SCIENTIFIC DISCUSSION

Name of the Finished Pharmaceutical Product:	ARTECAP [1]
Manufacturer of Prequalified Product:	Strides Pharma Science Limited KRS Gardens Soft Gel Capsules Block 36/7, Suragajakkanahalli Indlavadi cross Anekal Taluk Bangalore – 562 106 India
Active Pharmaceutical Ingredient (API):	Artesunate
Pharmaco-therapeutic group (ATC Code):	Antimalarial: artemisinin derivative, ATC Code P01BE03
Therapeutic indication:	ARTECAP is indicated for pre-referral treatment of suspected or proven severe malaria in patients aged between 2 months and 6 years, who are unable to take oral medication or obtain injectable antimalarial treatment.

1 Introduction

ARTECAP is indicated for pre-referral treatment of suspected or proven severe malaria in patients aged between 2 months and 6 years, who are unable to take oral medication or obtain injectable antimalarial treatment.
The patient should be immediately referred to a facility where accurate diagnosis and complete treatment with effective antimalarials can be instituted.

2 Assessment of Quality

The assessment was done in accordance with the requirements of *WHO's Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part.*

Active pharmaceutical Ingredient (API)

Artesunate used in the manufacture of ARTECAP has been prequalified by WHO according to WHO's Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in pharmaceutical products (WHO Technical Report Series No. 953, 2009, Annex 4). This procedure provides an assurance that artesunate, used in the manufacture of ARTECAP, is of good quality and manufactured in accordance with WHO Good Manufacturing Practices. API prequalification consists of a comprehensive evaluation procedure that has two components: Assessment of the API master file (APIMF) to verify compliance with WHO norms and standards, and assessment of the sites of API manufacture to verify compliance with WHO GMP requirements.

[1]Trade names are not prequalified by WHO. This is the national medicines regulatory authority's (NMRA) responsibility. Throughout this WHOPAR the proprietary name is given as an example only.

Artesunate is critically insoluble (of BCS low solubility across the physiological pH range). Since the API is present in the solid state in the product, particle size distribution (PSD) was regarded a CQA and forms part of the FPP manufacturer's API specifications. The acceptance criteria for PSD were set on information of the API lot used in the FPP biobatch. XRPD is not controlled in the API specifications since it has been demonstrated that the manufacture produces consistently one polymorphic form. It has also been demonstrated that polymorphic form of the API is not affected when micronized by jet milling.

Other ingredients

The capsule fill blend contains medium-chain triglycerides and hard fat. The capsule shell contains gelatin, glycerol and titanium dioxide. None of the excipients, except gelatin, is derived from animal origin. The supplier of gelatin provided an EDQM CEP demonstrating TSE/BSE-compliance of this excipient.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The rectal capsules are ivory coloured, elongated shaped soft gelatin capsules, containing white to of white coloured oily mass. The rectal capsules are presented in Alu-Alu blisters. The primary packaging protects the capsules from moisture.

The development of the product has been described. The objective was to obtain a stable, robust and reproducible formulation of soft rectal capsules that is bioequivalent to the WHO recommended comparator product, Artesunate rectal capsules 100 mg of Scanpharm, Birkerod, Denmark.

Based on the clinical, pharmacokinetic and physicochemical characterization of the comparator product, the initial formulation strategy was (1) to keep the qualitative composition similar to the reference product to have a stable and bioequivalent generic product and (2) to use suitable grades of excipient to achieve rapid and complete dissolution, targeting the profile of the comparator product. Considering the qualitative composition of the comparator product and compatibility with the API, medium-chain triglycerides were selected as a vehicle and hard fat as base. To enhance the dissolution rate the API is in the micronized form.

The manufacturing process involves gelatin shell preparation and preparation of the fill, followed by encapsulation and drying. The fill preparation involves melting of the base and vehicle, addition of micronized API and homogenization. The gelatin preparation and encapsulation process are largely standard for soft gels.

Specifications

The finished product specifications include appropriate tests for description, identification of the API (HPLC and UV), disintegration time, loss on drying (shell), dissolution (HPLC detection), physical behaviour of capsule (softening, rupture and complete collapse times), related substances (HPLC), uniformity of dosage units (by content uniformity), assay (HPLC) and microbial limits. The test procedures have been adequately validated.

Stability testing

Stability studies have been performed at 25°C/60%RH (zone II) and 30°C/75%RH (zone IVb) as long-term storage conditions and for six months at 40°C/75%RH as accelerated condition in the packaging proposed for marketing of the product. Significant changes were seen at the accelerated condition – indicating that excursions above 30°C should be avoided – and relatively rapid changes at the zone IVb condition compared to zone II. This was mainly due to degradation of the API.

Based on the available stability data, the proposed shelf life and storage conditions as stated in the SmPC are acceptable.

Procurers and distributers should take care to avoid excursions above 30°C during storage and transport of the product. However, it is understood that this storage requirement may not always be adhered to when the product is handled by community health workers (CHWs) located in areas where the ambient temperature is above 30°C. Therefore, procurers and distributors need to ensure that the product is distributed to CHWs located in such areas only as a short term stock, generally not

exceeding 4-6 months depending on the remaining shelf life of a given batch and severity of the ambient conditions where the batch is to be distributed.

Conclusion
The quality part of the dossier is accepted.

3. **Assessment of Bioequivalence**

The following bioequivalence study has been performed in 2017 according to internationally accepted guidelines.

An open label, balanced, randomized, single-dose, two-treatment, three-sequence, three-period, partial replicate, reference scaled average bioequivalence, crossover bioequivalence study of Artesunate Rectal capsules 100mg of Strides Shasun Limited, India and Artesunate Rectal Capsules 100mg of SCANPHARM A/S, Topstykket 12, DK-3460 Birkerod, Denmark after single dose administration of 100mg capsules intra rectally in healthy, adult, human male subjects under fasting condition (study no. 16-VIN-0442).

The objective of the study was to compare the bioavailability of the stated Artesunate 100 mg rectal capsule manufactured by/for Strides Shasun Limited, India (test drug) with the reference formulation Artesunate 100 mg rectal capsule (SCANPHARM A/S) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, partial replicate, crossover study in healthy subjects under fasting conditions. Each subject was assigned to receive rectally each of the following two treatments in a randomized fashion, of which the Reference was administered twice:

Treatment T:	Test – 1 rectal capsule Artesunate 100 mg (artesunate 100 mg) Batch no. 7224326.
Treatment R:	Reference – 1 rectal capsule Artesunate 100 mg (artesunate 100 mg) Batch no. 142103B.

A 7 day wash-out period was observed between administration of test and references. Serial blood samples (1 pre-dose sample and 19 samples within 12h post dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for artesunate were analyzed using a validated LC-ESI-MS/MS method. The limit of quantification was stated to be about 0.8 ng/ml for artesunate.

The study was performed with 72 participants; data generated from a total of 69 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for artesunate as well as statistical results are summarised in the following table:

Artesunate

Pharmacokinetic Parameter	Test formulation (T) arithmetic mean ± SD (*)	Reference (R) arithmetic mean ± SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (h)	0.92 ± 0.57	0.90 ± 0.71	-	-
C_{max} (ng/ml)	100 ± 63 (85)	111 ± 66 (97)	87.3	79.0 – 96.4
AUC_{0-t} (ng.h/ml)	142 ± 90 (119)	147 ± 94 (126)	94.3	86.2 – 103.2
AUC_{0-inf} (ng.h/ml)	145 ± 91 (--)	151 ± 96 (--)	--	--

* geometric mean

Conclusion
The results of the study show that preset acceptance limits of 80 -125 % are met for AUC values regarding rifampicin. For Cmax the widened acceptance limits, based upon an intra-subject variability of 39.3%, are met for C_{max} values. Accordingly, the test Artesunate 100 mg rectal capsule meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Artesunate rectal 100 mg capsule (SCANPHARM A/S).

4. **Summary of Product Safety and Efficacy**

Severe *Plasmodium falciparum* malaria in children is a medical emergency that requires prompt, effective treatment. Children bear the greatest burden of this disease, and the risk of death from severe malaria is greatest in the first 24 hours. Because isolated rural communities often do not have timely access to health care facilities and effective treatment, these populations are at highest risk of dying from severe malaria.

In situations where complete treatment of severe malaria is not possible, current WHO Malaria Treatment Guidelines recommend pre-referral treatment options as follows: for children under 6 years, in descending order of preference, intramuscular artesunate, rectal artesunate, intramuscular artemether, and intramuscular quinine.

A rectally administered pediatric formulation of artesunate is intended as emergency treatment while the ill child is transferred to a facility which can provide complete curative therapy.

Evidence for reduction of malaria-related death and disability in children by rectal artesunate is derived primarily from a large placebo-controlled study conducted at 3 sites in Africa and one in Asia, Study 13, which utilized a rectal suppository formulation developed in collaboration with the WHO (the “TDR formulation”).

The “TDR” is the WHO Special Programme for Research and Training in Tropical Diseases.

Safety and efficacy data were derived from several sources, including: 1) the Study 13 Final Report, as well as other material submitted by the WHO TDR as part of the US FDA New Drug Application, 2) the published Study 13 from The Lancet in 2009, Gomes M et al, and 3) proceedings of an FDA Anti-infective Drugs Advisory Committee, which was convened to consider the TDR NDA.

The 100 mg strength (or matching placebo) was used in children ≤6 years of age, and a 400 mg strength (or matching placebo) in children ≥7 years of age and adults. A separate analysis was pre-specified for children ≤ 6 years old, who received the 100 mg artesunate suppositories.

Assessment of efficacy of the 100 mg suppository was assessed based on the results from 8050 children 6 years of age and younger (4063 artesunate and 3987 placebo).

Treatment with artesunate 100 mg rectal suppositories was associated with substantial reductions in mortality and rates of persistent neurological disability which were consistent across a variety of analyses.

For the primary efficacy analysis, a statistically significant decrease was seen in deaths recorded at 7-30 days, with 123 (3.0%) deaths in the artesunate group compared to 163 (4.1%) deaths in the placebo group (RR=0.74; p=0.01, 95% CI 0.59-0.93). Similar results were seen for the co-primary efficacy analysis, a combined endpoint of deaths and persistent serious neurological disability, with 125 cases (3.1%) observed in the artesunate group, versus 176 cases (4.4%) in the placebo group (RR 0.69, p=0.001).

Prospectively collected safety data in Study 13 was limited chiefly to neurological adverse events, and data concerning other adverse events were not collected systematically. No clear safety signal was

evident in Study 13 in children aged 6 years of age and younger. Assessment of safety was bolstered by examination of the non-modified Intent-to-Treat population with negative malaria smears, including 1839 patients who received artesunate suppositories, and 1889 patients who received placebo.

In the segment of the study conducted in Asia where both children and adults were studied and the 400 mg formulation was used for age 7 and above, a favourable outcome was observed in young children $\leq$ age 6 given rectal artesunate (7 deaths vs 19), but an adverse outcome was seen in older patients $\geq$ age 7 (22 deaths vs 9). Thus, in children above 6 years and adults, the current evidence suggests more deaths with treatment. Rectal artesunate suppositories should not be given over age 6.

5. Benefit risk assessment and overall conclusion

Quality

ARTECAP has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the comparator product. According to the submitted data on quality and bioavailability ARTECAP is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Artesunate Rectal 100 mg capsule for which benefits have been proven in terms of clinical efficacy.

Bioequivalence

ARTECAP has shown to be bioequivalent with Artesunate Rectal 100 mg capsule (SCANPHARM A/S, Denmark).

Efficacy and Safety

Study 13 supports the efficacy of the TDR formulation 100 mg artesunate rectal suppository as a pre-referral treatment for severe malaria in children 6 years of age and younger, if complete treatment is not possible and the patient will be referred immediately to an appropriate facility for definitive treatment. In this age group, treatment resulted in a 26% decrease in mortality and a 30% reduction in combined mortality and permanent disability due to severe malaria. Numerical decreases in mortality were seen across all study sites in all ages, up to 6 years.

The Prequalification Team considers that the consistency of the Study 13 data for the 100 mg suppository from Africa and Asia in children 6 years of age and younger supports a positive benefit-risk assessment for the TDR 100 mg artesunate suppository for pre-referral treatment of severe malaria. While replication of Study 13 would be ideal, especially to clarify the issues in persons age 7 and above, it is highly unlikely that this will ever occur, due to ethical considerations.

In 2017 the WHO produced a document based on pharmacokinetic considerations, recommending a dose of 100 mg of rectal artesunate for children age 2 months to 3 years, and a higher dose (200 mg) for children age 3 to 6 years. (Rectal artesunate for pre-referral treatment of severe malaria, World Health Organization Global Malaria Programme, October 2017 (Rev May 2018), http://apps.who.int/iris/bitstream/handle/10665/259356/WHO-HTM-GMP-2017.19-eng.pdf?sequence=1

This dosing recommendation has been followed in the SmPC and PIL for the Strides rectal artesunate product.
The Prequalification Team believes that the overall benefit-risk balance is favourable for use of the 100 mg suppository in children 6 years of age and younger, when used within the restrictions of the Summary of Product Characteristics. Text in the SmPC and PIL clearly warns against rectal artesunate use in children over age 6.

The accepted indication is: “As pre-referral treatment for suspected or proven severe malaria in patients aged between 2 months and 6 years, who are unable to take oral medication or obtain

injectable antimalarial treatment. The patient should be immediately referred to a facility where accurate diagnosis and complete treatment with effective antimalarials can be instituted."

Benefit Risk Assessment

Based on WHO's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit risk profile of ARTECAP was acceptable for the following indication: **"pre-referral treatment of suspected or proven severe malaria in patients aged between 2 months and 6 years, who are unable to take oral medication or obtain injectable antimalarial treatment."** and has advised that the quality, efficacy and safety of ARTECAP are acceptable to allow inclusion of ARTECAP, manufactured at Strides Pharma Science Limited, KRS Gardens, Soft Gel Capsules Block, Anekal Taluk, Bangalore, 562 106, India in the list of prequalified medicinal products.