1 SYNOPSIS

Name of Sponsor/Company: Medicines Development for Global Health	***(For National Authority use only)***
Name of Finished Product: Moxidectin tablets 2 mg	
Name of Active Ingredient: Moxidectin	

Title of Study: An open-label study of the pharmacokinetics and safety of a single dose of moxidectin per oral in subjects aged 4 to 17 years with (or at risk of) onchocerciasis to identify an optimal dose for treatment of children 4 to 11 years

Investigators: Dr Nicholas Obuobisa Opoku

Study Centre: School of Public Health Research Centre, University of Health and Allied Sciences, Hohoe Municipal Hospital, Hohoe, Oti Region, Ghana

Publication (reference): None.

Studied period: 18 months 29 March 2021 (date first consent obtained) to 28 September 2022 (date of last subject visit)	**Phase of development:** Phase I

Objectives:

Primary

- Identify an optimal dose of moxidectin for the treatment of children aged 4 to 11 years with onchocerciasis.

Secondary

- Evaluate the safety and pharmacokinetics (PK) of a single dose of moxidectin in children and adolescents aged 4 to 17 years.

Methodology: This was a Phase I, prospective, age-stratified, adaptive, open-label, PK and safety study in which healthy children and adolescents aged 4 to 17 years were assigned on the basis of age to one of three cohorts to receive a single oral dose of moxidectin. Subjects were recruited from communities in the Kpassa sub-district of the Oti region in Ghana, which is endemic for *Onchocerca volvulus (O. volvulus)*.

Parental consent and, as age-appropriate, child or adolescent assent (or lack of expression of "deliberate objection"), was obtained in the community up to 30 days prior to Baseline. Children meeting eligibility criteria assessed in the community were brought to the study site in Hohoe together with a parent or guardian for completion of Screening assessments and determination of eligibility. Subjects who failed to meet all of the inclusion criteria or who met any of the exclusion criteria were returned to their community the next day. Subjects meeting all of the inclusion criteria and none of the exclusion criteria received moxidectin treatment on the morning of Day 0 and remained at the study site for post-treatment safety monitoring and collection of blood samples for PK analysis until Day 7, before being returned to their community. Subjects subsequently returned to the study site for safety assessments and PK sample collection at Day 14, Day 28, and Week 12, and a final safety assessment at Week 24. Additional visits and/or assessments may have been conducted as clinically indicated.

Three age-defined cohorts were to be recruited:

- Cohort I (12 to 17 years, n=9) received moxidectin 8 mg (4 x 2 mg tablets);
- Cohort II (8 to 11 years, n=9) received moxidectin 8 mg (4 x 2 mg tablets).; and
- Cohort III (4 to 7 years, n=9) received moxidectin at the dose determined from analyses of Cohorts I and II.

Initially, a sentinel group of 3 subjects was enrolled in each of Cohorts II and III. If safety up to and including Day 3 in these subjects was acceptable, the additional 6 subjects were enrolled.

Once all Cohort I and II subjects completed Day 28, a Data and Safety Monitoring Board (DSMB) reviewed safety and PK data to recommend an alternative dose be administered to another group

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in Cohort II (per protocol requirements) and/or enrolment of Cohort III and the dose of moxidectin to be administered.

If for Cohorts II and III, the starting dose resulted in at least 3 of the subjects having moxidectin exposures above the target range (predicted mean 90th percentile area under the concentration-time curve from time 0 extrapolated to infinity [AUC_{0inf}] using a population PK model of moxidectin based on PK data from healthy adult volunteers and adult patients infected with *O. volvulus*), a revised dose was to be determined in decrements of 2 mg and the Cohort was to be repeated with at least 9 new subjects enrolled at the new dose. If for Cohort III, the starting dose resulted in at least 3 subjects having moxidectin exposures below the target range (mean 10th percentile AUC_{0inf} predicted from the population PK model of moxidectin based on adult PK data), a revised dose was to be determined in increments of 2 mg to a maximum dose of 8 mg.

The DSMB of independent experts was established, with a charter that defined in detail its roles and responsibilities. The DSMB met as required during the study and may have recommended to the Sponsor whether the trial could continue as planned or if the trial should have been modified or stopped. The DSMB reviewed the safety and PK data following completion of enrolment and PK data analysis for Cohorts I and II (enrolled concurrently) and advised the Sponsor on the dose for Cohort III. The DSMB also reviewed the safety and PK data following completion of Cohort III and advised the Sponsor on the need for revised doses for both Cohorts II and III.

Number of subjects (planned and analyzed):

The planned enrolment was approximately 27 subjects, with approximately 9 subjects per cohort (up to a maximum of 63 subjects, depending on PK outcomes).

The actual enrolment total was 36 subjects, comprised of the following:

- Cohort I (12 to 17 years): 8 mg moxidectin, n=9;
- Cohort II (8 to 11 years): 8 mg moxidectin, n=9;
- Cohort II (8 to 11 years): 6 mg moxidectin, n=9;
- Cohort III (4 to 7 years): 4 mg moxidectin, n=9.

Diagnosis and main criteria for inclusion:

1. Aged 4 to 17 years, inclusive:

- Cohort I: 12 to 17 years;
- Cohort II: 8 to 11 years;
- Cohort III: 4 to 7 years.

2. Living in a region designated by the World Health Organization (WHO) as endemic for O. volvulus infection (World Health Organization 2019). Specifically, participants were recruited from the Kpassa sub-district of the Nkwanta North district. The specific communities included Wii, Jagri-Do, and Azua, where mass drug administration with ivermectin for onchocerciasis commenced in October 2017;

3. Willing and able to remain at the research center from Screening up to Day 7;

4. Provision of parental or guardian written informed consent and child assent / lack of expression of 'deliberate objection' (as appropriate for age);

5. Females of childbearing potential must have committed to using a highly effective method of contraception as per local family planning guidelines from Baseline (pre-treatment on Day 0) until approximately 6 months (Week 24) after treatment with study drug.

Test product, dose and mode of administration, batch number:

Test product: Moxidectin oral tablets 2 mg.

Dose: Subjects in Cohort I (12 to 17 years, n=9) and Cohort II (8 to 11 years, n=9) received a single oral dose of 8 mg moxidectin (4 x 2 mg tablets) under fasting conditions on Day 0. Once all Cohort I and II subjects completed Day 28, the DSMB reviewed safety and PK data to recommend if i) an

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alternative dose should be administered to another group of subjects (n=9) in Cohort II (per protocol requirements); and ii) if Cohort III (4 to 7 years, n=9) could be enrolled, and if so, the dose of moxidectin to be administered. Cohort III subjects then received a single oral dose of moxidectin at the recommended dose on Day 0. Once all Cohort III subjects completed Day 28, the DSMB reviewed safety and PK data to recommend if an alternative dose should be administered to another group of subjects (n=9) in Cohort III (per protocol requirements).

Batch Number/s: 400842

Duration of treatment:

Treatment was a single oral dose of moxidectin on Day 0.

For each subject the total study duration was approximately 28 weeks, consisting of the following periods:

- up to 30 days prior to Day 0 for consent and prescreening;
- up to 7 days prior to Day 0 for Screening;
- 7 days in-center; and
- 23 weeks outpatient follow-up post-treatment.

Reference therapy, dose and mode of administration, batch number:

Not applicable. There was no reference therapy or comparator used in this study.

Criteria for evaluation:

Primary endpoint

- Dose(s) for children aged 4 to 11 years were to be selected based on non-compartmental exposure metrics including -AUC assessed up to and including Day 28 and a population PK model.

Secondary endpoints

- Safety endpoints included the incidence and severity of adverse events (AEs), physical examination findings, changes in vital signs, and laboratory safety parameters at all time points in the study.
- Pharmacokinetic parameters of moxidectin in children and adolescents aged 4 to 17 years, including maximum observed plasma concentration (C_{max}), time to maximum observed plasma concentration (T_{max}), and other PK parameters determined by non-compartmental analysis (NCA) or other methods, as appropriate.

Statistical methods:

No formal sample size determination was undertaken. Approximately 9 subjects in each Cohort at a given dose was considered to be an adequate sample size for full characterization of the PK of a single dose of moxidectin.

No formal hypothesis testing was performed in this study. All analyses were descriptive.

All planned analyses, including non-compartmental PK, population PK modeling and safety analyses, were described in a Statistical Analysis Plan (SAP) that was finalized prior to commencing data analysis.

At the conclusion of analysis of data for Cohorts I and II, the existing population PK model was updated with these data and simulations of $AUC_{0\text{-}inf}$ and C_{max} were performed by age and other possible covariates to support ongoing dose decisions and initiation of Cohort III. At the end of the study, the population PK model was updated with data from all cohorts to support the dose rationale for children.

SUMMARY AND CONCLUSIONS:

A total of 36 subjects were enrolled into the study: 9 subjects into Cohort I (moxidectin 8 mg), 18 subjects into Cohort II (moxidectin 8 mg [n=9] or moxidectin 6 mg [n=9]), and 9 subjects into Cohort III (moxidectin 4 mg). Within Cohort II, dosing of an additional 9 subjects in the 6 mg moxidectin group was recommended by the DSMB based on PK outcomes, as specified in the protocol. No subjects were prematurely withdrawn from the study and all subjects completed the study as planned.

A total of 92 protocol deviations were recorded in the study, all of which were considered minor and to not have adversely impacted the results of the study.

SAFETY RESULTS

Moxidectin was well tolerated, with no treatment-emergent adverse events (TEAEs) considered related to study drug, no serious adverse events (SAEs), and no TEAEs leading to study withdrawal or resulting in death reported. The most frequently reported TEAE overall was malaria, followed by upper respiratory tract infection, abdominal pain, diarrhea and conjunctivitis.

The majority of TEAEs reported were Grade 1 (mild) in severity, with the remainder assessed as Grade 2 (moderate) and Grade 3 (severe). There were no Grade 4 (life-threatening) TEAEs reported. Grade 2 (moderate) severity TEAEs included malaria, upper respiratory tract infection, and false positive investigation result. Grade 3 (severe) TEAEs included hookworm infection and anemia in the same subject.

There were no clinically significant trends in changes in safety laboratory parameters, vital signs or physical examination findings observed and no notable trends or differences in concomitant medication usage between cohorts.

PHARMACOKINETIC RESULTS

Moxidectin was quantifiable post-dose in all subjects up to Day 28. Fewer than 50% of the subjects in Cohort I and II, and none of the subjects in Cohort III had quantifiable concentrations at Week 12.

The median T_{max} was 3.98, 3.98. 3.95, and 3.95 hours after dosing for Cohort I, Cohort II 6 mg and 8 mg moxidectin groups, and Cohort III, respectively.

The geometric mean (GCV%; range) C_{max} following a single oral moxidectin dose in Cohort I, Cohort II 6 mg and 8 mg moxidectin groups, and Cohort III was 83.1 nanograms (ng)/milliliter (mL) (19.1%; 67.0 –129 ng/mL), 82.1 ng/mL (41.2%; 59.1 – 187 ng/mL), 115 ng/mL (25.6%; 70.7 – 149 ng/mL), and 86.4 ng/mL (28.3%; 55.9 – 131 ng/mL), respectively. Geometric mean (GCV%; range) $AUC_{0\text{-}D28}$ was 2680 hr*ng/mL (24.7%; 1880 – 4060 hr*ng/mL), 2230 hr*ng/mL (52.3%; 1190 – 6160 hr*ng/mL), 3310 hr*ng/mL (23.0%; 2120 – 4270 hr*ng/mL), and 1880 hr*ng/mL (26.5%; 1310 – 2750 hr*ng/mL) for Cohort I, Cohort II 6 mg and 8 mg moxidectin groups, and Cohort III, respectively.

The geometric mean terminal half-life ($t_{1/2}$) after a single oral moxidectin dose in Cohort I, Cohort II 6 mg and 8 mg moxidectin groups, and Cohort III was 351, 258, 278, and 201 hours, respectively.

The existing population PK model for moxidectin in adults was updated using data from adolescents and children obtained in this study. The model in adults was retained and included a transit absorption process with 3 compartment disposition and first-order elimination. Covariates retained from the model developed in adults included food and formulation on absorption, with sex on peripheral compartment parameters. Moxidectin PK in children (4 to 11 years) were adequately predicted when allometry was included on non-compartmentally-derived apparent plasma clearance (CL/F), and estimated for all clearances and volumes.

Overall, dosing simulations indicated that exposures equivalent to those in adults receiving the approved dose of moxidectin 8 mg were obtained with the following doses in children:

- 8 mg moxidectin in adolescents aged 12 to 17 years;
- 6 mg moxidectin in children aged 8 to 11 years; and
- 4 mg moxidectin in children aged 4 to 7 years.

CONCLUSION

Overall, single oral doses of moxidectin at 4 to 8 mg in children and adolescents with (or at risk of) onchocerciasis were well tolerated, with no safety issues identified in this study. The PK data demonstrate that exposures equivalent to those in adults receiving the approved dose of moxidectin 8 mg were obtained with doses of 8 mg in adolescents aged 12 to 17 years, 6 mg in children aged 8 to 11 years and 4 mg in children aged 4 to 7 years.

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The results obtained from this study will support further assessment through modeling and simulation and dose optimization for children under 12 years of age. Date of the report: 14 Mar 2023	