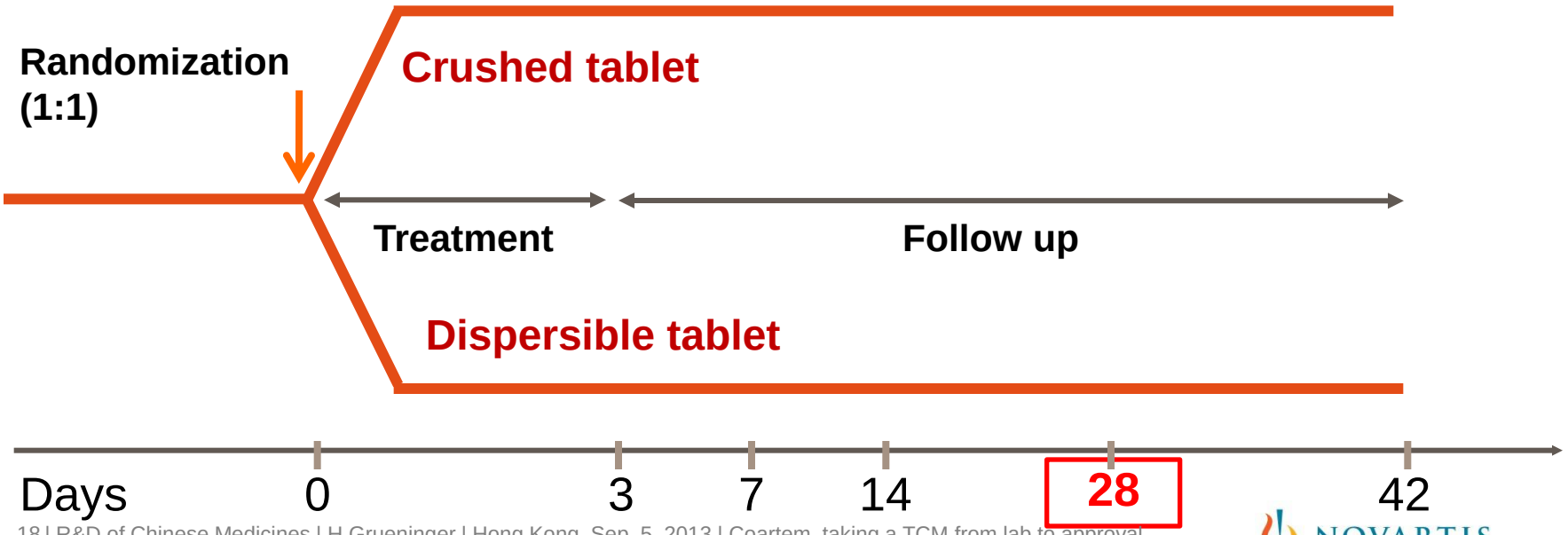
Phase III safety and efficacy study

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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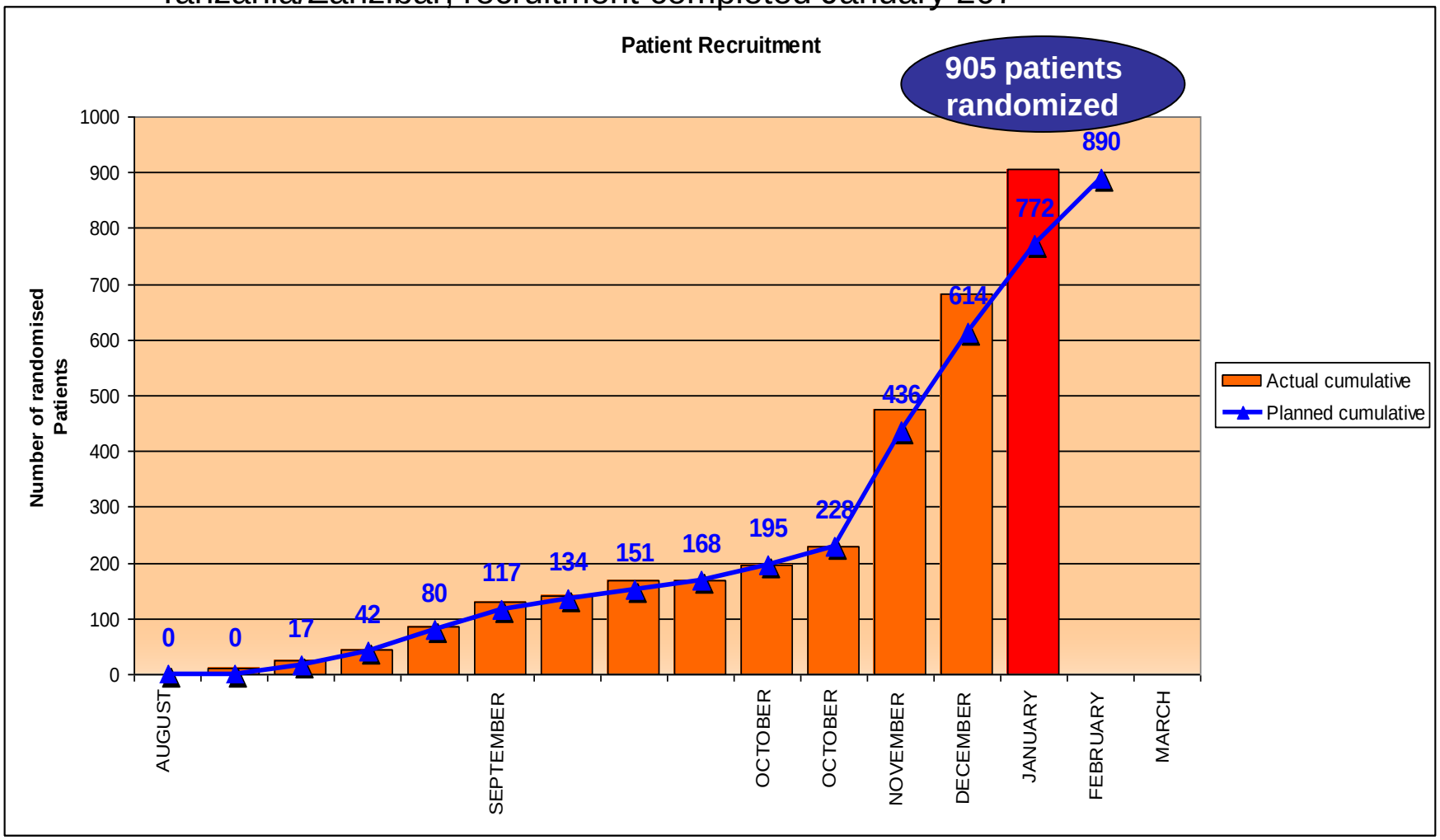
Enrolling patients into phase III study

Slow start, rapid finish

899 patients, 8 sites in 5 countries: Benin, Kenya, Mali, Mozambique, Tanzania/Zanzibar; recruitment completed January 207



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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)

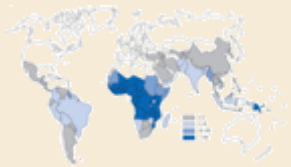
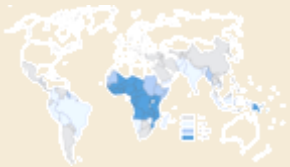
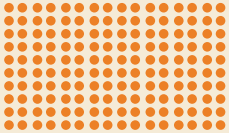
	28-day PCR-corrected cure rate (%)	Median time to fever clearance (h)	Median time to parasite clearance (h)
Dispersible tablet (N=403)[a]	98	8	34
Crushed tablet (N=409)[a]	99	8	35

[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

Abdulla S et al. Lancet 2008; 372(9652): 1819–1827

Reducing the disease burden of malaria
Global efforts are yielding positive results

	2004	2011
Malaria Cases	243 million 	216 million* 
Malaria Deaths	947,000 	655,000* 
Child mortality	Every 30 seconds 	Every 60 seconds 
Treatment guidelines	Treat every fever case with an antimalarial 	Use Rapid Diagnostic Tests 
Number of ACT doses procured worldwide	5 million	216 million* 

** 2010*

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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 arte-mether 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

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Thank you!

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