



SYMPOSIUM HIGHLIGHTS

Artemether/ Lumefantrine Dispersible -

ACTs Addressing
Children's
Therapeutic
Needs



The American Society of Tropical
Medicine and Hygiene

56th Annual Meeting

4th-8th November 2007

Philadelphia Marriott Downtown
Philadelphia, Pennsylvania USA

Symposium Session:

Monday, November 5th, 2007,
8:00 am - 9:45 am, Salon AB

Artemether/Lumefantrine Dispersible - ACTs Addressing Children's Therapeutic Needs



3 Chair
Professor Umberto
D'Alessandro

4 Artemether/
Lumefantrine crushed
tablet
– a clinical overview
Michael Makanga

7 Public-private
partnership develops
the new standard of care
for pediatric malaria
patients: rationale for
developing a dispersible
formulation
Christopher Hentschel

9 Early development steps
of the Artemether/
Lumefantrine dispersible
tablet: palatability and
pharmacokinetics
Salim Abdulla

11 Efficacy of Artemether/
Lumefantrine dispersible
tablet – Phase III results
Bernhards R. Ogutu

13 Safety and tolerability
of Artemether/
Lumefantrine dispersible
tablet
– Phase III results
Philip G. Sasi

This symposium shared the rationale for developing a dispersible formulation of the artemisinin combination therapy Artemether/Lumefantrine, and presented Phase III data for the first time. Nearly 200 attendees contributed to an interested and enthusiastic audience, eagerly anticipating the launch of the dispersible tablet, which promises to ease administration of, and widen access to, this proven antimalarial for children.

Malaria is primarily a disease of infants and young children. However, currently there are no antimalarials that are registered to a stringent international standard and recommended by WHO specifically formulated for this vulnerable population. To address this critical gap, Medicines for Malaria Venture (MMV) and Novartis have joined forces to develop an innovative formulation of the effective fixed-dose formulation of Artemether/Lumefantrine. This proved a surprisingly challenging task. Not only did the new formulation have to be as safe and effective as the current tablet formulation, it also had to meet the practical requirements deemed essential for widespread use - including palatability, stability and affordability.

Chair: Professor Umberto D'Alessandro

Prince Leopold Institute of Tropical Medicine, Antwerp, Belgium.



The chair, **Umberto D'Alessandro**, introduced the meeting by explaining the background to artemisinin combination therapy (ACT). Artemisinin has been combined with several partner drugs, but importantly, Lumefantrine, the partner in the WHO recommended ACT, has never been used as monotherapy, so is one of the few artemisinin companions to be well preserved from resistance development.

“As we all know, artemisinin combination therapies are the most potent antimalarials available today.”

Professor D'Alessandro stressed that a malaria therapy is only as effective as it is accessible to those who need it most – young children. Easing administration should also be a priority – and this symposium, discussing the development of a dispersible formulation of Artemether/Lumefantrine, was also about increasing accessibility of and compliance with this effective therapy. Easing administration will not only improve malaria morbidity and mortality, but also extend the life of this treatment.

“Anyone who has treated a sick child with malaria knows how difficult it is to get the child to swallow tablets.”

Michael Makanga

European and Developing Countries Clinical Trials Partnership

Artemether/Lumefantrine Crushed Tablet – a Clinical Overview



Michael Makanga, of the European and Developing Countries Clinical Trials Partnership in Cape Town, South Africa provided a comprehensive overview of the efficacy and safety of the Artemether/Lumefantrine crushed tablet in children with uncomplicated falciparum malaria. Efficacy data came from both pooled analysis and a head-to-head study comparing the crushed tablet with the new dispersible formulation. Safety data was provided by the pooled analysis of data from all previous studies of Artemether/Lumefantrine involving children.

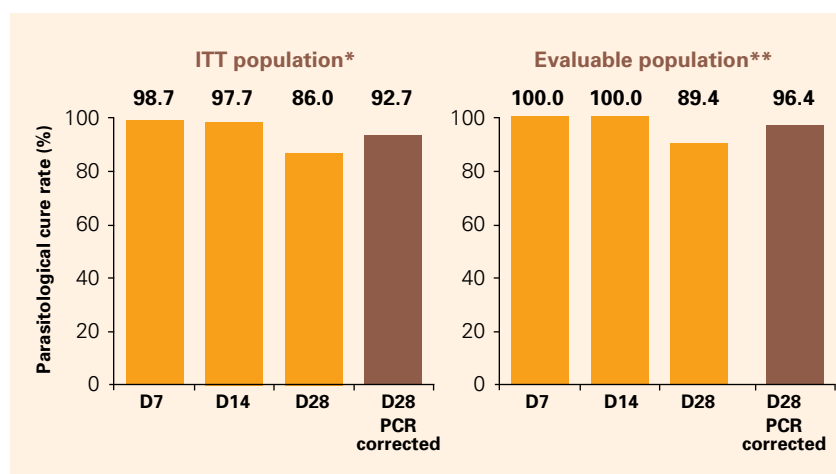
Efficacy of Artemether/Lumefantrine

The efficacy data was from the pooled analysis of three studies, which were conducted as part of the clinical development program, in 343 children.

Children were ≤ 12 years old (5–35kg), with uncomplicated falciparum malaria, and a baseline parasitemia of 1,000-100,000/ μL , according to WHO guidelines at the time.

Parasitological cure rates at the different time points are shown below, with the PCR-adjusted cure rate being 93% in the ITT population and 96% in the evaluable population.

Parasitological cure rates

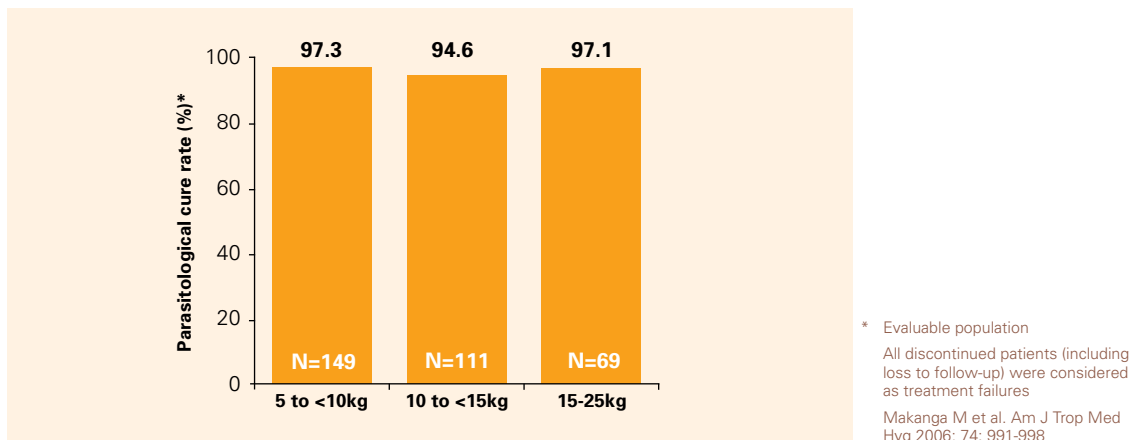


* All discontinued patients (including loss to follow-up) were considered as treatment failures

** ITT patients with evaluable data who took no other antimalarial therapy and who did not discontinue therapy due to *P. falciparum* recurrence Makanga M et al. Am J Trop Med Hyg 2006; 74: 991-998

Across the three body weight groups, there was an excellent parasitological cure rate.

28-day PCR-corrected cure rate across body weights



Looking at secondary endpoints, the median time to parasite clearance was 24.2 hours, and to fever clearance 7.9 hours. Dr Makanga pointed out that the use of anti-pyretics may have confounded the fever clearance results.

94.2% of patients had parasite clearance within 48 hours.

Gametocyte clearance was also rapid, the proportion of patients with gametocytes present reaching zero by day 8. The slight re-appearance of gametocytes seen during days 15-28 was probably due to re-infection, as the study was conducted in an area of high malaria transmission. Gametocytes (sexual stage parasites) do not cause malaria symptoms, but are responsible for the transmission of the disease when ingested by a mosquito in a blood meal from one person and then inoculated into the next person bitten.

Safety data – pooled analysis

Artemether/Lumefantrine crushed tablet safety data was pooled from all studies that included children ≤ 12 years old (815 children) using the 6-dose regimen for acute uncomplicated falciparum malaria. The four studies included were:

Study A2403 (Africa): multicenter, open-label, N=310*

Study A025 (Thailand): multicenter, double-blind, N=31*

Study A026 (Thailand): multicenter, double-blind, N=22*

Study B2303 (Africa): multicenter, investigator-blinded, N=452*

* Number of patients qualifying for pooled analysis

The crushed tablet was associated with very few serious adverse events (1.2%). There were four deaths across all the studies, and 12 patients (5%) discontinued the study drug due to vomiting or urticaria (1 patient). Other adverse events reported, e.g. anorexia, anemia, splenomegaly, were consistent with symptoms associated with the disease itself.

Cardiac and nervous system adverse events were closely examined. The incidence of cardiac adverse events was particularly relevant because of the structural similarity of Lumefantrine to Halofantrine, which is known to cause a prolonged QTc interval (although Lumefantrine is known to have a different profile). No serious adverse events affected the CV system – 9 patients (1.1%) reported a CV adverse event, but these resolved spontaneously without intervention. Neurological adverse events were reported in 105 patients (12.9%) – mostly headache – and there were no cases of loss or decrease in hearing.

Dr Makanga concluded that Artemether/Lumefantrine is a safe and effective antimalarial in children, resulting in high parasitological cure rates, rapid and complete parasite and fever clearance. The rapid and complete gametocyte clearance achieved may help to reduce disease transmission. Artemether/Lumefantrine is safe and well-tolerated, with most adverse events reported related to the malaria itself.

Question: You noted 3-5% resistance to Artemether/Lumefantrine in your study – did you take blood samples from these patients to assess drug levels and whether parasites present were resistant species?

Dr Makanga: I would not classify these patients as resistant, but as treatment failures. Pharmacokinetic data is available for these patients – there was no clear correlation found between treatment failure and lower drug levels, especially with Lumefantrine.

Christopher Hentschel

Medicines for Malaria Venture, Geneva, Switzerland

Public-Private Partnership Develops the New Standard of Care for Pediatric Malaria Patients: Rationale for Developing a Dispersible Formulation



Christopher Hentschel of Medicines for Malaria Venture, Geneva, Switzerland described how MMV aims to discover, develop and deliver safe and effective antimalarials that are affordable, accessible and appropriate. This led to the development, in partnership with Novartis, of a pediatric formulation of Artemether/Lumefantrine.

The unmet need

There are already many antimalarials in the market – for example, there are 760 antimalarials registered in Nigeria. However, none are specifically pediatric drugs, and very few, except Artemether/Lumefantrine from Novartis, meet WHO Prequalification standards or the stringent standards of international regulatory authorities.

The main driver for this project has been the unmet medical need for a pediatric formulation. The project has used a global technology platform: the final product will be produced in the US, the clinical trials have been conducted mainly in Africa, the active pharmaceutical ingredients (API) produced in Asia.

“ We don't have an optimal product for children, and we don't have an optimal way of getting products to the target child population. ”

Dr. Hentschel added that the aim of the project is to deliver an optimal antimalarial to those who need it most – infants and young children. The current standard of care, crushed tablets of Artemether/Lumefantrine, taste bitter, are not easy for caregivers to administer and are difficult for children to swallow.

The Novartis/MMV partnership is about optimising the product – making it more user-friendly for children and their caregivers.

Novartis has delivered over 130 million treatments of the gold standard Artemether/Lumefantrine to Africa since 2001 – 75% of which have been for children. But the bitter taste of crushed tablets results in difficult administration and a danger of under-dosing.

Challenges in developing a pediatric formulation

Dr. Hentschel suggested that many people think that ‘formulation’ is the low end of innovation – yet it is incredibly important for addressing this unmet need and ensuring compliance with this effective treatment. Many innovative formulations add a lot of cost to the finished product, and so Novartis/MMV are trying to produce a product with as low a cost as possible, and deliver an affordable treatment to the target population, children. Changes in formulation often merit changes in packaging, which can also add cost.

A comprehensive development program evaluated palatability, bioavailability and efficacy and safety. The result is a cherry flavored formulation. Rapidly dispersible in water, suitable for infants and children 5kg and above, with Phase III results confirming a >97% parasitological cure rate.

Timelines – the regulatory phase is imminent, the dossier is about to be submitted to Swissmedic, one of the reference regulatory authorities used by WHO.

“Our expectation is that this product will be rolled out in 2008.”

This was all achieved through a unique partnership between Novartis and MMV.

Salim Abdulla

Ifakara Health Research & Development Centre, Dar-es-Salaam, United Republic of Tanzania

Early Development Steps of the Artemether/Lumefantrine Dispersible Tablet: Palatability and Pharmacokinetics



Salim Abdulla, of the Ifakara Health Research & Development Centre, Dar-es-Salaam, United Republic of Tanzania, described the 3-step approach that was taken to evaluate the palatability and bioavailability of dispersible Artemether/Lumefantrine. First, the palatability of three different flavors was tested in children, then the relative bioavailability of the dispersible formulation versus the crushed tablet was evaluated in healthy adults, followed by the bioavailability of the dispersible formulation versus the crushed tablet in children with malaria.



Which flavor is most acceptable?

As already mentioned, there is a need to deliver a formulation of Artemether/Lumefantrine that is specifically suited to children, to improve ease of administration. The first step was to ensure that the new formulation would be acceptable to infants and children, and palatability is key to acceptance of an oral medication.

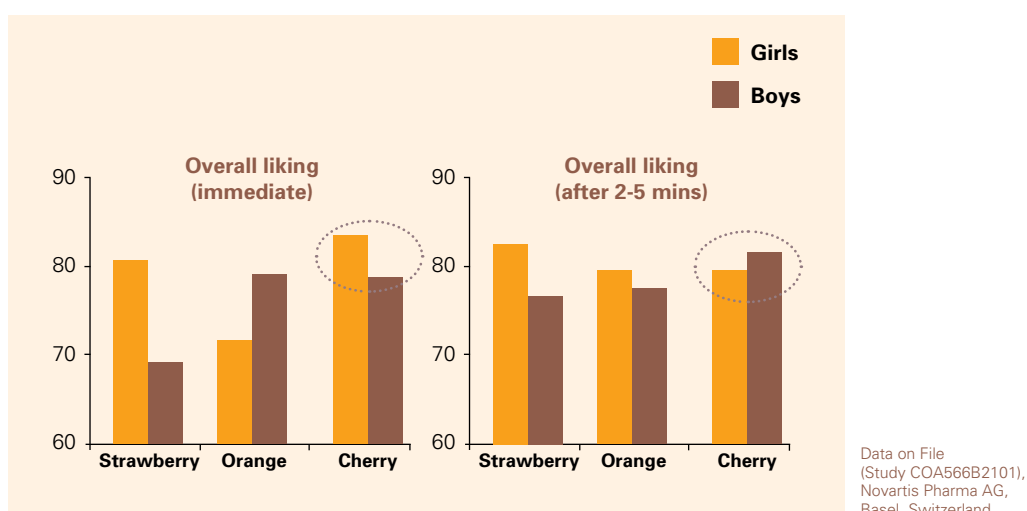
A randomized, single-center cross-over study was conducted in Tanzania to evaluate the palatability of three different flavors of Artemether/Lumefantrine oral suspension (orange, strawberry and cherry flavored). Forty-eight healthy children (24 boys; 24 girls) were randomized to taste all three flavors in one day.

During development, other flavors, such as banana and mango, were considered, but these did not sufficiently mask the bitter taste of the product.

Children held 2mL (measured by syringe) of each flavor in their mouths for about 10 seconds before expelling. They used unsalted soda crackers and water to cleanse their palates in between each flavor. All samples had the same yellow appearance to prevent any subject bias. Children assessed the palatability using a visual analogue scale (incorporating a facial hedonic ['smile'] scale) to rate the flavor, smell and sweetness of each sample.

Cherry was the overall preferred flavor. This may seem surprising, as cherries are not often found in Africa. However, it is a flavor often found in soft drinks and in other medications, such as antibiotics.

Cherry was overall preferred flavor



Bioavailability in healthy adults

Before embarking on a large pharmacokinetic study in children, the bioavailability of dispersible Artemether/Lumefantrine was first investigated in adults, compared to the currently available tablet formulation.

A randomized, open-label, single-dose, cross-over study in 48 adults assessed the relative bioavailability of artemether, dihydroartemisinin (DHA, the active metabolite of artemether) and lumefantrine in both crushed tablet and dispersible formulations.

Both formulations had similar PK profiles, confirming similar bioavailability of the APIs in each.

Bioavailability in children with malaria

Following these encouraging results in adults, the next step was to conduct a large study in 809 children with malaria, recruited from 5 African countries. Children received the standard 3 days treatment with either crushed or dispersible Artemether/Lumefantrine, dosed according to weight.

Again, the plasma profiles of artemether, DHA and lumefantrine were very similar for both formulations.

In summary, children in Tanzania selected cherry flavor as the most acceptable for the Artemether/Lumefantrine dispersible formulation. Studies in both healthy adults and in children with malaria confirmed that bioavailability of the APIs in the dispersible formulation matches that of the crushed tablet.

Bernhards R. Ogutu

Centre for Clinical Research, Kenya Medical Research Institute, Kisumu, Kenya

Efficacy of Artemether/Lumefantrine Dispersible Tablet – Phase III Results

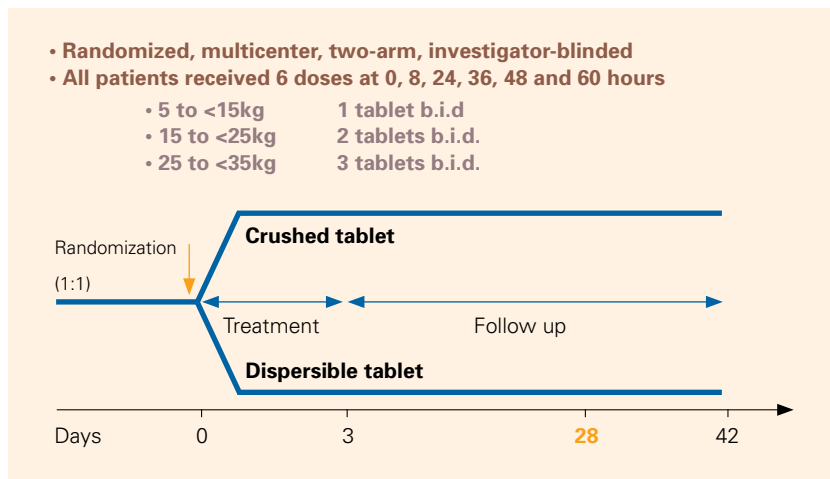


Bernhards R. Ogutu, of the Centre for Clinical Research, Kenya Medical Research Institute, Kisumu, Kenya, presented Phase III results from the B2303 study for the first time.

Study B2303, a randomized, multi-center, investigator-blinded study comparing the efficacy, safety and bioavailability of the crushed tablet of Artemether/Lumefantrine with the new dispersible formulation, has recently been completed in children in Africa. The primary objective was to demonstrate non-inferiority of the dispersible formulation to the crushed tablet for PCR-corrected cure rate at day 28.

Children were randomized to receive either crushed tablet or dispersible tablet of Artemether/Lumefantrine, in three different doses depending on the body weight of the child.

Study design



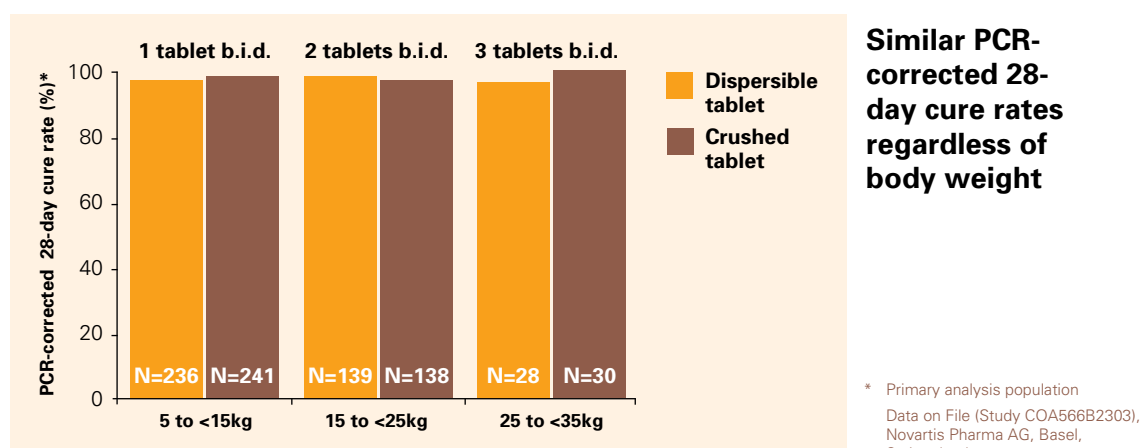
The primary endpoint was the cure rate at 28 days, although the children were followed up for an extended time period of 42 days, to assess treatment failure or reinfection. Secondary endpoints were parasitological cure rates at days 7 and 14 and time to parasite, fever and gametocyte clearance.

Non-inferiority confirmed

- The primary analysis (all ITT patients who completed 28 days with valid PCR evaluation at day 28) revealed the efficacy of both formulations to be above 97%
- Even the ITT analysis, performed in those children who took at least one dose of study drug, showed the cure rate to be above 95%, the current WHO recommended threshold for first-line treatment

“ The per protocol analysis (all primary analysis patients who took $\geq 80\%$ of study drug) showed an efficacy of over 98% for both formulations, which is consistent with previous studies of Artemether/Lumefantrine, reassuring us that no resistance seems to have developed. ”

- PCR-corrected 28-day cure rates were similar across the three body weight categories. This demonstrates that all children received sufficient drug to provide therapeutic efficacy, irrespective of body weight.



There were excellent PCR-corrected 42-day cure rates in all study populations, reaching over 96% in the primary and per protocol analyses, showing that there was very little re-infection or late treatment failure.

In summary, the efficacy of the Artemether/Lumefantrine dispersible tablet was confirmed by the non-inferiority demonstrated versus the crushed tablet. In all populations evaluated, the PCR-corrected cure rate at day 28 was >95%, the current WHO recommended threshold for cure rate.

Question: It is very laudable to have conducted these rigorous safety and efficacy studies – but as the crushed tablet has already proved itself, wouldn't it have been sufficient to just do PK studies?

Bernhards Ogutu: There is no way of knowing if the cure rates are going to be the same unless you conduct clinical trials. You can't know how the different formulation will affect the outcome. The only foolproof way is to conduct a clinical trial to confirm that the new formulation performs.

Philip G. Sasi

KEMRI/Wellcome Trust Research Programme in Kilifi, Kenya

Safety and Tolerability of Artemether/ Lumefantrine Dispersible Tablet – Phase III Results



Following the reassuring efficacy data, **Philip G. Sasi**, of the KEMRI/Wellcome Trust Research Programme in Kilifi, Kenya presented the safety and tolerability data from the same trial, B2303.

As this was an investigator-blinded study, the safety assessment was also blinded. Safety was assessed by monitoring and recording adverse events and serious adverse events, laboratory determined adverse events were monitored through hematological and clinical chemistry parameters, whereas clinical adverse events were monitored through clinical examinations. Cardiac safety was monitored through ECG recordings before and after treatment.

The dispersible Artemether/Lumefantrine tablet had a similar safety and tolerability profile to that of the crushed tablet. There was no significant difference in the proportion of patients with an adverse event (AE) or serious adverse event (SAE).

- There were 2 deaths in the dispersible tablet group and 1 in the crushed tablet group, but none of these was suspected to be related to study drug administration.
- Regarding cardiac safety, there were no clinical symptoms or AEs related to QTc prolongation.
- The incidence of neurological abnormalities was low, with no neurological AEs suspected to be related to study drug and no hearing loss reported.
- There was no evidence of hepatic impairment in either group, and haematological profiles were similar.

The majority of the AEs were most likely related to malaria disease. Vomiting was the only AE thought to be related to study drug. There was a trend towards fewer AEs suspected to be drug-related with the dispersible tablet.

There were very few study discontinuations due to AEs – 9 (2.0%) in the dispersible tablet group and 11 (2.4%) in the crushed tablet group.

**In summary, the good safety and tolerability profile of Artemether/
Lumefantrine was confirmed in both formulations in this large trial involving
899 children. Most AEs reported were related to malaria.**

Question: Do you have much evidence in infants? What is the recommendation for dosage children under 1 year? (Nick White)

Anne-Claire Marrast (Novartis): Most children under 1 have a body weight of around 5kg, so the dosage is 1 tablet bid. Most children in the trial were between 3 months and 3 years of age, with a few children under 3 months.

Michael Makanga: In the multicenter study with the crushed tablet, which contributed most of the data for the registration of the 6-dose regimen, the majority of the children were in the <10kg body-weight group. Looking at PK data across the three body weight groups in the study, there was no significant difference in Lumefantrine bioavailability between the groups.

In summary

This symposium brought together important data emphasizing the urgent need for a pediatric formulation of the current gold-standard antimalarial, Artemether/Lumefantrine. Young children are the most vulnerable population affected by malaria, and currently available tablets are not easy for caregivers to administer or for children to swallow.

Novartis and MMV have worked together to develop a dispersible formulation of Artemether/Lumefantrine specifically for children. They have researched the most acceptable flavor, and rigorously evaluated efficacy, safety and bioavailability. This new formulation will be easy to take, and will hopefully result in this proven antimalarial becoming more accessible to those that need it most – infants and young children.



