Grant code	*RIA2019PD-2880*
Project title	*"Treatment for all: developing a paediatric formulation of moxidectin for neglected infectious diseases"*
Deliverable number	D1.1
Deliverable name	Moxidectin's paediatric formulation target product characteristics defined
Deliverable type	*R*
Work Package	WP1
Organisation and person responsible	MDGH, Sally Kinrade and Rebecca Smith
Dissemination level	Public
Contractual delivery date (month)	M3
Actual delivery date (month)	M4
Version	v1.0
Total number of pages	10

MiniMox

Treatment for all: developing a paediatric formulation of moxidectin for neglected infectious diseases

Grant Agreement Number: RIA2019PD-2880

Second European and Developing Countries Clinical Trials Partnership Programme (EDCTP2)

Thematic domain: BM - Life Sciences, Biology and Medicine

Type of Action: Research and Innovation Action (RIA)

DELIVERABLE D1.1
Deliverable title: Moxidectin's paediatric formulation target product characteristics defined

Abstract: Deliverable 1.1 is the definition of the Target Product (Paediatric Formulation) Characteristics (TPC) for moxidectin. The TPC developed was based on the stated goals in the grant application, further defined according to certain parameters and assumptions, and focussed on formulation characteristics. Its development involved all participants in Work Package 1 (WP1). This Deliverable was achieved and now informs selection of up to three candidate formulations for benchtop R&D in Work Package 3 (WP3).

Due date of deliverable: Month 3 **Actual submission date**: Month 4
Start date of the project: January 1st, 2021 **Duration**: 42 months
Project Co-ordinator organisation: Luxembourg Institute of Health
Work Package 1 lead organisation: Medicines Development for Global Health
Contributors: Luxembourg Institute of Health – LIH; University of Health and Allied Sciences – UHAS; University of Strathclyde – STRATH; Universitätsklinikum Bonn–UKB; Centre for Research on Filariasis and other Tropical Diseases–CRFilMT; UNDP/UNICEF/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR).
Dissemination level: PU
Revision N°: 1

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Executive Summary

Background	The first step in the "MiniMox" project and in Work Package 1 (WP1) was to develop the Target Product Characteristics for a paediatric formulation of moxidectin. The draft list of criteria, included in the grant application, was the starting point for the development of the full document. Final characteristics and 'Required' and 'Desired' criteria for each characteristic in the final Target Product (Paediatric Formulation) Characteristics (TPC) document were determined based on the known physicochemical attributes of moxidectin and important considerations for a paediatric formulation that is anticipated for use in community directed field programs for onchocerciasis and other diseases.
Objectives	The objective of Deliverable 1.1 was to define moxidectin's paediatric formulation target product characteristics.
Methods	All participants in WP1 contributed to the strategy to develop the TPC document. Medicines Development for Global Health (MDGH) developed the first draft of the TPC, according to the known attributes and requirements for a formulation of moxidectin. The draft was then discussed and added to by other WP1 participants with formulation and field program experience. Several rounds of refinement were undertaken to ensure clarity of language and completeness of the information captured. Information from literature reviews and prior knowledge on the intrinsic attributes, R&D and manufacturing of moxidectin in human and veterinary formulations was considered. Assumptions and parameters for the development of the TPC were defined.
Results & implications	The TPC for the paediatric formulation of moxidectin has been defined, with the assumptions and within the parameters noted. The stated characteristics broadly align with those described in the grant application. Participants in WP3 will utilise the TPC to select up to three candidate formulations for small scale pharmaceutical development. As leader of WP1, MDGH considers that the objective of Deliverable 1.1 has been achieved.

1. Background

The first step in this project and in Work Package 1 is to establish moxidectin's paediatric formulation target product characteristics. Deliverable 1.1, which falls under grant Aim 1 and Work Package 1, addresses this goal. Please note the specific use of the Target Product Characteristics term. This Deliverable will not constitute what many drug developers or WHO would recognise as a "Target Product Profile" nor be quite as limited as a Chemistry Manufacturing and Controls (CMC)-focussed "quality Target Product Profile".

The draft Target Product Characteristics noted in the grant application have been used as a basis for discussions and the development of Deliverable 1.1. Note that these characteristics were drafted to allow inclusion of ≥ 1 year old children in onchocerciasis elimination programmes as well as treatment programmes for other diseases for which moxidectin efficacy is under evaluation.

Draft Target Product Characteristics from the grant application:

1) Dose Form and Packaging:
   a) Form to be determined within this grant.
   b) Trade dress (packaging) and presentation that minimises pack volume for easy transportation
   c) Easily differentiated from common concomitant medication, and moxidectin tablets
2) Formulation characteristics
   a) Palatable (for children in the African setting)
   b) Availability of cGMP excipients and mixing/filling equipment
   c) Compatible with existing release assays
   d) Not requiring licensed intellectual property/royalties
3) Stability of formulated product
   a) Stable at least 24 months under Zone 4b conditions.
   b) In-use stability supportive of use in mass drug administration
4) Target price
   a) Donated
5) Regulatory
   a) Addition of new formulation to the prescribing information in the United States
   b) Recommended for use by the WHO in onchocerciasis endemic countries intending to use moxidectin.

2. Objectives

The main objective was to define moxidectin's paediatric formulation target product characteristics.

3. Methods

Work Package 1 participants held four meetings on 14/15 December 2020, 28/29 January 2021, 18/19 March 2021 and 22/23 March 2021 to:

- develop a strategy and process for the development of the formulation target product characteristics for paediatric moxidectin, and
- identify, discuss and finalise the characteristics and 'Required' and 'Desired' criteria for each.

Initially, the Medicines Development for Global Health internal team, comprising project leadership for the moxidectin for onchocerciasis and scabies programs and CMC and regulatory functional experts, met to prepare the first draft of the TPC. This team prepared the draft to ensure that the characteristics and Required and Desired criteria:

- addressed potential needs for treating onchocerciasis, scabies and other diseases, and
- remained feasible considering what is already known about the physicochemical characteristics of moxidectin from previous and current R&D and manufacturing activities, including on human formulations and in a veterinary form, Simparica Trio ®, conducted at Wyeth, a previous sponsor of the moxidectin program.

The criteria developed were based on known attributes of paediatric formulations in use for treatment of neglected tropical diseases (NTDs) and the physicochemical characteristics of moxidectin and its manufacturability and acceptability standards.

This draft of the TPC was made available to all participants in WP1, who were invited to comment on the characteristics and criteria proposed. In particular, participants were asked to identify whether any important characteristics had been omitted. In Meeting #4 for WP1 on 22/23 March 2021, a 90-minute discussion focussed on the TPC document. Feedback received by email on additional characteristics and proposed changes to the criteria described were considered and debated.

In parallel, WP1 participants from the University Hospital Bonn and UNDP/UNICEF/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) commenced reviewing literature toward the delivery of Deliverables 1.2 and 1.3. The literature under review included: peer-reviewed literature, prescribing information, WHO and onchocerciasis-endemic country Essential Medicines Lists and WHO Target Product Profiles. It was agreed that any findings from the literature relevant to the development of the TPC were to be communicated promptly to all participants. Opportunities for this communication were provided at WP1 Meeting #3 and prompted with email reminders.

3.1 Assumptions made in developing Target Product Characteristics

The TPC for the paediatric formulation of moxidectin was developed with a number of assumptions in mind:

- The medicine will be able to serve a number of disease indications
- The medicine will be an oral dosage form

- The medicine and its packaging and labelling will be unique; that is, distinguishable from other medicines for children (especially those that may be administered at the same time)
- The medicine will be bioequivalent to the current 2mg tablet form
- Any food or liquid that aids administration must be safe and locally procured
- No secondary packaging
- Primary and tertiary packaging must be low weight and low volume for inexpensive transport and ease of logistics
- The formulation will not require intellectual property licensing, payment of royalties or unique excipients
- The formulation will be feasible considering the intrinsic properties of moxidectin
- The cost of the final finished product will be as low as possible.

3.2 Parameters established for the development of the Target Product Characteristics

It was detemined that the TPC should focus on the characteristics and criteria selected for the formulation, and, to a limited extent, the packaging to be used.

A number of excellent draft characteristics included in the grant application were not included in the final TPC for the reasons described below:

- *In-use stability supportive of use in mass drug administration:* this is not a characteristic of a formulation but rather information that may be generated once a formulation has been developed. Depending on the formulation and its packaging, an in-use stability program is typically implmented to reflect the anticipated circumstances and duration for which a container may continue to be used for dosing once it has been opened. The frequency of opening and closing the container and frequency of sampling the contents for testing is usually defined once a final product is reached and the package size and configuration determined. As there are significant costs attached to a large program of analytical work, the stability program is best determined once the product presentation is finalised.
- *Addition of new formulation to the prescribing information in the United States:* while submission of supplemental New Drug Application to the US FDA in support of addition of the paediatric formulation to the US prescribing information is the stated Aim 6 of the grant proposal, it is not a characteristic of the product (formulation).
- *Recommended for use by the WHO in onchocerciasis endemic countries intending to use moxidectin.* This is the intention for both the 2mg tablet form and paediatric formulation of moxidectin, however it is not a characteristic of the product (formulation) itself.

3.3 Characteristics and criteria described in the Target Product Characteristics

A number of characteristics were selected as important to the TPC for the moxidectin paediatric formulation. These can be broadly grouped into overlapping categories of “child-facing”,

"implementer-facing" and "other" characteristics. For each characteristic, a 'Required' and 'Desired' criterion was developed or a single target assumption described. The Required criterion describes the minimally acceptable criterion for that characteristic and represents a standard that must be met. The Desired criterion represents the preferred standard to be met.

4. Results & implications

4.1 Target Product Characteristics for the paediatric formulation of moxidectin

The Target Product Characteristics for the paediatric formulation for moxidectin are shown in Appendix 1.

4.2 Alignment with the grant application

In this section, we report on the alignment of this Deliverable with details provided in the grant application, considering:

- The draft Target Product Characteristics listed in the grant
- Use of outputs from Aim 1 and Aim 2

Draft Target Product Characteristics

In almost all aspects, the assumed characteristics or stated Target Product Characteristics align with the list drafted in the grant application:

- Trade dress (packaging) and presentation is assumed to be of low weight and volume for each transportation (point 1b in draft list from grant application)
- Appearance of the medicine and labelling is assumed to be unique and easily distinguishable from other medicines that might be in common use in the areas in which the formulation will be used (point 1c)
- The formulation is Required to be acceptable to children in terms of smell, taste and flavour (point 2a)
- The formulation is Required to use minimal excipients and a simple manufacturing process with the minimum number of unit operations and using standard pharmaceutical industry processing equipment (points 2b)
- The formulation is Required to meet dissolution acceptance criterion for 2 mg tablet. *In vitro* similarity (f2 comparison) is not less than 50 (point 2c)
- The formulation is assumed to not require licencing of any intellectual property or payment of royalties for use of any technology (point 2d)
- The formulation is Required to be stable for at least 24 months at 30°C/75% relative humity (point 3a)
- The target price of the formulation is Required to be as low as possible (point 4a).

The aspects of the draft list of characteristics included in the grant application which have not been addressed are noted in the section above describing Parameters.

In the grant application, it was noted that the draft Target Product Characteristics should be written to allow inclusion of ≥ 1 year old children in onchocerciasis elimination programmes as well as treatment programmes for other diseases for which moxidectin efficacy is under evaluation, such as soil-transmitted helminths. This lower age limit of 1 year has been included as a Desired characteristic, acknowledging that achieving suitability of the formulation for children under 2 years and within the constraints of the criteria for other characteristics may not be feasible.

Use of outputs from Aim 1 and Aim 2

Due to the scheduling and sequencing of this deliverable, we have been:

- Able to incorporate limited findings from Aim 1 into the development of the Target Product Characteristics document.
- Unable to incorporate any findings from Aim 2 into the development of the Target Product Characteristics document.

4.3 Implications

The TPC for the paediatric formulation of moxidectin have been defined, with the assumptions and within the parameters noted above.

Participants in Work Package 3 will use this TPC to develop the paediatric formulation of moxidectin and to aid in selection of up to three candidates for small scale pharmaceutical development, which is the objective of Deliverable 3.1. As Deliverable 3.1 is submitted concurrently with Deliverable 1.1, a discussion of the use of the TPC to choose and exclude various oral dosage forms for benchtop R&D and manufacturing is detailed in Deliverable 3.1.

This formulation Target Product Characteristics document will continue to evolve, as benchtop R&D work commences and information becomes available from Aim 2.

The objective of this Deliverable has been achieved.

Appendix 1: Target Product (Paediatric Formulation) Characteristics for moxidectin

Characteristics	Required	Desired
Target age groups	Children aged 2 years and above	Children aged 1 to 4 years
Dose Strength	≥ 2mg to ≤ 8mg	Presentation allows for dosing flexibility from 2 to 36 mg
Formulation / Route of Administration	Oral solid dosage form, easy to prepare and administer with liquid (less desirable is administration with food), without requiring a device	Minimal sized, oral solid dosing form, ready to administer
Acceptability	Formulation is acceptable to children in terms of smell, taste and texture.	Formulation is acceptable to children in terms of smell, taste and texture and does not include taste masking or a sweetener.
Storage Conditions/ Stability Profile (before opening container)	Stable for at least 24 months at 30°C/75% RH	Stable for at least 36 months at 30°C/75% RH
Primary packaging	Minimally permeable to water; provides light protection	Minimally permeable to water; provides light protection; made of biodegradable material
Container Closure	Provides light protection and minimizes moisture ingress. Meets regulatory requirements for all target regions.	Provides light protection and minimizes moisture ingress to an extent that eliminates the need for a desiccant. Meets regulatory requirements for all target regions.
Secondary packaging	No secondary packaging	
Tertiary packaging (shipper)	Ideally made of biodegradable material	
Weight / volume	Low weight and volume	
Appearance	Medicine and labelling will be unique; that is, distinguishable from other medicines	
Bioequivalence	Bioavailability of paediatric formulation is equivalent to bioavailability of same dose of tablet form (i.e. the 90% confidence interval of the ratio of a log-transformed exposure in plasma (Area under the plasma concentration-time curve (AUC) and maximum (peak) plasma drug concentration (Cmax)) of the paediatric formulation falls completely within the range 80-125% of the tablet form).[1]	

[1] Adapted from Certara.com Knowledge Base. *Where Did the 80-125% Bioequivalence Criteria Come From?* Link: https://www.certara.com/knowledge-base/where-did-the-80-125-bioequivalence-criteria-come-from/

Drug Release testing	Meets dissolution acceptance criterion for 2 mg tablet. *In vitro* similarity (f2 comparison) is not less than 50.	
Manufacturing Process	Simple manufacturing process with a minimum number of unit operations and using standard pharmaceutical industry processing equipment. Minimal number of excipients/ingredients.	
Cost of Goods of final finished product	As low cost as possible	No more than 3 x cost per equivalent tablet dose of moxidectin (as presented in 500-count bottle)