RIAMET 20 MG/120 MG DISPERSIBLE TABLETS

(Artemether and lumefantrine)

PL 00101/0957

UKPAR

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PL 00101/0957

LAY SUMMARY

This is a summary of the public assessment report (PAR) for Riamet 20 mg/120 mg dispersible tablets. It explains how Riamet 20 mg/120 mg dispersible tablets were assessed and their authorisation recommended as well as their conditions of use. It is not intended to provide practical advice on how to use Riamet 20 mg/120 mg dispersible tablets.

What are Riamet 20 mg/120 mg dispersible tablets and what are they used for?
Riamet 20 mg/120 mg dispersible tablets contain two substances called artemether and lumefantrine. They belong to a group of medicines called anti-malarials.

Riamet is used for the treatment of malaria infections caused by a parasite called *Plasmodium falciparum.* This parasite, which is transmitted by mosquito bites, is a tiny organism that is found inside red blood cells. Riamet is not used to prevent malaria or to treat severe malaria (where it has affected the brain, lungs or kidneys).

Riamet 20 mg/120 mg dispersible tablets are used to treat children and infants weighing 5 kg to less than 35kg

How do Riamet 20 mg/120 mg dispersible tablets work?
The malaria parasite digests haemoglobin, the protein within red blood cells that is responsible for carrying oxygen. When this happens, the haemoglobin is divided into two parts; haem and globin. Haem is toxic to the malaria parasites. They protect themselves from it by producing a substance that converts the haem into a compound called haemozoin, which is not toxic to the parasites.

Artemether and lumefantrine both work by interfering with the ability of the malaria parasite to convert haem into haemozoin. This causes levels of the toxic haem to increase and helps to stop the infection.

How are Riamet 20 mg/120 mg dispersible tablets used?
The dispersible tablet(s) should be dropped into a glass of water (approximately 10mL per tablet) and the mixture stirred until the tablet dissolves completely. The entire contents of the glass should be drunk and then a little water should be added to what is left in the glass and that should also be drunk.

Six doses of Riamet are taken over 3 days. The first dose should be taken as soon as possible and should be followed by five further doses 8, 24, 36, 48 and 60 hours after the first dose. The dose of Riamet given will depend upon the weight of the child.

Please read section 3 of the package leaflet for detailed information on dosing recommendations and how to take Riamet.

The medicine can only be obtained with a prescription.

What benefits of Riamet 20 mg/120 mg dispersible tablets have been shown in studies?
In tests Riamet 20 mg/120 mg dispersible tablets have been shown to release artemether and lumefantrine in the body in the same way as the reference product, Riamet 20 mg/120 mg tablets, which has been authorised in the UK since 1999. Tests also showed that the dispersible tablets are as effective and safe to use as the reference product. In addition, a test was carried out to ensure that when the dispersible tablets are dissolved in water they have a taste that is acceptable to patients.

The benefits of Riamet 20 mg/120 mg dispersible tablets are, therefore, taken as being the same as those of the reference medicine.

What are the possible side effects from Riamet 20 mg/120 mg dispersible tablets?
The most common side effects with Riamet, which affect more than 1 in 10 people, are a fast heartbeat, headache, dizziness, cough, being sick (vomiting), stomach pain, feeling sick (nausea), joint or muscle ache, loss of appetite, general weakness, tiredness and difficulty sleeping.

For the full list of all side effects reported with Riamet, see section 4 of the package leaflet. For the full list of restrictions, see the package leaflet.

Why are Riamet 20 mg/120 mg dispersible tablets approved?
The MHRA decided that Riamet's benefits are greater than their risks and recommended that they be approved for use.

What measures are being taken to ensure the safe and effective use of Riamet 20 mg/120 mg dispersible tablets?
Suitable safety information has been included in the Summary of Product Characteristics and package leaflet for Riamet, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

Other information about Riamet 20 mg/120 mg dispersible tablets
The marketing authorisation for Riamet was granted on 13 April 2012.
For more information about treatment with Riamet, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in December 2014.

The full PAR for Riamet follows this summary.

RIAMET 20 MG/120 MG DISPERSIBLE TABLETS

PL 00101/0957

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Novartis Pharmaceuticals UK Ltd a Marketing Authorisation for the medicinal product Riamet 20 mg/120 mg dispersible tablets (PL 00101/0957) on 13 April 2012. This product is a prescription-only medicine (POM).

This is an application for a known active substance submitted according to Article 8.3 of Directive 2001/83/EC as amended, as a line-extension to Riamet 20 mg/120 mg tablets (PL 00101/0566) which was first authorised to Novartis Pharmaceuticals UK Ltd on 30 November 1999.

This application relates to a dispersible tablet formulation of Riamet, indicated for the treatment of acute uncomplicated *Plasmodium falciparum* malaria in infants and children weighing 5 kilograms (kg) to less than 35 kg. It is a line-extension application, as the Riamet tablet is already approved in this indication in this patient population.

Riamet 20 mg/120 mg dispersible tablets contain the active ingredients artemether and lumefantrine in a fixed ratio of 1:6 parts, respectively. Both of the active ingredients belong to the medicinal pharmacotherapeutic group, anti-malarials, blood schizontocide (ATC code: P01 BE52).

This application relates to a new pharmaceutical form of an approved medicinal product for use in the paediatric population. It has been considered under Article 16(1) of Regulation (EC) No 1901/2006, Article 20 (deferral request) and Article 13 of said regulation by the European Medicines Agency (EMA). The EMA agreed a paediatric investigation plan (PIP) and to grant a deferral and a waiver for artemether/lumefrantine in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council. The EMA decision (EMEA-000777-PIP01-09) was published on 21 September 2010.

The site of antiparasitic action of artemether and lumefantrine is the food vacuole of the malarial parasite, where they are thought to interfere with the conversion of haem, a toxic intermediate produced during haemoglobin breakdown, to the non-toxic haemozoin, malaria pigment. Lumefantrine is thought to interfere with the polymerisation process, while artemether generates reactive metabolites as a result of the interaction between its peroxide bridge and haem iron. Both artemether and lumefantrine have a secondary action, involving inhibition of nucleic acid and protein synthesis within the malarial parasite.

The anti-malarial activity of the combination of lumefantrine and artemether in Riamet 20 mg/120 mg dispersible tablets is greater than that of either substance alone.

No new non-clinical studies were submitted with this application, which is acceptable given that the product is a line-extension of an approved product licence containing a well-known active substance.

The clinical studies were conducted in accordance with Good Clinical Practice (GCP).

No new or unexpected safety concerns were raised during the assessment of this application and it was, therefore, judged that the benefits of using Riamet 20mg/120mg dispersible tablets outweigh the risks; hence a Marketing Authorisation has been granted.

PHARMACEUTICAL ASSESSMENT

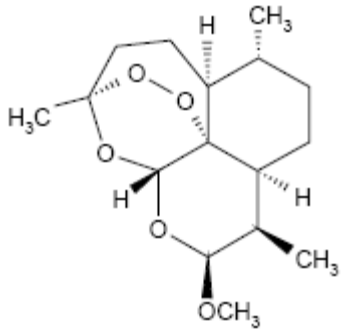
ACTIVE SUBSTANCES

The product contains two active substances, artemether and lumefantrine.

(1) Artemether

INN:	Artemether
Synonyms:	Dihydroartemisinin methyl ether Dihydroqinhaosu methylether O-Methyl dihydroartemisinin
Chemical name:	(3R,5aS,6R,8aS,9R,10S,12R,12aR)-Decahydro-10-methoxy-3,6,9-trimethyl-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzo-dioxepin

Structure:

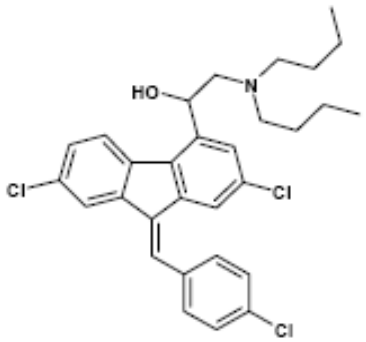


Molecular formula:	$C_{16}H_{26}0_5$
Molecular weight:	298.38
Appearance:	Artemether is a white to slightly yellow crystalline powder.

(2) Lumefantrine

INN:	Lumefantrine
Synonym:	Benflumetol
Chemical name:	(±)-2-Dibutylamino-1-[2,7-dichloro-9-(4-chlorobenzylidene)-9H-fluoren-4-yl]ethanol

Structure:



Molecular formula:	$C_{30}H_{32}Cl_3NO$
Molecular weight:	528.95
Appearance:	Lumefantrine is a yellow, crystalline powder.

Artemether and lumefantrine are not the subjects of European Pharmacopoeia monographs.

Synthesis of both active substances, artemether and lumefantrine, from the designated starting materials has been adequately described, and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

Appropriate specifications are provided for both the active substances. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Appropriate proof-of-structure data have been supplied for both of the active substances. All potential known impurities have been identified and characterised. Satisfactory certificates of analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specifications.

Suitable specifications have been provided for all packaging used for both of the active substances. The primary packaging has been shown to comply with current guidelines concerning contact with food. For both active substances, appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

MEDICINAL PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely microcrystalline cellulose, crospovidone, cherry dry flavour, croscarmellose sodium, saccharin sodium (8 mg/dispersible tablet), magnesium stearate, hypromellose, silica colloidal anhydrous and polysorbate 80.

Appropriate justification for the inclusion of each excipient has been provided.

With the exception of cherry dry flavour, all excipients used comply with their respective European Pharmacopoeia monograph. The cherry dry flavour is controlled to a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

None of the excipients contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of this product.

Pharmaceutical development

The aim of the development programme was to formulate a dispersible tablet containing 20 mg artemether and 120 mg lumefantrine specifically suited for the paediatric population.

Suitable pharmaceutical development data have been provided for this application.

Manufacture

A description and flow-chart of the manufacturing method have been provided.

Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished product specification
The finished product specification is satisfactory. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

Container Closure System
The packaging approved for use with this product is blisters made of aluminium foil and polyvinylchloride/polychlorotrifluoroethylene (PVC/PCTFE) or PVC/PCTFE/PVC foil. A pack size of 18 dispersible tablets was approved.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

Stability
Stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years, with the storage conditions “Do not store above 30°C, store in the original package in order to protect from moisture”.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SmPC, PIL and labelling are satisfactory.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA Form
The MAA form is satisfactory.

Expert Report
A quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
It is recommended that a Marketing Authorisation is granted for this application.

NON-CLINICAL ASSESSMENT

PHARMACODYNAMICS, PHARMACOKINETICS AND TOXICOLOGY

The pharmacological, pharmacokinetic and toxicological properties of artemether and lumefantrine are well-known. As this product is a line-extension of an approved product licence containing well-known active substances, no further data have been submitted and none are required. An overview based on a literature review is, thus, appropriate.

NON-CLINICAL EXPERT REPORT

The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

ENVIRONMENTAL RISK ASSESSMENT

In accordance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human use [EMEA/CHMP/SWP/4447/00], an environmental risk assessment (ERA) has been performed. The Fpen value for the Phase 1, environmental exposure assessment has been refined based on the low prevalence of malaria in the European Union (EU) and forecasted sales of the proposed product. The predicted environmental concentrations for artemether (0.03888 ng/L) and lumefantrine (0.2333 ng/L) are both below the threshold value of 0.01 µg/L; and hence no further assessment is necessary.

CONCLUSION

It is recommended that a Marketing Authorisation is granted for this application.

CLINICAL ASSESSMENT

In support of this application, the Marketing Authorisation Holder (MAH) has submitted the following studies:

- Two pharmacokinetic studies (study B2104 and B2106)
- One pivotal, main study (study B2303)
- One oral palatability study (study B2101)

PHARMACOKINETICS

The following pharmacokinetic studies were submitted to support this application:

Study B2104

A randomised, open-label, single-dose, three-period, two-sequence, crossover study to compare the pharmacokinetics of the test product Riamet 20mg/120mg dispersible tablets (Novartis Pharmaceuticals UK Ltd) versus the reference product Riamet 20mg/120mg tablets (Novartis Pharmaceuticals UK Ltd) administered crushed for oral suspension (primary comparison) and also with the reference product intact (secondary comparison) in healthy adult volunteers under fed conditions.

All volunteers were randomised to two sequences, each sequence comprising of three treatments. The test product and reference product (crushed) were administered in a crossover fashion, while the intact reference tablet was given in Period 3. All volunteers received a single oral dose (80mg/480mg) of either the test product (four dispersible tablets) or the reference product (four crushed tablets or four intact tablets). All doses were given under fed conditions. Blood samples were taken for the measurement of pharmacokinetic parameters pre- and up to 48 hours post dose for the analysis of artemether and its active metabolite dihydroartemisinin (DHA), and pre- and up to 264 hours post dose for the analysis of lumefantrine.

The pharmacokinetic results for artemether, DHA and lumefantrine are presented below:

Table 2-2 Artemether, DHA and lumefantrine PK parameters following administration of dispersible tablet, and tablet administered crushed and intact in healthy volunteers, Study B2104

Parameters Mean ± SD (except tmax)	Dispersible tablet (n=48)	Tablet (administered crushed) (n=48)	Tablet (administered intact) (n=48)
		Artemether	
Cmax (ng/mL)	58.4 ± 32.2	48.0 ± 22.2	83.8 ± 59.7
tmax[1] (h)	2.00 (0.50, 6.00)	2.00 (0.50, 6.00)	2.00 (0.75, 6.00)
AUClast(ng·h/mL)	208 ± 113	195 ± 93	259 ± 150
AUCinf (ng·h/mL)	281 ± 120(n=24)[2]	261 ± 116 (n=20)[2]	330 ± 158 (n=33)[2]
t½ (h)	2.20 ± 1.54 (n=29)[2]	2.71 ± 2.16 (n=25)[2]	2.25 ± 1.90 (n=36)[2]
		DHA	
Cmax (ng/mL)	57.3 ± 24.9	50.0 ± 18.9	90.4 ± 48.9
tmax[1] (h)	2.00 (0.75, 6.00)	2.50 (1.00, 8.00)	2.00 (0.75, 6.00)
AUClast (ng·h/mL)	206 ± 81	199 ± 84	285 ± 98
AUCinf(ng·h/mL)	266 ± 80 (n=26)[2]	261 ± 84 (n=25)[2]	326 ± 103 (n=38)[2]
t½ (h)	2.07 ± 0.88 (n=28)[2]	2.19 ± 1.10 (n=27)[2]	2.25 ± 1.46 (n=39)[2]
		Lumefantrine	
Cmax (µg/mL)	9.9 ± 3.0	10.8 ± 2.8	9.8 ± 4.2
tmax[1] (h)	8.00 (6.00, 12.00)	8.00 (6.00, 12.02)	8.00 (5.00, 12.00)
AUClast(µg·h/mL)	262 ± 107	291 ± 106	243 ± 117
AUCinf (µg·h/mL)	279 ± 106 (n=46)[2]	316 ± 119 (n=47)[2]	281 ± 133 (n=40)[2]
t½ (h)	118 ± 55 (n=46)[2]	115 ± 32 (n=47)[2]	119 ± 51 (n=41)[2]

[1] median and range (min, max), [2] Number of individuals available.

Table 2-2 Statistical analysis (dispersible tablet vs tablet 'crushed' and 'intact' ratios of geometric means and 90% confidence limits.

	Dispersible vs crushed		Dispersible vs intact	
	Ratio estimate*	90% CL	Ratio estimate*	90% CL
		Artemether		
Cmax (ng/mL)	1.17	1.06-1.29	0.73	0.65-0.82
AUClast (ng·h/mL)	1.03	0.94-1.13	0.80	0.73-0.88
AUCinf (ng·h/mL)	0.94	0.86-1.02	0.80	0.71-0.90
		DHA		
Cmax (ng/mL)	1.14	1.04-1.24	0.65	0.58-0.73
AUClast (ng·h/mL)	1.03	0.93-1.15	0.69	0.62-0.77
AUCinf (ng·h/mL)	1.05	0.99-1.11	0.78	0.72-0.84
		Lumefantrine		
Cmax (µg/mL)	0.91	0.86-0.96	1.07	0.97-1.18
AUClast (µg·h/mL)	0.89	0.84-0.94	1.12	1.02-1.23
AUCinf (µg·h/mL)	0.90	0.85-0.95	1.06	0.96-1.16

* back-transformed from log scale; CL = confidence limit

The pharmacokinetic parameters for the dispersible tablet compared with crushed tablet all fall within the predefined acceptance criteria specified in the 'Guideline on the Investigation of Bioequivalence' (CPMP/EWP/QWP/1401/98 Rev 1/, Corr**) for artemether, DHA and lumefantrine apart from the C-max for artemether. The pharmacokinetic parameters for the dispersible tablet compared with the intact tablet for artemether and DHA all fall outside the criteria of 80 to 125%.

These results are considered acceptable as the MAH has also conducted a parallel-group trial assessing the efficacy and safety of the dispersible tablet compared with standard crushed tablet.

Study B2106

A randomised, open-label, single-dose, six-sequence, three-period, crossover study to compare the pharmacokinetics of two different batches of test product Riamet 20mg/120mg dispersible tablets (Novartis Pharmaceuticals UK Ltd) versus the reference product Riamet 20mg/120mg tablets (Novartis Pharmaceuticals UK Ltd) administered crushed for oral suspension in healthy adult volunteers under fed conditions.

All volunteers were equally randomised to the following six sequences:

Table 9-1 Treatments allocation

	Period 1	Washout	Period 2	Washout	Period 3
Sequence A	1	5 weeks	2	5 weeks	3
Sequence B	1	5 weeks	3	5 weeks	2
Sequence C	2	5 weeks	1	5 weeks	3
Sequence D	2	5 weeks	3	5 weeks	1
Sequence E	3	5 weeks	1	5 weeks	2
Sequence F	3	5 weeks	2	5 weeks	1

1=Test dispersible tablet from batch made at new manufacturing site
2=Test dispersible tablet from scale up batch
3=Reference product (crushed)

Each volunteer completed the following treatments under fed conditions:

- Treatment 1: single dose of the test product made from new manufacturing site administered as an oral suspension (4 tablets of 20mg artemether and 120 mg lumefantrine to give a total dose of 80 mg artemether and 480 mg lumefantrine)

- Treatment 2: single dose of the test product made from scale up batch administered as an oral suspension (4 tablets of 20mg artemether and 120 mg lumefantrine to give a total dose of 80 mg artemether and 480 mg lumefantrine)
- Treatment 3: single dose of the reference product crushed and administered as an oral suspension (4 tablets of 20mg artemether and 120 mg lumefantrine to give a total dose of 80 mg artemether and 480 mg lumefantrine).

Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 24 hours post dose for the analysis of artemether and its active metabolite dihydroartemisinin (DHA) and up to 264 hours post dose for the analysis of lumefantrine. There was a washout period of at least 5 weeks between each treatment.

The pharmacokinetic results for artemether, DHA and lumefantrine are presented below:

Table-1 Summary statistics for PK parameters of artemether, DHA and lumefantrine after each treatment (mean ± SD (CV%))

	Test product new manufacturing site batch	Test product scale-up batch	Reference product
		Artemether	
	(n=54)	(n=50)	(n=50)
C_{max} (ng/mL)	73.3 ± 39.5 (54%)	72.7 ± 38.4 (53%)	67.4 ± 35.5 (53%)
t_{max}[a] (h)	2.02 [0.50-4.02]	2.98 [0.50-4.02]	2.05 [0.52-4.07]
AUC_{tlast} (ng·h/mL)	263 ± 142 (54%)	263 ± 124 (47%)	229 ± 136 (59%)
AUC_{∞} (ng·h/mL)	308 ± 130 (42%)[42]	307 ± 112 (37%)[38]	269 ± 115 (43%)[32]
$t_{½}$ (h)	2.0 ± 1.0 (53%)[46]	2.4 ± 2.9 (121%)[41]	1.9 ± 1.6 (86%)[36]
		Dihydroartemisinin	
	(n=54)	(n=50)	(n=50)
C_{max} (ng/mL)	48.6 ± 23.2 (48%)	47.5 ± 19.5 (41%)	48.8 ± 26.0 (53%)
t_{max}[a] (h)	2.98 [0.75-5.98]	3.00 [0.75-4.10]	2.54 [0.75-4.07]
AUC_{tlast} (ng·h/mL)	171 ± 59.5 (35%)	180 ± 58.5 (33%)	160 ± 68.0 (42%)
AUC_{∞} (ng·h/mL)	202 ± 53.1 (26%)[37]	231 ± 50.7 (22%)[31]	213 ± 63.3 (30%)[25]
$t_{½}$ (h)	2.1 ± 1.4 (69%)[48]	1.9 ± 0.8 (44%)[35]	1.9 ± 1.1 (56%)[31]
		Lumefantrine	
	(n=55)	(n=52)	(n=52)
C_{max} (µg/mL)	10.2 ± 3.08 (30%)	8.81 ± 2.43 (28%)	10.0 ± 2.57 (26%)
t_{max}[a] (h)	8.00 [4.98-24.02]	8.00 [5.98-12.02]	8.00 [4.98-24.02]
AUC_{tlast} (µg·h/mL)	295 ± 107 (36%)	257 ± 80.4 (31%)	280 ± 93.2 (33%)
AUC_{∞} (µg·h/mL)	321 ± 122 (38%)[52]	277 ± 88.8 (32%)[49]	308 ± 97.9 (32%)[47]
$t_{½}$ (h)	125 ± 58.7 (47%)	112 ± 35.0 (31%)[50]	117 ± 48.3 (41%)[47]

[a] median and range (min, max). Numbers in superscript indicate sample size.

Table 2: Test product batch from new manufacturing site versus test product from scale-up batch (ANOVA of pharmacokinetic parameters of artemether, DHA and lumefantrine)

Analyte	Parameter	Adjusted geometric means [a]		Ratio of geometric means [a]			
		Test product new manuf site batch	Test product scale-up batch	Ratio of geo means	90% CI lower bound	90% CI upper bound	Meets statistical bioequivalence criteria
Artemether	C_{max} (ng/mL)	62.98	65.86	0.96	0.85	1.07	Yes
	AUC_{tlast} (ng·h/mL)	228.33	241.58	0.95	0.85	1.05	Yes
	AUC_{∞} (ng·h/mL)	276.58	294.05	0.94	0.86	1.02	Yes
Dihydro-artemisinin	C_{max} (ng/mL)	43.68	45.30	0.96	0.86	1.08	Yes
	AUC_{tlast} (ng·h/mL)	163.70	174.79	0.94	0.85	1.03	Yes
	AUC_{∞} (ng·h/mL)	200.31	225.48	0.89	0.81	0.97	Yes
Lumefantrine	C_{max} (µg/mL)	9.72	8.42	1.15	1.08	1.23	Yes
	AUC_{tlast} (µg·h/mL)	271.42	239.47	1.13	1.06	1.21	Yes
	AUC_{∞} (µg·h/mL)	297.59	261.78	1.14	1.07	1.21	Yes

a – back-transformed from log scale

Table 3: Test product new manufacturing site batch versus reference product (ANOVA of pharmacokinetic parameters of artemether, DHA and lumefantrine)

Analyte	Parameter	Adjusted geometric means [a]		Ratio of geometric means [a]			
		Test product new manuf site batch	Reference product	Ratio of geo means	90% CI lower bound	90% CI upper bound	Meets statistical bioequivalence criteria
Artemether	C_{max} (ng/mL)	62.98	60.97	1.03	0.92	1.16	Yes
	AUC_{tlast} (ng·h/mL)	228.33	202.37	1.13	1.01	1.25[b]	No
	AUC_{∞} (ng·h/mL)	276.58	243.58	1.14	1.03	1.25[c]	Yes
Dihydro-artemisinin	C_{max} (ng/mL)	43.68	43.48	1.00	0.89	1.13	Yes
	AUC_{tlast} (ng·h/mL)	163.70	146.77	1.12	1.01	1.23	Yes
	AUC_{∞} (ng·h/mL)	200.31	200.51	1.00	0.91	1.10	Yes
Lumefantrine	C_{max} (µg/mL)	9.72	9.59	1.01	0.95	1.08	Yes
	AUC_{tlast} (µg·h/mL)	271.42	259.93	1.04	0.98	1.11	Yes
	AUC_{∞} (µg·h/mL)	297.59	283.81	1.05	0.98	1.12	Yes

a – back-transformed from log scale
b – value to 5 decimal places = 1.25496
c – value to 5 decimal places = 1.24620

Table 4: Test product scale-up batch versus reference product (ANOVA of pharmacokinetic parameters of artemether, DHA and lumefantrine)

Analyte	Parameter	Adjusted geometric means [a]		Ratio of geometric means [a]			
		Test product scale up batch	Reference product	Ratio of geo means	90% CI lower bound	90% CI upper bound	Meets statistical bioequivalence criteria

Artemether	C_{max} (ng/mL)	65.86	60.97	1.08	0.96	1.21	Yes
	AUC_{tlast} (ng·h/mL)	241.58	202.37	1.19	1.07	1.33	No
	AUC_{∞} (ng·h/mL)	294.05	243.58	1.21	1.10	1.32	No
Dihydro-artemisinin	C_{max} (ng/mL)	45.30	43.48	1.04	0.93	1.17	Yes
	AUC_{tlast} (ng·h/mL)	174.79	146.77	1.19	1.08	1.32	No
	AUC_{∞} (ng·h/mL)	225.48	200.51	1.12	1.02	1.24	Yes
Lumefantrine	C_{max} (µg/mL)	8.42	9.59	0.88	0.82	0.94	Yes
	AUC_{tlast} (µg·h/mL)	239.47	259.93	0.92	0.86	0.98	Yes
	AUC_{∞} (µg·h/mL)	261.78	283.81	0.92	0.86	0.98	Yes

a – back-transformed from log scale

The pharmacokinetic parameters for the test product for the batch manufactured at the new site compared with the scale-up batch all fall within the predefined acceptance criteria specified in the 'Guideline on the Investigation of Bioequivalence' (CPMP/EWP/QWP/1401/98 Rev 1/, Corr**). Thus the data support the clain that the test batch manufactured at the new site is bioequivalent to the test product scale-up batch.

The pharmacokinetic parameters for the test product new site batch compared with the reference product all fall within the standard bioequivalence criteria of 80 to 125% apart from the AUC_{last} for artemether. The Pharmacokinetic parameters for the scale up test product batch and the reference product were bioequivalent apart from the AUC_{last} and infinity for artemether and AUC_{last} for DHA.

The lack of bioequivalence between the scale up test product batch and the reference product (crushed tablet)is acceptable in this instance as it is agreed that bioequivence was demonstrated between the test product manufactured at the new site (the to-be marketed formulation) and reference product as the upper limit of the 90% CI is just within the accepted criteria.

Pharmacokinetic considerations in the paediatric population.

Pivotal (main) study B2303.

An investigator-blind, randomised, parallel group, multicentre trial performed in sub-Saharan Africa in which infants and children (body weight equal to or more than (≥) 5 kg and less than (<) 35 kg) with acute uncomplicated falciparum malaria received either the test product dispersible tablet or the reference tablet (crushed for administration).

This study contained a pharmacokinetic component (sparse collection). Two blood samples for the measurement of artemether and DHA in plasma were collected at 1 and 2 hours post first dose of artemether-lumefantrine (anticipated t_{max}) in those patients recruited until the interim analysis. After the interim analysis, the remaining patients had one blood sample taken from each patient at 6 different time-points in order to investigate lumefantrine plasma concentrations. Samples were taken for half of the patients (50%) at 6 hours after dose 6 (anticipated t_{max}), and at 5 other time-points (6 hours after doses 3 or 5, or on Days 3, 7, or 14) for 10% of the patients.

For artemether and DHA, C_{max} was defined as the concentration measured at 1 or 2 hours after the first dose of artemether-lumefantrine, whatever was the highest. For lumefantrine, mean plasma concentration-time profiles (for all patients per treatment arm, as well as for each body-weight group per treatment arm) were computed by averaging the concentrations of all samples collected in a specified collection interval and pharmacokinetic parameters, i.e. C_{max}, t_{max} and AUC_{last} were derived from the mean concentration-time profiles.

Results

Artemether and DHA

There were 93 patients with concentrations of artemether and/or DHA in the reference product (crushed tablet) group (55/56 patients in the body weight ≥5 to <15 kg group, 29 in the 15 to < 25 kg group, and 8 in the 25 to < 35 kg group), and 91 in the test product dispersible tablet group (52, 30 and 9 patients in the ≥5 to less than 15 kg, 15 to less than 25 kg and 25 to less than 35 kg groups, respectively).

No difference was apparent between the test product dispersible tablet and the reference product tablet (administered crushed) with respect to artemether and DHA plasma levels. The C_{max} for artemether for the whole population (all body weight groups pooled) after treatment with the reference tablet administered crushed and test product dispersible tablet were 211 ± 262 ng/mL (CV 124%, n=92) and 175 ± 168 ng/mL (CV 96%, n=91), respectively. The C_{max} for DHA were 63.4 ± 64.9 ng/mL (CV 102%, n=93) and 68.0 ± 64.4 ng/mL (CV 95%, n=91) for the reference product tablet (administered crushed) and test product dispersible tablets, respectively

Table 8.2-2 Descriptive statistics (mean ± SD) of artemether and DHA plasma maximum concentrations (C_{max}) per bodyweight group in pediatric patients treated with 6-dose regimen co-artemether crushed or dispersible tablets

	Bodyweight group (dose regimen)			
	5-15 kg (6 x 1 tablet)	15-<25 kg (6 x 2 tablets)	25-<35 kg (6 x 3 tablets)	Total 5-<35 kg
Crushed tablet	N = 55	N = 29	N = 8	N = 92
C_{max} artemether (ng/mL)	223 ± 309 (CV 139%)	198 ± 179 (CV 90%)	174 ± 145 (CV 83%)	211 ± 262 (CV 124%)
C_{max} DHA (ng/mL)	54.7 ± 58.9 (CV 108%)*	79.8 ± 80.5 (CV 101%)	65.3 ± 23.6 (CV 36%)	63.4 ± 64.9 (CV 102%)
Total dose artemether (mg/kg BW)[1]	11.1 ± 3.54 (n=56)	13.4 ± 1.76	13.2 ± 1.02	12.0 ± 3.1 (n=93)
Dispersible tablet	N = 52	N = 30	N = 9	N = 91
C_{max} artemether (ng/mL)	196 ± 204 (CV 104%)	150 ± 106 (CV 71%)	134 ± 56.7 (CV 42%)	175 ± 168 (CV 96%)
C_{max} DHA (ng/mL)	67.8 ± 74.7 (CV 110%)	66.5 ± 49.0 (CV 74%)	73.9 ± 48.7 (CV 66%)	68.0 ± 64.4 (CV 95%)
Total dose artemether (mg/kg BW)[1]	11.6 ± 2.87 (n=53)	13.4 ± 2.05	12.7 ± 1.21	12.3 ± 2.61 (n=92)

BW = bodyweight; CV = coefficient of variation (100·SD/mean); * n = 56; [1] patients with artemether or DHA concentrations available.

In total, lumefantrine plasma concentrations were available from 315 patients treated with the reference product crushed tablets and 310 patients treated with the test product dispersible tablets.

There was no apparent difference in population plasma profile of lumefantrine between the two treatment groups. The mean population C_{max} was 7.69 and 6.27 µg/mL after treatment with the reference tablet (crushed for administration) and test dispersible tablets, respectively. T_{max} was 66.3 hours after the first dose for both treatment groups. AUC_{last} was 636 and 574 ng.h/mL, for the reference tablet (crushed for administration) and test dispersible treatment groups, respectively.

Pharmacokinetic variables for lumefantrine are presented in the table below. Exposure to lumefantrine (C_{max} and AUC_{last}) was the lowest in the 5 to less than 15 kg group (lowest body weight group) and highest in the 25 to less than 35 kg group (highest body weight group) after both treatments, although the dose per kg body weight remained similar, in particular for the two highest body weight groups. However, it should be noted that lumefantrine plasma profiles in the 25to less than 35 kg group in both the reference tablet (crushed for administration) and test dispersible tablet groups might not have been as well characterised as for the other groups because of the limited number of values per sampling time in the 25 to less than 35 kg body weight group (for both treatments). Indeed, C_{max} in the reference tablet (crushed for administration) group was defined based on only one single (high) concentration (21.9 µg/mL), and no concentration was available on

Day 7 in the test dispersible tablet group, leading to probably overestimated C_{max} and AUC values in the 25 to less than 35 kg group for both treatments.

Table 8.2-5 Descriptive statistics of lumefantrine plasma concentrations per bodyweight group in pediatric patients treated with 6-dose regimen co-artemether crushed or dispersible tablets

Protocol time of sampling	5-<15 kg bodyweight			15-<25 kg bodyweight			25-<35 kg bodyweight			Total (5-<35 kg bodyweight)		
	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Crushed tablet												
6 h/Dose 3	3.88	3.10	22	6.63	4.70	9	9.71	-	2	4.98	3.86	33
6 h/Dose 5	4.63	3.14	22	7.30	4.96	8	21.9	-	1	5.87	4.79	31
6 h/Dose 6	6.13	5.62	101	9.37	4.26	53	15.3	8.26	9	7.69	5.86	163
Day 3	2.87	1.58	14	3.59	2.02	5	4.10	2.58	4	3.24	1.84	23
Day 7	0.410	0.469	16	0.504	0.271	16	0.336	-	1	0.454	0.374	33
Day 14*	1.20 (0.035)	3.51 (0.048)	19 (17)	0.069	0.074	11	0.182	-	2	0.748	2.73	32
	C_{max} = 6.13 µg/mL $AUC_{0\text{-last}}$ = 577 µg·h/mL			C_{max} = 9.37 µg/mL $AUC_{0\text{-last}}$ = 699 µg·h/mL			C_{max} = 21.9 µg/mL $AUC_{0\text{-last}}$ = 1150 µg·h/mL			C_{max} = 7.69 µg/mL $AUC_{0\text{-last}}$ = 638 µg·h/mL		
Dispersible tablet												
6 h/Dose 3	3.13	2.50	16	7.44	2.76	11	12.3	10.3	3	5.63	4.74	30
6 h/Dose 5	5.16	3.41	14	6.66	4.16	15	6.61	-	1	6.15	3.68	30
6 h/Dose 6	5.10	3.67	102	8.03	4.78	48	10.1	7.22	9	6.27	4.55	159
Day 3	2.16	1.87	14	4.05	2.79	11	4.82	-	1	3.06	2.30	26
Day 7	0.296	0.237	27	0.461	0.285	4	-	-	0	0.317	0.245	31
Day 14*	0.535 (0.113)	1.82 (0.292)	18 (17)	0.107	0.084	13	0.09	0.16	3	0.322	1.32	34
	C_{max} = 5.16 µg/mL $AUC_{0\text{-last}}$ = 441 µg·h/mL			C_{max} = 8.03 µg/mL $AUC_{0\text{-last}}$ = 704 µg·h/mL			C_{max} = 12.3 µg/mL $AUC_{0\text{-last}}$ = 1260 µg·h/mL			C_{max} = 6.27 µg/mL $AUC_{0\text{-last}}$ = 574 µg·h/mL		

* values in brackets exclude outliers (i.e. patients 170/center 301 (12.2 µg/mL) and 198/center 601 (10.0 µg/mL) in crushed tablet arm, and patient 50/center 201 (7.72 µg/mL) in dispersible tablet arm). Mean of actual times in the specified collection interval was used to calculate $AUC_{0\text{-last}}$ (all patients at Day 14 were included in calculations)

The analysis show that the mean population C_{max} for artemether and DHA; (211± 262ng/mL and 68.0 ± 64.4ng/mL respectively); are higher than the C_{max} obtained in the two bioequivalence studies (B2104 and B2106), but there was a very high inter-subject variability.

The C_{max} for lumefantrine is also lower than that obtained in the bioequivalence studies.

Influence of food.
The food effect (Food and Drug Administration (FDA) standard breakfast) has been initially investigated with Riamet standard tablet (intact tablet) in a single dose study in healthy volunteers (Lefèvre and Thomson 1999). In this study, food intake was shown to enhance the bioavailability of artemether and DHA by approximately 2-fold compared with fasted conditions.

No formal food effect study was specifically conducted with the test dispersible tablet or the standard tablet administered crushed (reference). However, two biopharmaceutics studies (the bioavailability study B2104 and the bioequivalence study B2106) were conducted with the test dispersible tablet, the reference crushed tablet and/or the intact tablet. The studies showed that artemether and DHA exposure was similar following the test dispersible tablet and the standard tablet given crushed (the usual way of administration in children so far), which were both given under fed conditions (standardised FDA meal).

Study B2104 also compared the test dispersible tablet to the intact tablet. Artemether and DHA total exposure (AUC) was 20% to 30% lower after the dispersible tablet compared with the intact tablet, both given under fed conditions. This 20-30% difference is considered small and is attributed to a partial acid-related degradation of artemether in the stomach after the test dispersible tablet (given as a suspension) versus the reference intact tablet rather than a difference in the effect of food on artemether absorption. Under fasting conditions, the AUC of artemether and DHA is expected to be 50% lower than under fed conditions. Thus, the food effect actually seen for the intact tablet is

about 2-fold larger than the difference observed between the test dispersible and the intact tablet when both were given under fed conditions.

Based on the above, food is considered to have the same effect on the bioavailability of artemether and DHA with both dispersible and intact tablets.

The clinical relevance of the lower bioavailability of artemether with the test dispersible tablet (as compared to the reference intact tablet) with respect to efficacy of Riamet in children is considered to be insignificant since crushing tablets has been the standard way of administration in paediatric patients so far and the to-be-marketed formulation of the dispersible tablet is considered to be bioequivalent to the crushed tablet. Excellent efficacy results have been obtained with the crushed tablet in an earlier study in children with malaria and subsequently in a study comparing the test dispersible and crushed tablets in paediatric malaria patients (study B2303). In the pivotal study B2303, in infants and children with malaria, the dispersible tablet was shown to be highly effective in terms of all efficacy parameters measured, and in particular with 28-day PCR-corrected parasitological cure rates of 97.8%, which was in line with cure rates (consistently 95% or higher) observed in clinical studies using the intact standard tablet (Lefèvre et al 2001). Patients should therefore be encouraged to take the medication with a diet as soon as food can be tolerated, as is currently recommended in the label. Published data, together with data from study B2303 (Borrmann et al 2010) confirm that a normal diet is adequate in this respect.

Assessor's overall conclusions on pharmacokinetics
There is a suggestion of a high inter-subject variability with regards to the bioavailability of artemether and DHA as evident in the two bioequivalent studies (B2104 and B2106). In study B2104 for the test dispersible tablet the C_{max} for artemether was not bioequivalent to the reference crushed tablets and in study B2106, although the two test batches of dispersible tablets were bioequivalent to each other for the three components artemether, DHA and lumefantrine. When compared to the reference crushed tablets artemether and DHA were not bioequivalent in terms of AUC.

The high inter-subject variability for artemether and DHA was also quite significant in the population pharmacokinetic analysis performed as part of study B2303.

Overall, the data obtained appears to be in-line with what is known about artemether and DHA.

PHARMACODYNAMICS

Primary pharmacodynamics and mechanisms of action
No studies have been submitted on the primary pharmacodynamics of artemether-lumefantrine.

Secondary pharmacodynamics
The following pharmacodynamic study (A2101) on QTc prolongation was submitted to support this application:

STUDY A2101
A randomised, single-blind, parallel group study to evaluate the effects of artemether-lumefantrine tablet on cardiac safety in healthy adult subjects versus placebo, with positive control moxifloxacin hydrochloride.

A total of 126 healthy adult subjects were enrolled. Forty-two subjects received artemether-lumefantrine over 3 days, 42 received placebo over 3 days, and 42 subjects received placebo on

each of 5 occasions except for the last (sixth) dose on Day 3 when 1 of the placebo tablets was replaced with a dose of moxifloxacin hydrochloride (i.e. subjects received 3 placebo tablets and one 400-mg moxifloxacin tablet). Extensive 12-lead ECGs and pharmacokinetic blood samples were collected from baseline (Day -1) up to 168 hours post dose.

No subject had a greater than 30 milliseconds (msec) increase from baseline or an absolute increase to greater than 500 msec. The moxifloxacin positive control was associated with a QTcF increase as compared to placebo, occurring between 1 and 12 hours after dosing; with a maximum change in comparison to placebo of 14.1 msec. Artemether-lumefantrine was associated with a mean maximum increase in QTc relative to placebo of 7.45 msec, with the lower 90% confidence interval greater than zero. The upper 90% confidence interval for the mean change from baseline in QTcF for artemether-lumefantrine relative to placebo was slightly above 10 msec for three time-points: 68, 72 and 108 hours, and the mean changes from baseline with their 90% CI's were 7.45 (4.41, 10.48), 7.29 (4.2, 10.38) and 6.84 (3.16, 10.51) msec, respectively. At the follow-up time-points of 156 and 168 h after dose, the changes from baseline for QTcF with their 90% CI's were 3.47 (-0.18, 7.12) and 2.93 (-0.36, 6.22) msec indicating no significant difference from zero effect.

A post hoc analysis which looked at the pharmacokinetic/pharmacodynamic (PK/PD) correlation analysis showed an association between maximum observed values of QTcF changes adjusted from placebo and baseline and the concentrations of lumefantrine.

Table 11-2 Confidence intervals for treatment comparisons of change from mean baseline in ECG interval by time

Time point (h post- first dose of COA566)	QTcF (msec)		QTcB (msec)	
	COA566 vs placebo	Moxifloxacin hydrochloride vs placebo[1]	COA566 vs placebo	Moxifloxacin hydrochloride vs placebo[1]
28	2.06, 7.62	-	3.54, 10.31	-
52	3.22, 9.56	-	4.46, 11.52	-
61	3.52, 9.75	10.93, 17.27	4.57, 11.66	13.01, 19.68
62	3.61, 9.55	9.50, 16.04	4.76, 11.70	10.70, 17.89
64	2.08, 8.43	8.16, 14.98	3.52, 11.04	11.17, 18.71
66	3.03, 9.18	7.53, 14.23	4.03, 11.76	8.64, 17.30
68	4.41, 10.48	9.15, 15.19	6.71, 14.08	10.95, 18.41
72	4.20, 10.38	9.98, 16.62	5.37, 12.94	11.84, 19.38
96	3.22, 9.56	3.22, 9.56	4.07, 12.62	1.23, 9.98
108	3.16, 10.51	1.10, 8.15	4.85, 13.83	-0.14, 8.23
156	-0.18, 7.12	-1.11, 5.75	3.58, 12.52	-2.59, 6.04

[1] The first dose of moxifloxacin hydrochloride was given at time 60 h

Data are only shown for time point where one of the confidence intervals for one of the treatments was greater than 10 msec

The study demonstrates that there is an increase in QTc relative to placebo when artemether-lumefantrine tablets are administered.

In addition to study A2101 above, supportive information on QTc is also provided from pivotal study B2303:

Study B2303

The mean increase in QTc interval from baseline was less than 8 msec using Bazett's formula and less than 19 msec using Fridericia's formula. There were no significant differences in QTc values across time between the two treatments groups (dispersible versus crushed tablets).

Shift table analysis of QTc interval based on Bazett's formula showed that of the patients with normal QTc interval at baseline, 23.3% of dispersible tablet patients and 24.5% of crushed tablet patients were borderline prior to or on Day 5 whilst 4.9% of dispersible tablet patients and 5.0% of

crushed tablet patients had QTc prolongation. Of those patients with borderline QTc interval at baseline the majority were normal or borderline prior to or on Day 5. Of those patients with QTc prolongation at baseline the majority were borderline or prolonged prior to or on Day 5.
Shift table analysis of QTc interval based on Fridericia's formula showed no patients with QTc prolongation at baseline in either treatment group. Of those patients with normal QTc at baseline, 1.8% in the dispersible tablet group and 1.1% in the crushed tablet group were borderline prior to or on Day 5. One patient in the dispersible tablet group with a normal QTc interval at baseline had QTc prolongation.

There were no patients with QTc intervals greater than 500 msec (calculated using either formula). The majority of patients had changes from baseline in QTc interval of less than 30 msec. The proportion of patients with a QTc increase of 30-60 msec (using either formula) was higher in the dispersible tablet group compared to the crushed tablet group. A low rate of QTc interval increases of more than 60 msec were observed in both treatment groups, with a slight higher incidence in the crushed tablet group.

Table 10-5 QTc values (msec) across time (Safety population)

	Dispersible tablet (N=447) Mean (SD)	Crushed tablet (N=452) Mean (SD)	Dispersible tablet minus crushed tablet 95% CI
Bazett's formula			
Baseline	426.6 (23.8)	425.9 (22.2)	
Post-baseline*	434.2 (20.5)	433.0 (19.3)	
Change	7.6 (24.9)	7.1 (24.3)	(-2.8, 3.7)
Fridericia's formula			
Baseline	376.5 (26.8)	375.0 (25.3)	
Post-baseline*	394.7 (21.6)	393.1 (20.5)	
Change	18.2 (24.4)	18.1 (24.6)	(-3.1, 3.4)

*If a patient had more than one post-baseline value the mean was used for summarization.
Bazett's formula: QTc = QT/(RR**0.5)
Fridericia's formula: QTc = QT/(RR**1/3)

The above findings are in keeping with what is known about artemether-lumefantrine tablets.

Study B2101 (oral palatability study).
A randomised, single-blind, crossover study in 48 healthy children age 7 to 10 years was carried out. The study consisted of a 5-day screening period, followed by one tasting period of Riamet provided as powder-in-bottle (PIB) with flavour, and an end-of-study visit prior to discharging the subjects from the study. To control possible variation in tasting due to time of day, all flavour tasting was conducted between 09:30 and 13:00. Subjects were randomised to taste all three of the following flavours in one day:

- PIB for oral suspension, Strawberry flavour
- PIB for oral suspension, Orange flavour
- PIB for oral suspension, Cherry flavour

Subjects tasted all three flavours during the tasting period. For each flavour, a 2.0 mL dose of the respective oral suspension was administered via plastic syringe. Subsequent flavour taste tests occurred after an interval of at least 45 minutes following the previous flavour. Following each tasting, the subjects evaluated the taste for the following attributes: sweetness, bitterness, odour, overall feel of the formulation in the mouth cavity, overall liking of the flavour and aftertaste. There were no drug related adverse events. This study did not have any pharmacokinetic component. There was no statistically significant difference in preference between the three

flavours in any of the questions. Although all three flavours had an average visual analog scale (VAS) score in the range of 70 to 95, the cherry flavour had the higher VAS score (mean or median) in many questions.

Assessor's overall conclusions on pharmacodynamics
The primary and secondary pharmacodynamics for artemether-lumefantrine tablets has previously been characterised. The applicant has provided one QTc study in support of this application. It appears that prolongation of the QTc interval which occurs with artemether-lumefantrine tablets is most likely because of lumefantrine as noted in study A2101. In study B2303, there appears to be some prolongation of QTc intervals but these did not appear to be associated with any significant adverse event as a result of this.

CLINICAL EFFICACY
Study B2303 has been submitted in support of this application (see below).

Dose-response studies
No dose response study has been submitted in support of this application. This is acceptable since artemether-lumefantrine dispersible tablet contains the same quantities of artemether and lumefantrine as the reference tablet and studies B2104 and B2106 demonstrated similar exposure to lumefantrine, artemether and dihydroartemisinin with the dispersible tablet compared with the reference tablet (crushed for administration). Also, the current recommended dose regimen for the artemether-lumefantrine tablet, b.i.d (twice daily) administration for 3 days with dose adjustment according to patient body weight range, is well-established as a reference treatment for uncomplicated falciparum malaria. An identical dose regimen was therefore selected for the dispersible tablet.

Pivotal (main study) B2303.
A randomised, investigator-blinded, multicentre, parallel-group study to compare efficacy, safety and tolerability of Coartem®* dispersible tablet versus Coartem® 6-dose crushed tablet in the treatment of acute uncomplicated *Plasmodium falciparum* malaria in infants and children.

*Coartem® is the trade name of artemether-lumefantrine (Riamet®) in endemic countries, South Africa and the USA.

Objectives
The primary objective was to confirm the efficacy of the Coartem® dispersible tablet in infants and children with a body weight of more than or equal to (≥) 5 kg and less than (<) 35 kg suffering from *P. falciparum* malaria by testing the hypothesis that Coartem® 6-dose dispersible tablet is non-inferior to the presently used Coartem® 6-dose regimen of crushed tablet on the 28-day Polymerase Chain Reaction (PCR) - corrected parasitological cure rate.

The secondary objectives were:
- To compare the 7-day parasitological cure rate, and the PCR-corrected 14-day parasitological cure rates between the two treatment groups
- To compare time to parasite, fever, and gametocyte clearance between the two treatment groups
- To compare the safety and tolerability profile of the two treatment groups (AEs, general laboratory, vital signs, and ECG measurements)
- To investigate drug plasma levels (sparse sampling) with the aim to assess any potential relationship between Coartem® exposure and safety and/or efficacy.

The exploratory objectives were to explore the PCR-corrected 42-day parasitological cure rate of the two treatment groups, the incidence of Early Treatment Failures, the incidence of Late Clinical Failure, the incidence of Late Parasitological Failure and the Adequate Clinical and Parasitological Response.

Study Treatments
Investigational drug: Coartem® was provided as dispersible tablets (each tablet containing 20 mg artemether and 120 mg lumefantrine) and supplied up to three blisters according to body weight as follows:
BWG 1: ≥5 kg – <15 kg = 1 blister
BWG 2: ≥15 kg – <25 kg = 2 blisters
BWG 3: ≥25 kg – <35 kg = 3 blisters
Each blister contained eight dispersible tablets: six for regular treatment and two for replacement in case of vomiting. Tablets given should have been followed whenever possible by food/drink.

Reference therapy: Coartem® was provided as standard tablets (each tablet containing 20 mg artemether and 120 mg lumefantrine) and supplied in up to three blisters of eight tablets according to body weight as same as above. Each blister contained eight standard tablets:six for regular treatment and two for replacement in case of vomiting. Tablets given should have been followed whenever possible by food/drink. Tablets were to be crushed and dissolved before being taken.

Duration of treatment: Patients entered a 3-day treatment phase. All treatments were given under hospital supervision. Patients remained under medical surveillance (if possible within hospital grounds) for the following 4 days. These patients were then followed until Day 42 and accounted for the primary and secondary assessment of the study.

Treatment assignment
Patients were assigned to one of the following two treatment arms in a ratio of 1:1 and received active treatment based on body weight as follows:
BWG 1: ≥5 kg – <15 kg = 6 doses of 1 dispersible tablet or 1 crushed standard tablet
BWG 2: ≥15 kg – <25 kg = 6 doses of 2 dispersible tablets or 2 crushed standard tablets
BWG 3: ≥25 kg – <35 kg = 6 doses of 3 dispesible tablets or 3 crushed standard tablets

Primary endpoints
The proportion of patients who were clinically free of parasitemia (PCR corrected if *P. falciparum* asexual forms present) at 28 days as measured by a 28-day PCR-corrected parasitological cure rate.

Secondary endpoints
7-day parasitological cure rate (not PCR-corrected), PCR-corrected 14-day parasitological cure rate, time to parasite clearance (PCT), time to fever clearance (FCT), and time to gametocyte clearance (GCT).

Exploratory efficacy variables included PCR-corrected 42-day cure rate, early treatment failure (ETF), late clinical failure (LCF), late parasitological failure (LPF), adequate clinical and parasitological response (ACPR), and development of danger signs or severe malaria.

Safety: The safety information collected included adverse events (AEs) and serious adverse events (SAEs), results of physical examinations, data on vital signs, weight and laboratory evaluations.

Additional safety evaluations included ECG and neurological examinations, and details of treatment emergent signs and symptoms (TESS).

Results

Patient disposition

Table 7-1 Patient disposition (Randomized population)

	Dispersible tablet	Crushed tablet	Total
Total number of patients - n (%)			
Randomized	447 (100.0)	452 (100.0)	899 (100.0)
Treated (at least one dose)	447 (100.0)	452 (100.0)	899 (100.0)
Treated (at least one full dose)[a]	444 (99.3)	446 (98.7)	890 (99.0)
Completed treatment period[b]	431 (96.4)	435 (96.2)	866 (96.3)
Completed study	394 (88.1)	388 (85.8)	782 (87.0)
Discontinuations - n (%)			
Total	53 (11.9)	64 (14.2)	117 (13.0)
Primary reason			
Adverse event(s)	30 (6.7)	40 (8.8)	70 (7.8)
Lost to follow-up	15 (3.4)	12 (2.7)	27 (3.0)
Subject withdrew consent	6 (1.3)	11 (2.4)	17 (1.9)
Death	2 (0.4)	1 (0.2)	3 (0.3)

[a]A dose that was not vomited, or a dose that was vomited and replaced and the replacement was not vomited, was considered a full dose.
[b]A patient was considered to have completed treatment if he/she was not withdrawn from study prior to having taken the final dose of study medication.
Note: Percentages are based on the number of randomized patients.

Baseline characteristics and variants

Table 7-4 Baseline demographic summary (Safety population)

Variable	Dispersible tablet (N=447)	Crushed tablet (N=452)	Total (N=899)
Age (yrs)			
N	447	452	899
Mean ± SD	3.6 ± 2.69	3.7 ± 2.84	3.7 ± 2.77
Median	3.0	3.0	3.0
Range	0.0 - 12.0	0.0 - 12.0	0.0 - 12.0
Age categories - n (%)			
<3 months	1 (0.2)	1 (0.2)	2 (0.2)
3-<6 months	6 (1.3)	7 (1.5)	13 (1.4)
6-<12 months	23 (5.1)	28 (6.2)	51 (5.7)
12-<24 months	81 (18.1)	73 (16.2)	154 (17.1)
2-<4 yrs	145 (32.4)	149 (33.0)	294 (32.7)
4-<6 yrs	92 (20.6)	89 (19.7)	181 (20.1)
6-12 yrs	99 (22.1)	105 (23.2)	204 (22.7)
Sex - n (%)			
Male	232 (51.9)	247 (54.6)	479 (53.3)
Female	215 (48.1)	205 (45.4)	420 (46.7)
Race - n (%)			
Black	447 (100.0)	452 (100.0)	899 (100.0)
Body weight (kg)			
N	447	452	899
Mean ± SD	14.4 ± 5.51	14.5 ± 5.53	14.4 ± 5.52
Median	13.0	13.1	13.0
Range	5.0 - 34.0	6.0 - 34.0	5.0 - 34.0
Body weight categories - n (%)			
5-<15 kg	274 (61.3)	273 (60.4)	547 (60.8)
15-<25 kg	144 (32.2)	145 (32.1)	289 (32.1)
25-<35 kg	29 (6.5)	34 (7.5)	63 (7.0)

Table 7-5 Baseline disease characteristics (Safety population)			
Variable	Dispersible tablet N=447	Crushed tablet N=452	Total N=899
Parasitological diagnosis, n (%)			
P. falciparum asexual forms	445 (99.6)	452 (100.0)	897 (99.8)
P. falciparum gametocytes	21 (4.7)	21 (4.6)	42 (4.7)
Other species			
P. vivax	0 (0.0)	0 (0.0)	0 (0.0)
P. ovale	1 (0.2)	2 (0.4)	3 (0.3)
P. malaria	2 (0.4)	0 (0.0)	2 (0.2)
Other	0 (0.0)	1 (0.2)	1 (0.1)
Parasite density asexual forms (/µL)			
Median	26364	32288	29241
Range	0 - 196840	1581 - 628571	0 - 628571
n (%)			
<2000 /µL	3 (0.7)	1 (0.2)	4 (0.4)
2000-<5000	53 (11.9)	58 (12.8)	111 (12.3)
5000-<15,000	80 (17.9)	93 (20.6)	173 (19.2)
15,000-<50,000	177 (39.6)	139 (30.8)	316 (35.2)
50,000-<100,000	76 (17.0)	89 (19.7)	165 (18.4)
100,000-<200,000	56 (12.5)	70 (15.5)	126 (14.0)
≥200,000	0 (0.0)	2 (0.4)	2 (0.2)
None	1 (0.2)	0 (0.0)	1 (0.1)
Missing	1 (0.2)	0 (0.0)	1 (0.1)
Body temperature (°C)			
Mean ± SD	38.0 ± 1.12	38.0 ± 1.07	38.0 ± 1.09
Median	37.9	37.9	37.9
Range	36.0 - 41.5	35.6 - 41.1	35.6 - 41.5
n (%)			
<37.5°C	133 (29.8)	127 (28.1)	260 (28.9)
37.5-<39.0°C	220 (49.2)	227 (50.2)	447 (49.7)
≥39.0°C	92 (20.6)	97 (21.5)	189 (21.0)
Missing	2 (0.4)	1 (0.2)	3 (0.3)
Anti-malarial taken in past 2 months, n (%)	49 (11.0)	49 (10.8)	98 (10.9)

Primary efficacy analysis

PCR-corrected 28-day cure rates were comparable between the treatment groups for the primary analysis (PA) population. The non-inferiority of treatment with the dispersible tablet compared to the crushed tablet is statistically proven, since the lower limit of the one-sided 97.5% CI for the PA population is greater than the lower limit of -5% (for dispersible tablet minus crushed tablet) that was specified as the non-inferiority margin in the protocol.

Treatment with the dispersible tablet was also comparable to the crushed tablet for the per-protocol (PP) and intent-to treat (ITT) populations for the PCR-corrected 28-day cure rates.

Table 9-1 PCR-corrected 28-day cure rate, by treatment (PA, PP and ITT population)

Population	Statistic	Dispersible tablet	Crushed tablet
PA (primary)	N	403	409
	n (%) cured	394 (97.8)	403 (98.5)
	Asymptotic 95% CI	(96.3 - 99.2)	(97.4 - 99.7)
	Treatment group difference, (%)[a]	-0.8	
	One-sided asymptotic 97.5% CI[b] *	(-2.7 - 100)	
	p-value[c] *	<0.0001	
PP	N	398	406
	n (%) cured	391 (98.2)	400 (98.5)
	Asymptotic 95% CI	(96.9 - 99.5)	(97.3 - 99.7)
	Treatment group difference, (%)[a]	-0.3	
	One-sided asymptotic 97.5% CI[b] *	(-2.2 - 100)	
	p-value[c] *	<0.0001	
ITT	N	418	423
	n (%) cured #	397 (95.0)	407 (96.2)
	Asymptotic 95% CI	(92.9 - 97.1)	(94.4 - 98.0)
	Treatment group difference, (%)[a]	-1.2	
	One-sided asymptotic 97.5% CI[b]	(-4.0 - 100)	
	p-value[c]	0.0039	

[a]Dispersible minus crushed tablet group.
[b]Reference CI for non-inferiority is -5% to 100%.
[c]For testing the null hypothesis of inferiority of proportions versus the alternative hypothesis of non-inferiority of proportions.
#Patients with unclear or missing PCR results were considered not cured.
*Hauck-Anderson correction.

Table 9-2 PCR-corrected 28-day cure rate, by treatment and body weight group (PA population)

Body weight group	Statistic	Dispersible tablet	Crushed tablet
5-<15 kg	N	236	241
	n (%) cured	230 (97.5)	239 (99.2)
	Asymptotic 95% CI	(95.4-99.5)	(98.0-100.0)
15-<25 kg	N	139	138
	n (%) cured	137 (98.6)	134 (97.1)
	Asymptotic 95% CI	(96.6-100.0)	(94.3-99.9)
25-<35 kg	N	28	30
	n (%) cured	27 (96.4)	30 (100.0)
	Asymptotic 95% CI	(89.6-100.0)	(100.0-100.0)

Secondary efficacy analyses

Cure rates

PCR-corrected 14-day cure rates were high and comparable between the treatment groups for the ITT, PA and PP populations. For the PA population, cure rates at 14 days were comparable between the body weight groups in each treatment group and between treatment groups

The dispersible tablet was comparable to the crushed tablet for the uncorrected 7-day cure rate in the ITT, PA and PP population.

Population	Time point	Statistic	Dispersible tablet	Crushed tablet
ITT	14-days #	N	429	433
		N (%) cured	417 (97.2)	424 (97.9)
		Asymptotic 95% CI	(95.6 - 98.8)	(96.6 - 99.3)
PA	14-days	N	403	409
		N (%) cured	401 (99.5)	408 (99.8)
		Asymptotic 95% CI	(98.8 - 100.0)	(99.3 - 100.0)

Patients with unclear or missing PCR results were considered not cured.

The uncorrected 7-day cure rate for the ITT population was 97.2% for the dispersible tablet group and 98.4% for the crushed tablet group. The uncorrected 7-day cure rates were 99.5% in the dispersible tablet group and 100% in the crushed tablet group for the PA population and 100% for both groups in the PP population.

Treatment with the dispersible tablet was comparable to the crushed tablet for uncorrected 14- and 28-day cure rates for the ITT population. The uncorrected 28-day cure rate was 87.6% in the dispersible tablet group and 87.0% in the crushed tablet group for the ITT population. The uncorrected 28-day cure rates were 92.1% in the dispersible tablet group and 90.5% in the crushed tablet group in the PA population and 92.5% in the dispersible tablet group and 90.4% in the crushed tablet group in the PP population.

Time to parasite clearance and time to fever clearance

Table 9-4 Time to parasite clearance and time to fever clearance in hours (ITT population)

Statistic	Dispersible tablet	Crushed tablet
Time to parasite clearance		
N	442	444
Median (95% CI)	34.3 (24.6 - 35.5)	34.9 (25.2 - 35.6)
25% percentile (95% CI)	23.9 (23.8 - 23.9)	23.9 (23.8 - 23.9)
75% percentile (95% CI)	36.1 (35.9 - 36.3)	36.0 (36.0 - 36.2)
Time to fever clearance[a]		
N	441	443
Median (95% CI)	7.9 (7.8 - 8.0)	7.8 (7.8 - 7.9)
25% percentile (95% CI)	7.6 (7.5 - 7.6)	7.5 (7.4 - 7.6)
75% percentile (95% CI)	23.8 (23.2 - 24.4)	23.5 (20.5 - 23.9)

[a] Patients who had no fever at baseline were considered censored at the time point 0 hours.

Table 9-5 Number (%) of patients with patients with parasite clearance by hours (ITT population)

PCT in hours	Dispersible tablet (N=442) n (%)	Crushed tablet (N=444) n (%)
>0 - 24 hours	170 (38.5)	166 (37.4)
>24 - 48 hours	221 (50.0)	231 (52.0)
>48-72 hours	33 (7.5)	33 (7.4)
>72 hours	3 (0.7)	3 (0.7)
Parasite clearance not achieved	15 (3.4)	11 (2.5)

Table 9-6 Number (%) of patients with gametocytes by time in the trial (ITT population)		
Time window[a]	Dispersible tablet (N=442) n/ M (%)	Crushed tablet (N=444) n/ M (%)
Baseline	20/441 (4.5)	21/444 (4.7)
>0-72 hours	43/442 (9.7)	47/444 (10.6)
>72 hours to Day 8 (7 days after start of treatment)	6/424 (1.4)	5/424 (1.2)
After Day 8	2/424 (0.5)	5/428 (1.2)

[a] Number (%) of patients with at least one positive slide within the corresponding time interval is presented. M is the number of patients with at least one slide within the corresponding time interval.

The PCR-corrected 42-day cure rates for the ITT population were 91.0% in the dispersible tablet group and 93.3% in the crushed tablet group.

Efficacy conclusions

- The 6-dose Coartem® dispersible tablet was comparable to the 6-dose Coartem® crushed tablet in the treatment of acute uncomplicated *Plasmodium falciparum* in infants and children ≤12 years of age and ≥5kg and <35 kg. No notable differences were observed in the response to treatment between the body weight groups.
- The 6-dose Coartem® dispersible tablet was statistically non-inferior to the 6-dose Coartem® crushed tablet for the PCR-corrected 28-day cure rate.
- The 6-dose Coartem® dispersible tablet was comparable to the 6-dose Coartem® crushed tablet for the 7-day (uncorrected) cure rate and the 14-day PCR-corrected cure rate.
- Time to parasite clearance and time to fever clearance was rapid and comparable between treatment with the Coartem® dispersible tablet and the Coartem® crushed tablet.
- The majority of patients achieved rapid gametocyte clearance and this was comparable between the Coartem® dispersible tablet and the Coartem® crushed tablet groups.
- Exposure to lumefantrine as well as artemether and DHA was similar after treatment with the dispersible tablet and the crushed tablet, and was consistent with previous findings, including those in adult patients. It would thus appear that drug exposure is comparable in paediatric and adult patients treated with the 6-dose regimen of Coartem®.

Assessors overall conclusions on clinical efficacy

The applicant has conducted a randomised, parallel-group study to compare the efficacy, safety, and tolerability of artemether-lumefantrine dispersible tablet compared with artemether-lumefantrine crushed tablets. Overall, the design and conduct of the study are acceptable. The non-inferiority margin chosen and the rationale given for this margin are considered acceptable as this is in line with current WHO recommendations.

The efficacy endpoint points chosen are acceptable. The results demonstrate a high PCR-corrected 28-day cure rate in both treatment groups and the dispersible tablet was found to be non-inferior to the crushed tablets in the treatment of uncomplicated malaria in the ITT, PA and PP population. Cure rates were similar and comparable between the different body groups and between the two treatment groups. In terms of the secondary end-points and the exploratory end-points, the results were comparable in both treatment groups.

As mentioned previously in the pharmacokinetic (PK) section, the PK characteristics of artemether-lumefantrine tablets demonstrate a high inter-subject variability and the PK results obtained in study B2303 are different from the values obtained in the bioequivalence studies.

In conclusion, artemether-lumefantrine (Coartem/Riamet) dispersible tablets have been demonstrated to be non-inferior to the crushed tablets when used for the treatment of uncomplicated malaria.

CLINICAL SAFETY

INTRODUCTION

Evaluation of safety and tolerability for the dispersible tablet in the paediatric population is mainly provided by study B2303, which is a direct comparison of the safety of the dispersible tablet and the tablet (administered crushed) in children with acute uncomplicated falciparum malaria, and on post marketing data.

Specific studies have also been performed in patients or healthy volunteers to evaluate specific aspects of safety: auditory function; QTc prolongation (Study A2101 submitted in support of this application); and pregnancy. It should be noted that in these studies the tablet was used, rather than the dispersible tablet, and the study populations were mainly or exclusively adults and adolescents. The results of these studies may however be considered supportive of the safety data for the dispersible tablet in the paediatric population.

Two pooled safety populations were used to provide a larger sample size (totals of 1798 paediatric patients and 1959 adult and adolescent patients) to assess rates of specific adverse events of interest using MedDRA (Version 13.0) Standardised MedDRA Query (SMQs), and to identify potential cases of hepatotoxicity using Hy's law criteria.

The pooled populations provide a large sample size that facilitates an overview of the adverse event profile of artemether-lumefantrine as a whole (irrespective of formulation or dose regimen) and detection of less frequent adverse events. However, comparisons between the dispersible tablet and the tablet (administered crushed or intact) in the paediatric pooled population should be interpreted with caution and regarded as purely descriptive (no such comparison is possible in the adult and adolescent pooled population, as this population does not include patients treated with the dispersible tablet).

Patient Exposure

Patient exposure in study B2303

Table 5-1 Overall study drug exposure (Safety population, Study B2303)

	Dispersible tablet (N=447) n (%)	Tablet (administered crushed) (N=452) n (%)
Patients who took		
1 dose	5 (1.1)	8 (1.8)
2 doses	6 (1.3)	5 (1.1)
3 doses	3 (0.7)	2 (0.4)
4 doses	1 (0.2)	1 (0.2)
5 doses	1 (0.2)	1 (0.2)
6 doses	431 (96.4)	435 (96.2)
Patients who vomited		
No dose	404 (90.4)	394 (87.2)
One dose	33 (7.4)	47 (10.4)
Two doses	9 (2.0)	11 (2.4)
>Two doses	1 (0.2)	0 (-)
Patients who received dose replacement for		
No dose	404 (90.4)	394 (87.2)
One dose	34 (7.6)	47 (10.4)
Two doses	9 (2.0)	11 (2.4)
Patients who vomited replacement doses		
Any	4 (0.9)	11 (2.4)
First dose	3 (0.7)	6 (1.3)
Second dose	0 (-)	0 (-)
Any other dose	1 (0.2)	5 (1.1)
Patients for whom rescue treatment initiated		
No	441 (98.7)	441 (97.6)
Yes	6 (1.3)	11 (2.4)

The majority of patients received the full course of treatment in study B2303. Most patients who vomited a dose only vomited one dose. The majority of vomited doses were replaced; vomiting of replacement doses was very uncommon. The proportion of patients who switched to rescue medication due to vomiting of study medication (as mandated by the protocol if more than two doses of study drug were vomited within 1 hour of administration, or vomiting of a replacement dose occurred within 2 hours) was very low (<2.5%).

Deaths

Three patients died during study B2303. None of the deaths were suspected to be related to the study drug.

Serious Adverse Events (SAE).

Fewer than 2% of patients experienced serious adverse events. Majority of SAEs reported were infections. *P. falciparum* infection was the most commonly reported SAE. Other SAEs occurred in 0.2% of patients (i.e. single patients) in either treatment group. One patient (0.2%) in each treatment group had convulsions reported as an SAE. The patient in the dispersible tablet group developed convulsions (also fever reported) on Day 29. The patient in the tablet (crushed for administration) group reported convulsions and severe malaria on Day 42. None of these SAEs were suspected to be related to study drug.

Table 5-19 **Serious adverse events by system organ class and preferred term regardless of relationship to treatment (Safety population)**

System organ class / Preferred term	n (%) patients: Dispersible tablet (N = 447)	n (%) patients: Tablet (crushed for administration) (N = 452)
Patients with ≥ 1 SAE	7 (1.6)	6 (1.3)
Blood and lymphatic system disorders		
Anaemia	1 (0.2)	1 (0.2)
Iron deficiency anaemia	1 (0.2)	0 (-)
Gastrointestinal disorders		
Diarrhoea	1 (0.2)	0 (-)
Vomiting	1 (0.2)	0 (-)
General disorders and administration site conditions		
Pyrexia	1 (0.2)	1 (0.2)
Face oedema	0 (-)	1 (0.2)
Infections and infestations		
Plasmodium falciparum infection	2 (0.4)	4 (0.9)
Infection	1 (0.2)	0 (-)
Laryngotracheobronchitis	0 (-)	1 (0.2)
Lower respiratory tract infection	1 (0.2)	0 (-)
Pneumonia	0 (-)	1 (0.2)
Investigations		
Haemoglobin decreased	1 (0.2)	0 (-)
Metabolism and nutrition disorders		
Dehydration	1 (0.2)	0 (-)
Oral intake reduced	1 (0.2)	0 (-)
Nervous system disorders		
Convulsion	1 (0.2)	1 (0.2)
Vascular disorders		
Haemorrhage	1 (0.2)	0 (-)

A patient with multiple occurrences of an AE is counted only once in the corresponding AE category
Fatal and non-fatal SAEs are included

Common Adverse Events

Adverse events reported in Study B2303 are presented by primary system organ class (SOC) and preferred term in the table below. Overall, AE rates were comparable between treatment groups. The most frequently affected SOCs were general disorders and administration site conditions, infections and infestations, and gastrointestinal disorders. The most frequent preferred terms were pyrexia, cough, *P. falciparum* infection and vomiting. Diarrhoea was slightly more common in the dispersible tablet group compared to the tablet (administered crushed) group. Other frequent AEs were abdominal pain, headache, and anorexia all of which were comparable between the two treatment groups. Splenomegaly was reported in 6.7% of patients. This AE is not unexpected in children suffering from acute uncomplicated malaria and was pre-existing in 21% of patients at baseline. The majority of AEs were either mild or moderate in severity. Severe AEs were reported by 8.3% of patients in the dispersible tablet group and 7.3% of patients in the tablet (administered crushed) group; there were no major between-group differences in the profile of AE severity.

Table 5-2 **Number (%) of patients with most frequent AEs (>5% in any treatment group) by primary system organ class and preferred term (Safety population)**

	Dispersible tablet n (%)	Tablet (administered crushed) n (%)
Patients studied		
Total no. of patients	447	452
Total no. of patients with AEs	307 (68.7)	318 (70.4)
System organ class/AE[a]		
Blood and lymphatic system disorders	44 (9.8)	46 (10.2)
Splenomegaly	30 (6.7)	30 (6.6)
Gastrointestinal disorders	125 (28.0)	119 (26.3)
Vomiting	75 (16.8)	76 (16.8)
Abdominal pain	37 (8.3)	31 (6.9)
Diarrhea	36 (8.1)	26 (5.8)
General disorders and administration site conditions	169 (37.8)	169 (37.4)
Pyrexia	167 (37.4)	165 (36.5)
Infections and infestations	164 (36.7)	158 (35.0)
Plasmodium falciparum infection	86 (19.2)	101 (22.3)
Investigations	55 (12.3)	50 (11.1)
Aspartate aminotransferase increased	27 (6.0)	20 (4.4)
Metabolism and nutrition disorders	31 (6.9)	31 (6.9)
Anorexia	28 (6.3)	30 (6.6)
Nervous system disorders	36 (8.1)	38 (8.4)
Headache	33 (7.4)	33 (7.3)
Respiratory, thoracic and mediastinal disorders	107 (23.9)	117 (25.9)
Cough	105 (23.5)	113 (25.0)

[a] MedDRA primary system organ class/preferred term.
All adverse events that occurred on the date of first study drug administration (Day 1) until Day 43 inclusive were included.
A patient with multiple occurrences of an AE is counted only once in the corresponding AE category. Patients are only counted once in each system organ class regardless of the number of AEs experienced in that system organ class.

Discontinuation due to adverse events.
The proportion of patients who discontinued from the study due to AEs was low and comparable between the two treatment groups. The most frequent AE resulting in discontinuation was vomiting [1.3% of dispersible tablet patients vs. 2.4% of tablet (crushed for administration) patients]; discontinuation was mandated by the protocol for patients who vomited more than two doses of study drug within 1 hour of administration, or who vomited a replacement dose (for a previously vomited dose) within 2 hours. Other AEs resulting in patient discontinuation were anaemia, iron deficiency anaemia, *P. falciparum* infection, and lower respiratory tract infection.

Laboratory findings
Biochemistry and haematology
The range of laboratory parameters evaluated was relatively limited, as no serum electrolyte levels were evaluated and no urinalysis was undertaken.

Laboratory data were summarised by calculating standard summary statistics of raw data and changes from baseline over time. In general, laboratory parameters showed values and changes from baseline that were very similar with the dispersible tablet and tablet (administered crushed), and that were consistent with acute uncomplicated falciparum malaria and its resolution following successful treatment. For example, summary statistics showed that haemoglobin, hematocrit and erythrocyte counts all decreased slightly from baseline before recovering to levels higher than those at baseline.

Biochemistry assessments showed no major changes in serum creatinine, with no newly occurring or worsening notable abnormalities. Little change was observed in blood glucose. Liver function

tests (Aspartate aminotransferase [AST], alanine aminotransferase [ALT], and gamma glutamyl transferase) also showed improvements from baseline.

ECG and QTc

Malaria itself and its associated stress and anaemia, and recovery from malaria have some effects on cardiac electrophysiology and in particular on lengthening of the QT interval. This makes it difficult to assess the effects of antimalarials treatment on cardiac conduction. This is compounded by the fact that QT correction formulae are based on a normal heart rate of 60 beats/minute and patients with malaria tend to have elevated heart rates that decrease with successful treatment and defervescence. This leads to a trend to overcorrect QT. As even healthy small children typically have heart rates greater than 60 beats/minute, assessing the situation in paediatric malaria patients is even more difficult.

To evaluate the effects of artemether-lumefantrine on QTc interval, study A2101 was performed in healthy adult volunteers, using artemether-lumefantrine tablet and extensive ECG evaluations were undertaken in study B2303.

Study A2101 showed that artemether-lumefantrine slightly increased the QTcF interval compared to placebo, but to an extent which is not considered a risk to patients. Artemether-lumefantrine was associated with a mean maximum increase in QTcF relative to placebo 7.45 msec, with the lower 90% confidence interval greater than zero. A post hoc analysis which looked at the PK/PD correlation analysis showed an association between maximum observed values of QTcF changes adjusted from placebo and baseline and the concentrations of lumefantrine.

Study B2303

A summary of QTc signal values based on Bazett's and Fridericia's formulae is presented in the table below. Most patients in each treatment group had changes from baseline in QTc interval of <30 msec. The proportion of patients with a QTc increase of 30-60 msec (using either formula) was somewhat higher in the dispersible tablet group compared to the tablet (administered crushed) group. A low rate of QTc interval increases of >60 msec were observed in both treatment groups, with a slight higher incidence in the crushed tablet group. There were no patients with QTc intervals >500 msec (calculated using either formula).

Table: Number (%) of patients with QTc signal values (Safety population):

	Dispersible tablet (N=447)	Tablet (administered crushed) (N=452)
Parameter	**n/M (%)**	**n/M (%)**
Bazett's formula		
QTc increase from baseline to highest post-baseline value		
≤0 msec	161/429 (37.5)	168/436 (38.5)
>0 - <30 msec	183/429 (42.7)	196/436 (45.0)
30 - 60 msec	80/429 (18.6)	60/436 (13.8)
>60 msec	3/429 (0.7)	10/436 (2.3)
Baseline ECG not done	2/429 (0.5)	2/436 (0.5)
QTc >500 msec	0/429 (-)	0/436 (-)
Fridericia's formula		
QTc increase from baseline to highest post-baseline value		
≤0 msec	101/429 (23.5)	101/436 (23.2)
>0 - <30 msec	190/429 (44.3)	206/436 (47.2)
30 - 60 msec	121/429 (28.2)	101/436 (23.2)
>60 msec	15/429 (3.5)	26/436 (6.0)
Baseline ECG not done	2/429 (0.5)	2/436 (0.5)
QTc >500 msec	0/429 (-)	0/436 (-)

Percentages are calculated using the total number of patients with a post-baseline ECG (=M) as denominator.
Bazett's formula: QTc = QT/(RR**0.5)
Fridericia's formula: QTc = QT/(RR**1/3)

Drug-specific safety considerations

Neurological

In animal models, artemisinin derivatives, such as artemether, have been associated with neurotoxicity, focused on pathways involved in hearing and balance. Such effects appear to occur with high doses of liposoluble compounds administered parenterally; oral administration and water-soluble compounds appear to be far less toxic. Neurotoxicity of this type has not been seen in humans even following repeated exposure to artemisinin derivatives and no evidence of such neuropathology was observed in a series of autopsies carried out on patients who died due to severe malaria despite treatment with high-dose intramuscular artemether. There have been case reports of neurological problems (including ataxia, nystagmus, tremor and slurred speech), occurring after administration of herbal artemisinin or artesunate monotherapy.

Few patients in Study B2303 had AEs affecting the nervous system other than headache, which occurred in 7.4% of patients in the dispersible tablet group and 7.3% of patients in the tablet (crushed for administration) group. Other nervous system AEs reported included somnolence, convulsions, dyskinesia, epilepsy, dizziness and tremor. None of these AEs were suspected to be related to study drug.

Three patients had convulsions: one severe case in the dispersible tablet group (also reported as an SAE, reported on Day 29 and with concomitant fever); one moderate case at Day 2 in the tablet (crushed for administration) group, in a patient with a concomitant diagnosis of anaemia and pneumonia; and one mild case (reported on Day 42, with a concomitant diagnosis of severe malaria, also in the tablet (crushed for administration) group. The latter case was also reported as an SAE. The convulsion SAEs occurred in patients with concomitant malaria or other infections, and it is likely that they represent febrile convulsions.

One patient receiving the dispersible tablet experienced mild dyskinesia on Day 2, which resolved without treatment, and was not suspected to be related to study medication. The patient experienced no other nervous system AEs. Another patient, also in the dispersible tablet group in study B2303 was diagnosed with mild epilepsy, not suspected to be related to study drug, on Day 41. This patient's only other AE was pneumonia, reported on the same day. Both conditions were ongoing at the end of the study.

Results of systematic neurological clinical examinations performed in study B2303 at each visit including baseline reported the following: seven of the 899 patients (0.8%) had abnormalities, most commonly tandem walk and gait abnormal, at baseline; only one patient had any post-baseline abnormalities and this was a patient treated with the dispersible tablet who had gait abnormal and tandem walk at 8 and 24 hours. Both abnormalities were already present at baseline. All reported abnormalities were mild.

Table 5-6 **Nervous system adverse events by system organ class and preferred term (Safety population, B2303)**

	n (%) patients	
System organ class Preferred term	Dispersible tablet (N = 447)	Tablet (administered crushed) (N = 452)
Nervous system disorders		
Headache	33 (7.4)	33 (7.3)
Somnolence	2 (0.4)	1 (0.2)
Convulsion	1 (0.2)	2 (0.4)
Dyskinesia	1 (0.2)	0 (-)
Epilepsy	1 (0.2)	0 (-)
Dizziness	0 (-)	1 (0.2)
Tremor	0 (-)	1 (0.2)

In the pooled paediatric safety population, nervous system disorders were reported in 11.7% of patients who received the current regimen. It should be noted that in several earlier studies (particularly those performed with the 4-dose regimen), the Case Report Forms were pre-printed with check boxes for certain AEs, including some neurological AEs, and this may have contributed to apparent differences in AE rates between dose regimens.

The most common AE was headache (9.5%), followed by dizziness (1.6%). No other nervous system disorders were reported in more than 1% of patients.

Other reported nervous system AEs related to involuntary muscle contractions. To assess the frequency and potential relationship to drug of these AEs, the following preferred terms were considered relevant, as they all relate to involuntary muscle contractions: clonus; myoclonus; muscle spasms; and muscle twitching (the latter two preferred terms are included in the MedDRA SOC 'Musculoskeletal and connective tissue disorders').

Clonus was reported in 1.3% of patients for the 4 dose regimen and 0.8% for the current dose regimen) and myoclonus in 0.2% of patients for the current regimen (no cases for the 4-dose regimen). Muscle twitching was reported in 0.8 % of patients for the 4 dose regimen, with no cases for the current regimen. No cases of muscle spasm were reported. All cases were mild except one case of myoclonus assessed as moderate. None of the cases were serious. All cases were reported in only 3 of the 11 studies contributing to the paediatric pooled safety population. In each study, cases were reported in one single center. Moreover, there may be an effect of the center on the choice of reported term to describe the symptoms. While clonus was reported in all three studies, all cases of muscle twitching were reported in the same single study.

In the pooled adult and adolescent safety population nervous system disorders were reported in 51.8% of patients treated with the current regimen. Headache (47.9%) and dizziness (34.6%) were the most common AEs, and the only other nervous system AEs to occur in more than 1% of patients were clonus and tremor (each in 2.0% of patients). As in the paediatric safety population, AEs related to involuntary muscle contractions, namely clonus, myoclonus, muscle spasms, and muscle twitching were assessed. No cases of myoclonus or muscle twitching were reported. Clonus was reported in 0.5% of the patients for the 4 dose regimen and 2.0% of patients for the current regimen, and muscle spasms in 0.1% of patients for each regimen. Most cases were mild in severity, except one case of muscle spasm and one case of clonus, both assessed as moderate. None of the cases was serious. All cases were reported in only 3 of the 15 studies contributing to the adults and adolescents pooled safety population.

Adverse events affecting the ear and hearing

In study B2303, one case of ear pain was reported in a patient in the tablet (crushed for administration) group. Ear infections were reported in 2.0% of patients in the dispersible tablet group and in 1.5% of patients in the tablet (crushed for administration) group. There were no other AEs related to the auditory system.

In the pooled paediatric safety population, AEs in the MedDRA primary SOC 'ear and labyrinth disorders' were reported in 0.5% of patients who received the current regimen.

The most frequent AE affecting the ear was ear pain, reported in 0.2% of patients who received the current regimen. There were no reports of AEs related to hearing loss in patients who received the current regimen. Hypoacusis was reported in 0.8% of patients who were treated with the 4-dose

regimen (all were patients in the same study). In this population, ear infections were reported in 1.3%, otitis media in 0.8% and otitis externa in 0.2% of the total current regimen group.

In the adult and adolescent pooled safety population, AEs affecting the primary SOC 'ear and labyrinth disorders' were reported in 3.4% of patients treated with the current regimen, the most common AE being vertigo (2.4%), followed by tinnitus (0.5%). Deafness was reported in 1 patient (0.1%) who received the current regimen in the adult and adolescent population (this was mild worsening of hearing loss that was present at baseline, and was reported to have resolved by Day 4), and 1.1% of patients treated with the 4-dose regimen reported hypoacusis, which was ongoing at study end in 3 of 12 cases. Otitis media was reported in 0.2% of patients treated with the current regimen.

Table 5-9 Adverse events affecting the ear and hearing by system organ class and preferred term (Pooled pediatric safety population)

	n (%) patients				
Primary system organ class Preferred term	4-dose tablet N=521	Current regimen tablet N=830	Current regimen dispersible N=447	Total current regimen N=1277	Total N=1798
Ear and labyrinth disorders					
Ear pain	0 (-)	3 (0.4)	0 (-)	3 (0.2)	3 (0.2)
Cerumen impaction	0 (-)	1 (0.1)	0 (-)	1 (0.1)	1 (0.1)
Ear pruritus	0 (-)	1 (0.1)	0 (-)	1 (0.1)	1 (0.1)
Otorrhoea	0 (-)	1 (0.1)	0 (-)	1 (0.1)	1 (0.1)
Hypoacusis	4 (0.8)	0 (-)	0 (-)	0 (-)	4 (0.2)
Infections and infestations					
Ear infection	0 (-)	8 (1.0)	9 (2.0)	17 (1.3)	17 (0.9)
Otitis media	5 (1.0)	7 (0.8)	3 (0.7)	10 (0.8)	15 (0.8)
Otitis externa	6 (1.2)	3 (0.4)	0 (-)	3 (0.2)	9 (0.5)

Haematology and haemolysis-related adverse events

Study B2303

In Study B2303, there were no major differences between treatment groups; the most common AEs were splenomegaly and anaemia: these were the only AEs in the 'Blood and lymphatic system disorders' SOC that occurred in more than 0.5% of patients. There were four SAEs related to haematology: two cases of anaemia, one case of iron deficiency anaemia and one case of haemoglobin decreased. These events are discussed further below, with other serious adverse events. Other haematology-related AEs were in the 'Investigations' SOC and related to laboratory abnormalities in blood cell counts, most commonly decreased leucocyte counts or platelet counts.

Data obtained from study B2303 are consistent with malaria and its resolution after treatment, in general showing a high rate of low haemoglobin levels at baseline, with a subsequent further decrease (reflected in anaemia as an AE) followed by an increase to levels higher than those at baseline.

Table 5-12 Hematology-related adverse events by system organ class and preferred term (Safety population, B2303)

System organ class Preferred term	n (%) patients Dispersible tablet (N = 447)	 Tablet (administered crushed) (N = 452)
Blood and lymphatic system disorders		
Splenomegaly	30 (6.7)	30 (6.6)
Anaemia	11 (2.5)	17 (3.8)
Leukocytosis	2 (0.4)	1 (0.2)
Thrombocytopenia	2 (0.4)	1 (0.2)
Iron deficiency anaemia	1 (0.2)	0 (-)
Lymphadenitis	0 (-)	1 (0.2)
Neutropenia	0 (-)	1 (0.2)
Investigations		
White blood cell count decreased	11 (2.5)	2 (0.4)
Platelet count decreased	10 (2.2)	9 (2.0)
Haematocrit decreased	6 (1.3)	6 (1.3)
Lymphocyte morphology abnormal	5 (1.1)	4 (0.9)
Platelet count increased	4 (0.9)	0 (-)
Haemoglobin decreased	3 (0.7)	4 (0.9)
White blood cell count increased	2 (0.4)	5 (1.1)
Eosinophil count increased	2 (0.4)	2 (0.4)
Neutrophil count decreased	2 (0.4)	1 (0.2)
Reticulocyte count increased	1 (0.2)	3 (0.7)
Reticulocyte count decreased	1 (0.2)	2 (0.4)
Red blood cell count decreased	1 (0.2)	1 (0.2)
Eosinophil count decreased	1 (0.2)	0 (-)
Lymphocyte count decreased	1 (0.2)	0 (-)
Lymphocyte count increased	0 (-)	2 (0.4)
Haemoglobin increased	0 (-)	1 (0.2)
Monocyte morphology abnormal	0 (-)	1 (0.2)

In the pooled paediatric population, the only reported preferred term was reticulocyte count increased, which was reported in 0.3% of all patients receiving the current regimen (dispersible or tablet). This increase in reticulocyte count is consistent with recovery from malaria. No haemolytic disorders were reported in the adult & adolescent population. In summary, artemether-lumefantrine does not appear to be associated with a significant risk of haematology-related adverse events or haemolysis. While anaemia and low haemoglobin were common, the pattern observed was consistent with anaemia due to malaria and successful treatment.

Adverse events affecting the liver

In study B2303, AEs in the SOC 'Hepatobiliary disorders' were reported in 1.1% of patients who received the dispersible tablet and 1.5% of those who received the tablet. In all but one patient the AEs were hepatomegaly. The remaining patient (in the tablet group) had hepatitis which was asymptomatic, mild and reported to have resolved at Day 8.

Table 5-13 Hepatic adverse events by system organ class and preferred term (Safety population, B2303)

System organ class Preferred term	n (%) patients Dispersible tablet (N = 447)	 Tablet (administered crushed) (N = 452)
Hepatobiliary disorders		
Hepatomegaly	5 (1.1)	6 (1.3)
Hepatitis	0 (-)	1 (0.2)
Investigations		
Aspartate aminotransferase increased	27 (6.0)	20 (4.4)
Alanine aminotransferase increased	3 (0.7)	7 (1.5)
Gamma-glutamyltransferase increased	2 (0.4)	6 (1.3)
Hepatic enzyme increased	1 (0.2)	(-)

In the pooled paediatric safety population, hepatobiliary disorders were reported in 5% of all patients who received the current regimen (tablet or dispersible tablet). The most common preferred term was hepatomegaly. Jaundice and hepatosplenomegaly each occurred in 0.1-0.2% of patients who received the current regimen of the tablet. Elevations of serum levels of hepatic enzymes; were also reported as AEs in the SOC 'Investigations', most commonly AST.

In the adult and adolescent pooled population, hepatobiliary AEs were reported in 9.1% of patients who received the current regimen. As in the paediatric population, the most common preferred term was hepatomegaly (8.5% of patients who received the current regimen). Jaundice (0.3%) was the only other AE in this SOC reported in more than 0.1% of patients. Abnormalities of liver function tests, reported as AEs in the SOC 'Investigations' were reported in ≤ 0.3% of patients who received the current regimen.

Post marketing experience
In addition to the safety profile of artemether-lumefantrine being well-characterised in Novartis-sponsored clinical trials, including over 3600 patients, comprising approximately 1800 infants and children between 2 months and ≤12 years of age (447 of them having received the dispersible tablet), there is extensive post-marketing safety data for artemether-lumefantrine.

The cumulative patient exposure since the first launch of the artemether-lumefantrine tablet until 30 Sep 2010 is estimated to be approximately 360 million treatments, including 40 million dispersible tablets. Based on sales data, it is estimated that 77 % is used for the treatment of children (< 35kg body weight), and 23 % is used for the treatment of adults (> 35kg body weight). The great majority of these treatment courses (> 95%) are distributed by diverse international organisations such as WHO and United Nations Children's Fund (UNICEF) without profit.

The safety of artemether-lumefantrine tablet and dispersible tablet has been effectively managed by standard pharmacovigilance activities and data analysed in 13 Periodic Safety Update Reports (PSURs), spanning the time period from launch up to 31 October 2009. When appropriate, changes have been made to the SmPC, e.g. hypersensitivity reactions, as a class effect of artemisinin and its derivatives, have been recently added to Section 4.8 of the SmPC. Findings discussed in the most recent PSUR include: haemolysis, hemoglobinuria, anaemia, cardiac disorders (including QT prolongation), auditory function, severe skin reaction, hepatic disorders, mood swings/disorder, and pregnancy.

Extensive post-marketing experience of artemether-lumefantrine tablet and dispersible tablet (the former for more than 10 years) confirms that the combination has a well-characterised safety profile. The frequency of reported adverse events has remained stable. No areas of concern have been identified in terms of unusual frequencies or seriousness of events or in terms of special patient populations such as the paediatric population or during pregnancy, that need further evaluation beyond routine pharmacovigilance activities. All risks identified in both the clinical trials and the post-marketing setting, including special patient populations such as pregnancy, are adequately addressed in the European Union (EU) SmPC for tablets and the labelling for the dispersible tablets. Post-marketing data do not indicate any new safety findings with the dispersible tablet.

Assessor's overall conclusions on clinical safety
In study B2303, 431 patients received six doses of artemether-lumefantrine dispersible tablets and 435 patients artemether-lumefantrine crushed tablets. A very low incidence of nervous system

adverse events (AE) was observed with no difference between the two treatment groups and none were considered related to Coartem® by the investigator. No hearing losses AEs were reported. A very low incidence of cardiac AEs was observed with no difference between the two treatment groups. No clinical symptoms or AEs attributable to QTc prolongation were observed. Treatment with the 6-dose Coartem® dispersible tablet appeared to be well-tolerated, safe and comparable with the Coartem® 6-dose crushed tablet.

The adverse events were comparable in both the dispersible and crushed tablet group. The most frequent events were pyrexia, vomiting and cough. The frequencies were comparable in both treatment groups.

There were very few serious adverse events (less than 2%) in both treatment groups. Overall, the adverse events profile is similar to what has previously been described for artemether-lumefantrine tablets.

In terms of cardiovascular safety, the results from study B2303 showed no serious cardiovascular events occurred. However, there was evidence of QTc prolongation, which has been previously demonstrated. It is considered that the precautionary wording in the current SmPC for artemether-lumefantrine tablets should be retained and cardiovascular events should continue to be monitored.

Overall, the occurrence of neurological events was comparable in the dispersible and crushed tablet groups and was overall low (7.4%) with one case of convulsion in the dispersible group. However, there were no adverse events related to the auditory system.

Overall, the adverse event profile for the dispersible tablet in the paediatric population is similar to what has previously been reported for artemether-lumefantrine tablets.

No new or unexpected safety issues were raised by the clinical study data.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The SmPC, PIL and labels are acceptable. The PIL is consistent with the SmPC and in-line current guidelines. The labelling is in-line with current guidelines.

Clinical Expert Report
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Paediatric Development Programme
This application relates to a new pharmaceutical form of an authorised medicinal product for use in the paediatric population. It has been considered under Article 16(1) of Regulation (EC) No 1901/2006, Article 20 (deferral request) and Article 13 of said regulation by the European Medicines Agency (EMA). The EMA agreed a paediatric investigation plan (PIP) and to grant a deferral and a waiver for artemether/lumefrantine in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council. The EMA decision (EMEA-000777-PIP01-09) was published on 21 September 2010.

Pharmacovigilance System and Risk Management Plan
The pharmacovigilance system, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for

pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A suitable justification has been provided for not submitting a Risk Management Plan for this product.

Conclusion
There are no objections to the approval of this product from a clinical viewpoint.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Riamet 20 mg/120 mg dispersible tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

NON-CLINICAL

No new non-clinical data were submitted and none are required for an application of this type.

EFFICACY

Bioequivalence has been demonstrated between the applicant's Riamet 20mg/120mg dispersible tablets (batch to be marketed formulation from the new manufacturing site) and its respective reference product (Riamet 20mg/120mg tablets, Novartis Pharmaceuticals UK Ltd).

Non-inferiority of this product in comparison to Riamet 20mg/120mg tablets (Novartis Pharmaceuticals UK Ltd) has been established when used for the treatment of uncomplicated malaria, with no statistically/clinically significant differences observed between products.

SAFETY

No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE

The SmPC, PIL and labelling are satisfactory.

BENEFIT-RISK ASSESSMENT

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Bioequivalence has been demonstrated between the applicant's Riamet 20mg/120mg dispersible tablets and its respective reference product (Riamet 20mg/120mg tablets, Novartis Pharmaceuticals UK Ltd). The pivotal main study (study B2303) supports the claim that the applicant's product is non-inferior to Riamet 20mg/120mg tablets. Extensive clinical experience with artemether and lumefantrine is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.

RIAMET 20 MG/120 MG DISPERSIBLE TABLETS

PL 00101/0957

STEPS TAKEN FOR ASSESMENT

1 The MHRA received the marketing authorisation application on 17 December 2010.

2 Following standard checks and communication with the applicant the MHRA considered the application valid on 01 February 2011.

3 Following assessment of the application the MHRA requested further information relating to the the quality dossier on 11 May 2011, 02 October 2011 and11 January 2012.

4 The applicant responded to the MHRA's requests, providing further information on the quality dossier on 04 August 2011, 08 December 2011, and 26 January 2012.

5 The application was determined on 13 April 2012.

RIAMET 20 MG/120 MG DISPERSIBLE TABLETS

PL 00101/0957

STEPS TAKEN AFTER ASSESSMENT

Date submitted	Application type	Scope	Outcome
13/02/2013	Type 1A variation	To register a new ATC code for artemether-lumefantrine, which was amended by the World Health Organisation from P01BE52 TO P01BF01.	Approved - 05/03/2013
31/01/2014	Type 1A variation	To register the introduction of the summary of Pharmacovigilance System Master File (PSMF). Consequentially, the description of the pharmacovigilance system has been updated.	Approved - 26/02/2014
03/07/2012	Type II variation	To update section 4.6 (Pregnancy and lactation) of the SmPC following final analysis of safety data from the observational pregnancy study.	Approved - 09/09/2014
03/07/2012	Type II variation	To update section 4.5 (Interactions) of the SmPC in line with results of interaction studies. The result of the interaction studies also impact the information in section 4.3 (Contraindications), section 4.4 (Special warnings and precautions for use) and section 4.6 (Pregnancy and lactation). The pharmacokinetics of Riamet were also assessed in patients with hepatic	Approved - 09/09/2014

		impairment during these studies and the results have been used to update section 5.2 (Pharmacokinetic properties). As a consequence, the PIL has been updated.	
03/07/2012	Type II variation	To update sections 4.2 (Posology) and 5.2 (Pharmacokinetic properties) of the SmPC to include new information on renal and hepatic excretion.	Approved - 20/11/2014
03/07/2012	Type II variation	To update section 5.1 (Pharmacodynamic properties) of the SmPC on the basis of relevant clinical studies conducted by Novartis.	Approved - 20/11/2014

SUMMARY OF PRODUCT CHARACTERISTICS

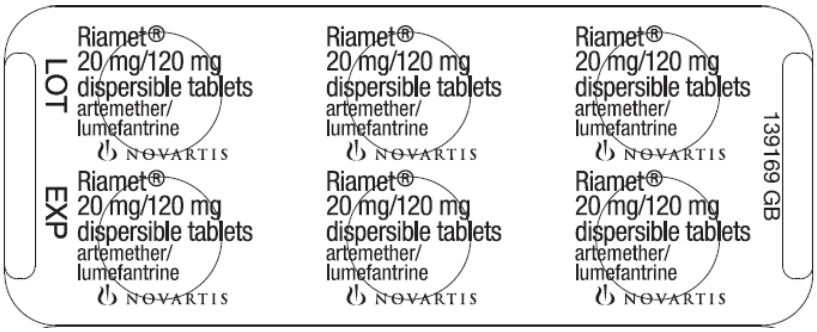
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) for products granted Marketing Authorisations at a national level are available on the MHRA website.

Module 3
PATIENT INFORMATION LEAFLET

In accordance with Directive 2010/84/EU the Patient Information Leaflets for products granted Marketing Authorisations at a national level are available on the MHRA website.

Module 4
LABELLING

Blister:



Carton:


Riamet® 20 mg/120 mg dispersible tablets
18 Tablets
Keep out of reach and sight of children
Do not store above 30°C, store in the original package in order to protect from moisture.
PL 00101/0957
Novartis Pharmaceuticals UK Ltd
Frimley Business Park, Frimley,
Camberley, Surrey, GU16 7SR, England
Riamet® 20 mg/120 mg dispersible tablets
artemether
lumefantrine
NOVARTIS
For oral use
18 Tablets
POM
Riamet® 20 mg/120 mg dispersible tablets
18 Tablets
Other ingredients include microcrystalline cellulose, crospovidone, cherry dry flavour, croscarmellose sodium, saccharin sodium (8 mg / dispersible tablet), magnesium stearate, hypromellose, silica colloidal anhydrous, polysorbate 80.
One dispersible tablet contains 20 mg artemether and 120 mg lumefantrine
Dosage: As directed by a physician.
For oral use
5 010678 918021
139179
GB
Riamet® 20 mg/120 mg dispersible tablets
LOT
MFD
EXP
Riamet® 20 mg/120 mg dispersible tablets
Attach dispensing label here.

ANNEX 1 – VARIATION ASSESSMENT REPORTS

CLINICAL VARIATION ASSESSMENT REPORT I

Reason:
To update sections 4.2 (Posology) and 5.2 (Pharmacokinetic properties) of the SmPC to include new information on renal and hepatic excretion

Proposed change:
The Marketing Authorisation Holder (MAH) has submitted a type II variation to update sections 4.2 "Posology and method of administration" and 5.2 "Pharmacokinetic properties" of the SmPC to include new information on renal excretion based on data from a pharmacokinetic study. The paragraph on elimination previously included in the SmPC reported only urinary data in animals as information was not available in humans.

Evaluation:
As part of a randomised, open-label, single-dose (80 mg artemether/480 mg lumefantrine), three-period, six-sequence crossover study of Coartem®***** in sixty healthy volunteers to evaluate bioequivalence between a new dispersible tablet manufactured in the USA, the dispersible tablet from a scale up batch similar to the batch used in Novartis clinical studies and the commercial tablet crushed for oral suspension.

- To evaluate the safety and tolerability of single doses of Coartem in three different formulations: new dispersible tablet manufactured in the USA, dispersible tablet from a scale-up batch and commercial tablet crushed
- To explore the urinary excretion of artemether, dihydroartemisinin (DHA), lumefantrine and desbutyllumefantrine in a subset of the subjects receiving the crushed commercial tablets. This objective was included in order to gain data on urinary excretion and to increase knowledge of artemether-lumefantrine as this has been lacking so far.

Test product, dose and mode of administration
- Coartem dispersible tablet (USA batch) for oral suspension (each tablet contains 20 mg artemether + 120 mg lumefantrine; four tablets administered at once to give 80 mg artemether + 480 mg lumefantrine)

- Coartem dispersible tablet (scale up batch) for oral suspension (each tablet contains 20 mg artemether + 120 mg lumefantrine; four tablets administered at once to give 80 mg artemether + 480 mg lumefantrine)

Reference therapy, dose and mode of administration
- Coartem commercial tablet crushed for oral suspension (each tablet contains 20 mg artemether + 120mg lumefantrine; four tablets administered at once to give 80 mg artemether + 480 mg lumefantrine)

Methodology
The study had a randomised, open-label, single-dose, six-sequence, three-period, crossover design. Each subject participated in a screening period, a baseline period before each treatment, three treatment periods including a 5-week washout period between each dose, and a study completion evaluation.

Population studied

A total of 58 healthy male and female subjects aged 18 to 50 years were enrolled in this study. Fifty subjects completed all three treatments, 52 completed the commercial crushed tablet arm, 52 the dispersible scale up batch arm, and 55 the USA-manufactured dispersible batch arm.

Pharmacokinetic criteria for evaluation

Blood samples were taken by either direct venipuncture or through an indwelling cannula inserted in a forearm vein at pre-dose and at intervals up to 24 hours post-dose for the analysis of artemether and dihydroartemisinin (DHA). Similarly, blood was withdrawn at pre-dose and at intervals up to 264 hours post-dose for the analysis of lumefantrine in plasma.

Urine collection

Urine was collected for exploratory investigation in a subset of 16 subjects who received the commercial crushed tablet. For analysis of artemether and DHA, aliquots of the completely collected and homogenized fractions (collected pre-dose and at intervals up to 48 hours) were kept.
For analysis of lumefantrine and desbutyl-lumefantrine, aliquots of the completely collected and homogenized fractions (collected pre-dose and at intervals up to 48 hours) were kept.

Analytical methods

Artemether, DHA and lumefantrine were determined in plasma by reversed-phase HPLC with tandem mass spectrometry (MS/MS) detection. The limit of quantification (LLOQ) was 5ng/mL for artemether and DHA, and 50ng/mL for lumefantrine. The same HPLC-MS/MS methods were used to measure artemether, DHA and lumefantrine in urine. LOQ was 5ng/mL for artemether and DHA, and 50ng/mL for lumefantrine. Because no lumefantrine was detected, the decision was made not to measure its metabolite, desbutyl-lumefantrine.

Statistical methods

$AUC_{t\text{-}last}$, AUC_{∞}, and C_{max} for lumefantrine, artemether and DHA were logarithmically transformed (base e) and statistically analysed using a mixed linear model. The model included the overall mean, sequence, period, and treatment as fixed effects, and subject as a random effect. An estimate of the treatment differences together with their 90% confidence intervals was obtained based upon the log-transformed observations for the following comparisons: 1) Coartem dispersible tablet (USA batch) *versus* Coartem dispersible tablet (scale up batch); 2) Coartem dispersible tablet (USA batch) *versus* Coartem commercial tablet crushed; 3) Coartem dispersible tablet (scale up batch) *versus* Coartem commercial tablet crushed. The estimates and confidence intervals were 'back-transformed' to the original scale, giving the ratios of geometric means for the two products being compared together with 90% confidence intervals for the ratios. Bioequivalence was assessed for each assessment individually base

Pharmacokinetic results

Plasma data

Based on the standard bioequivalence criteria (0.80, 1.25), the Coartem dispersible tablet batch produced in the USA was shown to be bioequivalent to the dispersible tablet scale up batch (a batch similar to the one used in clinical trials). Bioequivalence was demonstrated for C_{max}, AUC_{tlast} and AUC_{∞} of artemether, DHA and lumefantrine.

Bioequivalence was also demonstrated for the three analytes (except AUC_{tlast} for artemether for which the upper 90% CI was 1.25496) between the Coartem dispersible tablet and the Coartem commercial crushed tablet.

Bioequivalence of the Coartem dispersible tablet scale up batch and the Coartem commercial crushed tablet was demonstrated for C_{max} of artemether, C_{max} and AUC_{∞} of DHA, and C_{max}, AUC_{tlast} and AUC_{∞} of lumefantrine.

Urinary data

Neither lumefantrine nor artemether were detected in any of the urine samples. Because no lumefantrine was detected, the decision was made not to measure its metabolite desbutyl-lumefantrine (exposure (AUC) to desbutyl-lumefantrine in plasma was previously shown to represent less than 1% of the parent exposure). DHA was quantified in nine subjects. When detected, DHA was measured in the first collection time intervals after co-artemether administration. DHA was present in urine in trace amounts only, not exceeding a total amount per individual of 7.4µg, which represented less than 0.01% of the artemether dose.

Conclusion

Neither lumefantrine nor artemether were present at quantifiable concentrations in any of the urine samples. Trace amounts of DHA (<0.01% of the artemether dose) were found in urine of some subjects.

Recommendation:

The changes to the SmPC made as a result of the study summarised above are acceptable as they are identical to the changes made to the SmPC for Riamet 20mg/120mg tablets (PL 00101/0566). The variation application may be approved.

Date: 21/11/2014

*Coartem® is the trade name of artemether-lumefantrine (Riamet®) in endemic countries, South Africa and the USA.

CLINICAL VARIATION ASSESSMENT REPORT II

Reason:
To update section 5.1 (Pharmacodynamic properties) of the SmPC on the basis of relevant clinical studies conducted by Novartis

Proposed change:
The Marketing Authorisation Holder (MAH) has submitted a type II variation to update section 5.1 "Pharmacokinetic properties" of the SmPC by including information obtained from clinical studies.

Evaluation:
The changes proposed to the SmPC in this variation were not based on new study information. The MAH confirmed that all studies referred to in the updated text have been previously approved through variations for Riamet 20mg/120mg tablets (PL 00101/0566). The addition of relevant clinical study information to section 5.1 is in line with the Notice to Applicants: A guideline on summary of product characteristics September 2009.

The information added to the SmPC is judged to be relevant to the prescriber and includes statistically compelling and clinically relevant results.

Recommendation:
The changes are acceptable as they are in line with the changes made to the SmPC for Riamet 20mg/120mg tablets (PL 00101/0566). The variation application may be approved.

Date: 21/11/2014