30 January 2025
EMA/59142/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ivermectin / Albendazole

International non-proprietary name: ivermectin / albendazole

Procedure No. EMEA/H/W/005186/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ACh	Acetylcholine
^{13}C-NMR	Carbon nuclear magnetic resonance spectroscopy
^{1}H-NMR	Proton nuclear magnetic resonance spectroscopy
A. ceylanicum	*Ancylostoma (A.) ceylanicum*
A. duodenale	*Ancylostoma duodenale*
A. lumbricoides	*Ascaris lumbricoides*
A. suum	*Ascaris suum*
ABZ Diamine	2-amino-4-propylthio aniline
ADR	Adverse reaction
AE	Adverse event
ALB	Albendazole
Alu	Aluminium
API	Active product ingredient
ASMF	Active substance master file
B. malayi	*Brugia malayi*
BCRP	Breast cancer resistance protein
b.w.	Body weight
BHT	2,6-bis(1,1-dimethylethyl)-4-methylphenol
C. elegans	*Caenorhabditis elegans*
CFA	Circulating filarial antigens
CHMP	Committee for Human Medicinal Products
CHO	Chinese hamster ovarian cells
CI	Confidence interval
CNS	Central nervous system
CP	Male-specific motor neurone or cell in ventral cord
CPP	Critical process parameters
CQA	Critical quality attributes
CR	Cure rate
CRS	Chemical reference substances
CTD	Common technical document
DSC	Differential scanning calorimetry
ECHA	European Chemicals Agency

EMA	European Medicines Agency
ERR	Egg reduction rate
EST	Stem cell test
EtOH	Ethanol/ethyl alcohol
EU	European Union
F	Female
FAO	Food and Agriculture Organization of the United Nations
FDC	Fixed dose combination
FT-IR	Fourier-transform infrared spectroscopy
FTS	Filariasis test strip
G. duodenalis	*Giardia duodenalis*
GABA	Gamma-aminobutyric acid
GC	Gas chromatography
GluCl	Glutamate-gated chloride channels
GMP	Good manufacturing practice
H. contortus	*Haemonchus contortus*
H. polygyrus	*Heligmosomoides polygyrus*
HDPE	High-density polyethylene
HPLC	High-pressure liquid chromatography
IC_{50}	Median inhibitory concentration
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IL	Interleukin
INN	International non-proprietary name
IP	Intraperitoneal
IPC	In-process control
IR	Infrared
ITT	Intention-to-treat
IVM	Ivermectin
KF	Karl Fisher
LC_{50}	Median lethal concentration
LD_{50}	Median lethal dose
LDPE	Low-density polyethylene

LOD	Limit of detection/ loss on drying
LOQ	Limit of quantitation
LoQ	List of questions
M	Male
MAO	Monoamine oxidase
MDA	Mass drug administration
MeOH	Methanol
MO	Major objection
MRP	Multidrug resistance protein
mRNA	Messenger ribonucleic acid
MRP	Multidrug resistance protein
MS	Mass spectrometry
N. americanus	*Necator americanus*
NCR	Negative conversion rate
ND	Not determined
NLT	Not less than
NMT	Not more than
NOAEL	No observed adverse effect level
NOEL	Non observed effect level
NTDs	Neglected tropical diseases
OC	Other concern
PA	Polyamide
PAM	Post-authorisation measure
PC	Preventive chemotherapy
PCR	Polymerase chain reaction
PDE	Permitted daily exposure
P-gp	P-glycoprotein
Ph.Eur.	European Pharmacopoeia
PO	Per os; oral
PP	per protocol
ppm	Parts per million
PT	Preferred term
PXRD	Powder X-ray diffraction

PVC	Polyvinyl chloride
QP	Qualified person
QTPP	Quality target product profile
RME	Ring motor neurone
RMP	Risk management plans
S. ratti	*Strongyloides ratti*
S. stercoralis	*Strongyloides stercoralis*
SAC	School-aged children
SAWP	Scientific Advice Working Party
SC	Subcutaneous
SLS	Sodium lauryl sulphate
SmPC	Summary of product characteristics
SOC	System organ classes

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Laboratorios Liconsa S.A. submitted on 22 December 2023 an application in accordance with Article 58 of (EC) No Regulation 726/2004 to the European Medicines Agency (EMA) for a scientific opinion in the context of cooperation with the World Health Organization for Ivermectin/Albendazole.

The eligibility by the World Health Organisation was agreed upon on 15 December 2022.

Ivermectin/Albendazole will exclusively be intended for markets outside the European Union.

The applicant applied for the following indication:

> Ivermectin/Albendazole orodispersible tablets are indicated in adults, adolescents and children aged ≥6 years with a body weight of ≥15 kg for the following indications:
>
> Treatment of soil-transmitted helminths infections, caused by one or more of the following parasites (section 5.1):
>
> - Hookworm infection caused by *Ancylostoma duodenale* and *Necator americanus*
>
> - Ascariasis caused by *Ascaris lumbricoides* (Roundworm)
>
> - Trichuriasis caused by *Trichuris trichiura* (Whipworm)
>
> - Strongyloidiasis caused by *Strongyloides stercoralis*
>
> Treatment of lymphatic filariasis (caused by *Wuchereria bancrofti*)
>
> Ivermectin/albendazole should be used in accordance with official guidance, which may include guidance provided by the World Health Organization and public health authorities.

1.2. Legal basis and dossier content

The legal basis for this application refers to:

This application is submitted under Article 58 of Regulation (EC) No 726/2004 and includes a complete and independent dossier, by analogy to Article 10b of Directive 2001/83/EC.

The application submitted is a new fixed combination medicinal product application, composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

1.3. Scientific advice

The clinical programme was subject to scientific advice from the CHMP. The most relevant interactions took place in 2020 and 2021, and advice was mainly given regarding the bioavailability study and the adaptive design study.

In general, the scientific advice was followed.

The relevant scientific advice is listed below:

EMEA/H/SA/4165/1/2019/III: 2019-10-17

EMEA/H/SA/4165/1/FU/1/2020/PED/II: 2020-05-28

EMA/SA/0000069418: 2021-11-11

1.4. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Fátima Ventura Co-Rapporteur: Janet Koenig

The application was received by the EMA on	22 December 2023
The procedure started on	1 February 2024
The CHMP Rapporteur's first assessment report was circulated to all CHMP and PRAC members on	29 April 2024
The PRAC Rapporteur's first assessment report was circulated to all PRAC and CHMP members on	7 May 2024
The CHMP agreed on the consolidated list of questions to be sent to the applicant during the meeting on	30 May 2024
The applicant submitted the responses to the CHMP consolidated list of questions on	15 August 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs' joint assessment report on the responses to the list of questions to all CHMP and PRAC members on	27 September 2024
The PRAC agreed on the PRAC assessment overview and advice to CHMP during the meeting on	03 October 2024
The CHMP Rapporteurs circulated the updated CHMP and PRAC Rapporteurs' Joint assessment report on the responses to the list of	11 October 2024

questions to all CHMP and PRAC members on	
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	17 October 2024
The applicant submitted the responses to the CHMP list of outstanding issues on	20 December 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs' joint assessment report on the responses to the list of outstanding issues to all CHMP and PRAC members on	15 January 2025
The CHMP Rapporteurs circulated the updated CHMP and PRAC Rapporteurs' joint assessment report on the responses to the list of outstanding issues to all CHMP and PRAC members on	24 January 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive scientific opinion to Ivermectin/Albendazole on	30 January 2025

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition & Epidemiology

Soil Transmitted Helminths (STH)

The STHs primarily comprise hookworm (*Ancylostoma duodenale* and *Necator americanus*), roundworm (*Ascaris lumbricoides*), and whipworm (*Trichuris trichiura*). *Strongyloides stercoralis* is also a STH of significant public health importance, although not currently covered by WHO control activities (Jourdan et al., 2018). However, it has been included as a target for control by 2030, therefore incorporated into the STH control activities (WHO, 2020).

Regarding the transmission, STHs live in the intestine of infected individuals where they produce thousands of eggs each day that are passed in the faeces. Where the environmental conditions are favourable, the eggs develop into infective stages. Humans become infected with eggs (*A. lumbricoides* and *T. trichiura*), or larvae (*A. duodenale*) found in contaminated water, food (e.g., vegetables that are not carefully cooked, washed or peeled), hands or utensils or through penetration of the skin by infective *S. stercoralis* or hookworm larvae in contaminated soil (*N. americanus* and *A. duodenale*). There is no direct person-to-person transmission or infection from fresh faeces because eggs passed in faeces need maturation in the soil before they become infective.

STH infections are widely distributed in tropical and subtropical areas and, since they are linked to a lack of adequate water and/or sanitation, occur wherever there is poverty. Infections are widely distributed in all WHO regions, with the greatest numbers occurring in sub-Saharan Africa, the Americas and Asia. More than 100 countries are endemic for STH infections. An estimated 1.5 billion individuals are infected with STHs worldwide and latest estimates indicate that more than 910 million children are in need of treatment for these parasites (Pullan and Brooker, 2012; WHO, 2016; WHO, 2017).

Taken together, soil-transmitted helminthiasis accounts for over 5.18 million disability-adjusted life years worldwide and is associated with anaemia, malnutrition, and impaired physical and cognitive development (WHO, 2017).

Filariasis

Lymphatic filariasis (LF) is a parasitic helminth disease caused by the filarial parasites *Wuchereria bancrofti, Brugia malayi* or *B. timori*. The filarial nematodes that cause this disease are transmitted by blood-feeding insects and produce chronic and long-term infection through suppression of host immunity. Mosquitos in the genera Culex, Anopheles, Mansonia and Aedes transmit the parasites from person to person. LF constitutes a serious public health issue in tropical regions.

As of 2010, more than 120 million people in approximately 80 countries were infected with these mosquito-transmitted filarial nematodes. It was estimated that 140 million people had chronic, disabling disease manifestations, including lymphoedema, hydrocele, and elephantiasis (Dembele et al., 2010). Despite successful elimination programs in some countries, transmission of lymphatic filariasis remains a problem in many regions of the world.

WHO established the Global Programme to Eliminate Lymphatic Filariasis (GPELF) to stop transmission of infection by MDA of anthelminthics. Since the start of GPELF the number of infections has been reduced by 74% globally. The latest estimate was that 51.4 million people are infected (Local Burden of Disease 2019 Neglected Tropical Diseases Collaborators, 2020).

2.1.2. Clinical presentation and diagnosis

Soil Transmitted Helminths (STH)

Intestinal worms produce a wide range of symptoms including intestinal manifestations such as diarrhoea and abdominal pain, general malaise and weakness.

Morbidity is directly related to worm burden: the greater the number of worms in the infected person, the greater the severity of disease. Also, STHs impair the nutritional status and physical and cognitive development of those infected.

Despite considerable progress to control STH over several decades, we are still far from identifying a fully adequate diagnostic test. Conventional microscopy-based methods such as direct Kato–Katz smear or mounts after stool centrifugation/flotation-based concentration techniques have been the mainstay of diagnosis, especially in resource-poor countries where these infections abound.

Filariasis

Disease pathogenesis is linked to host inflammation invoked by the death of the parasite, causing hydrocoele, lymphoedema, and elephantiasis. Most filarial species that infect people coexist in mutualistic symbiosis with Wolbachia bacteria, which are essential for growth, development, and survival of their nematode hosts. These endosymbionts contribute to inflammatory disease pathogenesis.

This disease can be diagnosed through the identification of microfilariae in blood smears.

2.1.3. Management

Increasing concerns about the success of monotherapy strategies and/or single dose administration for deworming campaigns opened the opportunities for evaluation of different treatment strategies.

Therefore, the use of drug combinations with dissimilar modes of action, like albendazole and ivermectin, might represent a more effective strategy against STH, as the recommended single dose monotherapies show limited efficacy, particularly against *T. trichiura*. The concomitant use of ivermectin and albendazole has been

shown to be more effective for treating *T. trichiura* compared to albendazole alone, while keeping an excellent safety profile.

Albendazole is widely used in preventive chemotherapy programs targeting STHs worldwide. Its anthelmintic properties differ slightly compared with other benzimidazole drugs, with albendazole being more active against hookworm. However, the efficacy of albendazole alone against *T. trichiura* is unsatisfactory, and low cure rates of single-dose administration have also been reported for hookworm infection. Other factors, such as suboptimal dissolution of the tablets, may further decrease their therapeutic effects (Belew et al., 2015).

Ivermectin has recently been recognised as a key anti-parasitic medicine approved for the treatment and control of strongyloidiasis and scabies and has been safely used for decades in MDA campaigns for onchocerciasis and lymphatic filariasis (LF). Ivermectin is also capable of killing arthropods – including some mosquito species – which has prompted its use in clinical trials for malaria control.

Ivermectin has been shown to have:

(i) an unusually broad anti-parasitic spectrum,

(ii) a wide therapeutic index and

(iii) a novel mode of action, lacking cross-resistance with any commonly used anti-helminthics (Geary, 2005; Omura and Crump, 2014).

Ivermectin shows a favourable benefit to harm ratio and high efficacy against *S. stercoralis* (WHO, 2017). For STHs, the use of ivermectin in combination with albendazole is more efficacious against *T. trichiura* than albendazole alone. This improved efficacy against *T. trichiura*, which has been confirmed in pilot clinical trials (Knopp et al., 2009), has also been proposed through modelling studies, to make transmission interruption goals, more rapidly achievable than with albendazole monotherapy. For the above reasons, it is considered the most promising tool to shift from morbidity control towards interruption of transmission of STH, as shown by recent mathematical models (Turner et al., 2016).

Beyond STHs, the combination of albendazole and ivermectin is a key component for the much-needed integrated approach against multiple neglected tropical diseases (NTDs). Recent developments in the management of LF, have placed the triple combination of albendazole-ivermectin-diethylcarbamazine as the critical new treatment for the achievement of elimination goals. Similarly, for scabies control, which in many areas overlaps with other NTDs, ivermectin is the drug of choice.

In addition, the concomitant use of ivermectin and albendazole against STH infections has been recently added to the WHO Model List of Essential Medicines paving the way for application in control programs (WHO, 2017; WHO, 2022).

2.2. About the product

Ivermectin is a semisynthetic, anthelmintic agent for oral administration derived from the avermectins, a class of highly active broad-spectrum, anti-parasitic agents isolated from the fermentation products of *Streptomyces avermitilis*. As part of the avermectin class of broad-spectrum antiparasitic agents, ivermectin

has a unique mode of action. Compounds of the class bind selectively and with high affinity to glutamate-gated chloride ion channels which occur in invertebrate nerve and muscle cells. This leads to an increase in the permeability of the cell membrane to chloride ions with hyperpolarisation of the nerve or muscle cell, resulting in paralysis and death of the parasite. Compounds of this class may also interact with other ligand-gated chloride channels, such as those gated by the neurotransmitter gamma-aminobutyric acid (GABA).

Albendazole is an orally administered broad-spectrum anthelmintic. As an anthelmintic, albendazole causes degenerative alterations in the intestinal cells of the worm by binding the colchicine-sensitive site of β-tubulin and inhibiting its polymerisation or assembly into microtubules. Albendazole leads to impaired glucose uptake by the larval and adult stages of the susceptible parasites and depletes their glycogen stores. Albendazole also prevents the formation of spindle fibres needed for cell division, which in turn blocks egg production and development; existing eggs are prevented from hatching. Cell motility, maintenance of cell shape and intracellular transport are also disrupted. At higher concentrations, it disrupts the helminths' metabolic pathways by inhibiting metabolic enzymes that will ultimately lead to less energy produced by the Krebs cycle. Due to diminished adenosine triphosphate (ATP) production, the parasite is immobilised and eventually dies. Some parasites have evolved to have some resistance to albendazole by having a different set of acids comprising β-tubulin, decreasing the binding affinity of albendazole.

2.3. Type of application and aspects on development

The applicant sought a scientific opinion under the EU-M4all procedure (based on Article 58 of Regulation (EC) No 726/2004), submitted in accordance with Article 10(b) of Directive 2001/83/EC, fixed combination application.

New active substance status

Not applicable.

Orphan designation

Not Applicable.

Information on paediatric requirements

Due to the legal basis for this application, no PIP was required.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as orodispersible tablets containing 9 mg/400 mg and 18 mg/400 mg of ivermectin and albendazole, respectively, as active substances.

Other ingredients are: croscarmellose sodium (E468), povidone, mannitol (E421), butylhydroxyanisole (E320), citric acid (E330), mango flavour (consisting of: flavouring preparations, flavouring substance, natural flavouring substance, maltodextrin, gum arabic (E414), triacetin (E1518), propylene glycol (E1520)), sodium stearyl fumarate.

The product is available in PA/alu/PVC/alu blisters and OPA/alu/desiccant/alu blister, as described in section 6.5 of the SmPC.

2.4.2. Active substance - Ivermectin

General information

An ASMF in CTD-format has been provided for the ivermectin active substance (also referred to as drug substance):

- Applicant's Part version: Version QS1-December 2022
- Restricted Part version: Version QS1-December 2022

The chemical name of ivermectin is:

Mixture of:

(2aE,4E,5′*S*,6*S*,6′*R*,7*S*,8E,11*R*,13*R*,15*S*,17a*R*,20*R*,20a*R*,20*S*)-7-[[2,6-dideoxy-4-*O*-(2,6-dideoxy-3-*O*-methyl-α-l-arabinohexopyranosyl)-3-*O*-methyl-α-l-arabino-hexopyranosyl]oxy]-20,20b-dihydroxy-5′,6,8,19-tetramethyl-6′-[(1*S*)-1-methylpropyl]-3′,4′,5′,6,6′,7,10,11,14,15,17a,20,20a,20btetradecahydrospiro[11,15-methano-2*H*,13*H*,17*H*-furo[4,3,2-pq][2,6]benzodioxacyclooctadecene-13,2′-[2*H*]pyran]-17-one (component H2B1a)

and

(2aE,4E,5′S,6S,6′R,7S,8E,11R,13R,15S,17aR,20R,20aR,20bS)-7-[[2,6-dideoxy-4-O-(2,6-dideoxy-3-O-methyl-α-l-arabinohexopyranosyl)-3-O-methyl-α-l-arabino-hexopyranosyl]oxy]-20,20b-dihydroxy-5′,6,8,19-tetramethyl-6′-(1-methylethyl)-3′,4′,5′,6,6′,7,10,11,14,15,17a,20,20a,20btetradecahydrospiro[11,15-methano-2H,13H,17H-furo[4,3,2-pq][2,6]benzodioxacyclooctadecene-13,2′-[2H]pyran]-17-one (component

H2B1b) corresponding to the molecular formulae H_2B_{1a}: $C_{48}H_{74}O_{14}$ and H_2B_{1b}: $C_{47}H_{72}O_{14}$. The components have relative molecular masses of H2B1a: 875 and H2B1b: 861 and the following structures:

Ivermectin is a mixture of compounds H_2B_{1a} and H_2B_{1b}

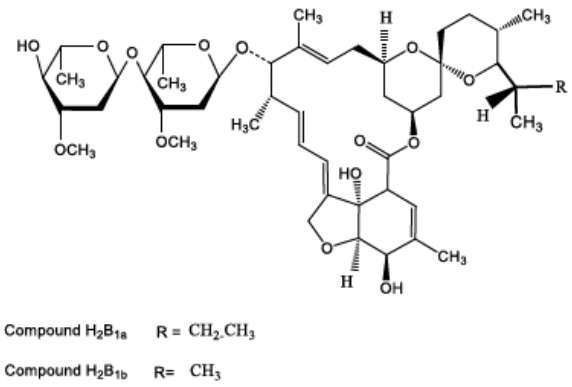


Figure 1: active substance structure

Ivermectin is a semisynthetic, anthelmintic agent for oral administration derived from the avermectins, a class of highly active broad-spectrum, anti-parasitic agents isolated from the fermentation products of *Streptomyces avermitilis*. A monograph for ivermectin is published in the European Pharmacopeia. Ivermectin is a mixture of two compounds identified as H2B1a and H2B1b. In line with the Ph.Eur. monograph, the H2B1a limit is not less than 90%.

It is consistently produced with same crystalline form.

Adequate information is given on physical characteristics of the active substance such as solubility profile, pka, partition coefficient, hygroscopicity, stereochemistry, polymorphism, and potential isomerism. Ivermectin has three pka values of 12.47, 13.17 and 13.80. Ivermectin is slightly hygroscopic, practically insoluble in water, it is considered a BCS Class II compound (low solubility, high permeability).

The chemical structure of ivermectin was elucidated by a combination of IR, mass spectrometry, ^{1}H and ^{13}C NMR and elemental analysis.

The solid-state properties of the active substance were measured by FT-IR, DSC and X-ray diffraction.

Ivermectin is presented as a white to yellowish-white crystalline powder, slightly hygroscopic.

Ivermectin exhibits stereoisomerism due to the presence of 19 and 18 chiral centres for H2B1a and H2B1b respectively. The chiral purity of ivermectin is controlled routinely by chiral specific optical rotation.

Polymorphism has not been observed for ivermectin.

Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

The manufacturing process consists of three steps. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented in the restricted part of the ASMF.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised. Related substances were detected and quantified by a validated HPLC method. The formation and control of non-pharmacopoeial related substances was explained. The qualification threshold stated in guideline EMA/CHMP/CVMP/QWP/199250/2009 corr. is applied, and thus the limits for these impurities are deemed acceptable.

The detailed discussion on origin, fate, and purge of impurities, including mutagenic impurities, residual solvents, and elemental impurities is sufficiently presented.

One reagent used in the purification of crude ivermectin is classified as class 2 mutagen. Its presence is routinely controlled in crude ivermectin intermediate, with a proposed limit which is lower than the acceptable intake. It has been demonstrated that it is adequately purged during the manufacturing process and therefore, the absence of a limit in the active substance specification is acceptable.

Solvents used in the last stages of the manufacturing process are controlled according to ICH limits.

Results from analysis show that any potential inorganic impurities that may be formed or carried over to active substance are within specification and have no impact on the quality of the active substance.

Risk assessment for potentially mutagenic impurities was conducted according to ICH M7. 1 potential class 3 impurity was identified. An Ames test confirmed the impurity is not mutagenic. The information available on the packaging materials is satisfactory.

Specification

The ivermectin specification includes tests for description, identity (IR and HPLC, Ph. Eur.), water content (Karl-Fischer, Ph. Eur.), appearance of solution, (Ph. Eur.), specific optical rotation(Ph. Eur.), sulphated ash (Ph. Eur.), related substances (HPLC, Ph. Eur.), assay (HPLC, Ph. Eur.), and residual solvents (GC); it also includes the test for particle size (laser diffraction).

The specification tests and limits for specified and unspecified impurities comply with the Ph. Eur. monograph, ICH Q3A, and for residual solvents, with ICH Q3C. The specification also includes three non-pharmacopeial impurities for which adequate information has been presented.

The omission of tests for microbial purity is adequately justified.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Non-compendial methods follow the principles described int eh Ph. Eur. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data, on 3 commercial scale batches of the active substance, were provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 8 commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial container according to the ICH guidelines were provided. Preliminary studies were conducted on 4 commercial batches stored for up to 24 months at 30°C / 60% RH and for up to 6 months at 40ºC / 75% RH in a container closure system representative of that intended for the market.

The analytical methods used were the same as for release. No changes to any of the measured parameters were observed under long term and accelerated conditions.

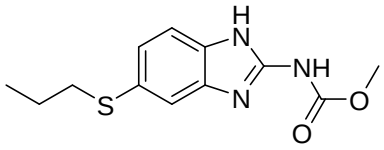
Photostability testing following the ICH guideline Q1B was performed on samples of the active substance which was also exposed to stressed conditions (alkali, acid, oxidant, heat, humidity). Test results from the stressed studies confirm that the HPLC method for determining related substances and assay is stability indicating. Ivermectin is photosensitive and should therefore be stored protected from light.

The stability results indicate that ivermectin manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period with storage conditions.

2.4.3. Active substance - Albendazole

General information

The chemical name of albendazole is 5-(propylthio)-1*H*-benzimidazol-2-yl] carbamicacid corresponding to the molecular formula $C_{12}H_{15}N_3O_2S$. It has a relative molecular mass of 265.3 and the following structure, see Figure 2:



Albendazole

Figure 2: albendazole structure

Albendazole is a white to slightly yellowish powder, practically insoluble in water. It is considered a BCS Class II compound (low solubility, high permeability). Albendazole has a non-chiral molecular structure. Two

polymorphic forms of albendazole are known – the active substance manufacturer routinely produces the same polymorphic form.

Manufacture, characterisation and process controls

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

Specification

The active substance specification includes tests for appearance, identification by IR (Ph. Eur.), appearance of solution (Ph. Eur.), related substances by HPLC (Ph. Eur.), loss on drying (Ph. Eur.), sulphated ash (Ph. Eur.), assay (dried substance) (Ph. Eur.), and residual solvents by GC (GC).The control tests were carried out to comply with the specifications and test methods of the Ph. Eur. monograph. Residual solvents are limited in line with ICH Q3C. The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data on two commercial scale batches of albendazole are provided. The results are within the specifications and consistent from batch to batch. As the active substance is supported by CEP, this is considered acceptable.

Stability

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

2.4.4. Finished medicinal product

Description of the product and pharmaceutical development

The finished product (also referred to as drug product) consists of orodispersible tablets containing ivermectin and albendazole in fixed-dose combinations of 9 mg/400 mg and 18 mg/400 mg.

Ivermectin/Albendazole 9/400 mg tablets are round, white tablets of approximately 16 mm in diameter, debossed with 9/400 in one side.

Ivermectin/Albendazole 18/400 mg tablets are round, white tablets of approximately 16 mm of diameter, debossed with 18/400 in one side.

Although the tablets are differentiated by the debossing, it is preferable to have at least two characteristics differentiating the two strengths. In order to further mitigate the risk of medication errors, the applicant is recommended to enable better differentiation between strengths and update the product information accordingly (REC2). The applicant has proposed to do this by changing the colour of one strength.

The finished product is packed in PA/alu/PVC/alu and OPA/alu/desiccant/alu non-peelable blisters.

The qualitative and quantitative composition of both strengths is almost the same except for the amount of Ivermectin. All excipients used in the formulation are compendial and controlled according to Ph. Eur. standards. Their functions and amounts used are well justified also in terms of safety for the intended paediatric population. No novel excipients or materials of animal origin are used in the finished product.

The compatibility of the active substances with the proposed excipients was demonstrated.

Pharmaceutical development was aimed at developing a fixed dose combination product containing ivermectin and albendazole in an orodispersible tablet formulation.

The development studies followed a risk-based approach, including a clear identification of the target product profile (QTPP) and its critical quality attributes (CQA), in line with the guideline ICH Q8.The QTPP took into consideration the dosing regimens and patient use of existing standalone formulations of ivermectin 3 mg tablets (Stromectol) and albendazole 400 mg chewable tablets (Eskazole).

Palatability (taste and feel) of the formulation for the proposed patient population has been carefully considered during the pharmaceutical development, and it is considered satisfactory.

In the initial submission, no information was provided on the development of the QC dissolution methods for release of both active substances. Furthermore, insufficient justification was provided for the proposed dissolution conditions, the inclusion and levels of surfactants and the discriminatory power of the methods; additionally, and the specifications were considered too wide. CHMP considered this issue to be a major objection.

In response, the applicant explained that the methods are based on pharmacopoeial dissolution methods for marketed mono-component formulations of ivermectin (Stromectol) and albendazole (Eskazole). The initially proposed specification limits were significantly tightened in line with published EU guidance. Discriminatory power was demonstrated. The dissolution methods are considered adequate for quality control purposes and the major objection is resolved.

The manufacturing process development is described in sufficient detail. The applicant identified finished product CQAs and then considered which material attributes and process parameters might affect these. A risk assessment was then carried out to identify unit operations that might affect finished product CQAs. The CPPs and in-process controls (IPCs) were presented and are considered justified. Results from stability testing are provided and indicate that both active substances are stable after the manufacturing process and under storage conditions (40°C/75% RH/6 months, 30°C/65% RH/12 months and 25°C/60% RH/18 months).The batches of the finished product used in the clinical study have the same composition and manufacturing process as future commercial batches. The CHMP recommends amending one of the formulations to allow better distinction between them (REC2).The finished product is supplied in

thermoformed blisters composed by aluminium/aluminium non-peelable blister with and without desiccant (PA/alu/PVC/alu and OPA/alu/desiccant/alu). The chosen container closure system has been selected based on considerations of product stability and the target population (including children aged ⩾5 years). Despite the intended paediatric population, the container closure system does not incorporate child-resistant features, since it is not intended to be taken by children on their own. This also facilitates the use of the product by the elderly. This was considered acceptable.

Manufacture of the product and process controls

The finished product is manufactured at one manufacturing site. Satisfactory GMP documentation has been provided. The manufacturing process of the finished product includes pre-blending, wet granulation drying, and sieving. Subsequent steps consist of pre-blending of ivermectin with the remaining excipients, followed by blending with albendazole granules, tablet compression and packaging. The manufacturing process is considered standard from a pharmaceutical technological point of view. The in-process controls are adequate for this type of manufacturing process.

Satisfactory data on three validation batches per strength have been provided. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form: description (visual), ivermectin and albendazole identification (HPLC, UV, both Ph. Eur.), uniformity of dosage units (Ph. Eur.), assay (Ph. Eur.), dissolution (Ph. Eur.), disintegration (Ph. Eur.), related substances (Ph. Eur.), water content (K.F., Ph. Eur.), residual solvents (ethanol, Ph. Eur.), BHA identification and content (Ph. Eur.) and microbial control (Ph. Eur.).

The proposed specifications at release and shelf-life are in accordance with the criteria set by ICH Q6A and generally include tests relevant to this dosage form.

Sufficient discussion on potential degradation impurities (referring to the results of stressed studies) and residual solvents has been provided. The limits for individual impurities, total impurities and water content were tightened in line with batch data at the request of CHMP. The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results were provided for three commercial scale batches per strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the “Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products” (EMA/409815/2020) and the “Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products” (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data from three commercial batches of each strength of the finished product stored for up to 12 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in both types of primary packaging proposed for marketing. Samples were tested in line with the shelf-life specification.Error! Reference source not found.The analytical procedures used are stability indicating. No significant changes under long term and accelerated storage conditions were observed and the results for all tested parameters complied with the specifications.

Stability data from two commercial bulk batches of each strength of the tablets stored for up to 6 months under long term conditions (25ºC / 60% RH) in the proposed container were provided. Samples were tested in line with the shelf-life specification. No significant changes were observed and the results for all tested parameters complied with the specifications. Based on the available stability data, the proposed bulk holding time in the proposed container is acceptable.

In addition, one batch of each strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Results indicate that the finished product is photostable.

Based on available stability data, the proposed shelf-life of 24 months without special storage conditions, as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.4.5. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. One major objection pertaining the development of the dissolution

methods for both active substances, justification of conditions, demonstration of discriminatory power and initially proposed specifications was adequately addressed during the procedure. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

At the time of the CHMP opinion, there were two minor unresolved quality issues having no impact on the benefit/risk ratio of the product, one pertains the provision of the updated CEP for albendazole and the other pertains to a change in formulation to enable better differentiation between strengths. These points are put forward and agreed as recommendations for future quality development.

2.4.6. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.7. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. The applicant is recommended to submit the revised CEP (CEP 2005-010-Rev 05) and update the dossier accordingly.
2. In order to further mitigate the risk of medication errors, the applicant is recommended to differentiate the two strengths by, for example, changing the colour/formulation of at least one of the strengths. The Product Information should be updated accordingly.

2.5. Non-clinical aspects

2.5.1. Introduction

This new product is developed primarily as a tool to fight the STH, a complex neglected parasitic burden consisting of single or mixed infections with hookworms *A. duodenale* and *N. americanus*, roundworms *A. lumbricoides*, whipworms *T. trichiura* and *S. stercoralis*.

Belonging to the WHO Model List of Essential Medicines, albendazole and ivermectin have both been used extensively as separate drugs and also in co-administration in adult and paediatric populations and their efficacy and safety are well established. A thorough bibliographic search was performed to support the dossier with concrete literature evidence on non-clinical aspects related to the active ingredients.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

Ivermectin's mechanism of action against nematodes involves the reduced resistance of muscle membranes and the opening of chlorine channels controlled by glutamate and GABA. Ivermectin targets the pharyngeal pump and somatic muscles in nematodes resulting in paralysis and death. On the other hand, albendazole acts through disruption of microtubule function by binding to β-tubulin in nematodes thus inhibiting the formation the structure of microtubules inside the cells resulting in the feeding incapability of nematodes as well as the inhibition of the production of eggs. Primary pharmacodynamics revealed that the efficacy of both drugs against L3 A. simplex was high *in-vitro* and *in-vivo* against the larvae in different organs of guinea pigs. Ivermectin also showed excellent activity against *A. ceylanicum* adults and L3 stages and no activity against adult forms of *H. polygyrus* and larval stages of *T. muris* was observed. No in-vitro efficacy of albendazole was reported for *T. muris* (L1), *A. ceylanicum (L3)*, *N. americanus* (L3), *H. polygyrus* (L3 and adult) and *S. ratti* (L3). Efficacy of albendazole was seen in adult forms of *T. muris* and *N. americanus*.

2.5.2.2. Secondary pharmacodynamic studies

Both molecules also have various secondary pharmacological actions against other forms of parasites (e.g., Arthropoda for ivermectin or plathelminths for albendazole). Both of them are also under investigation for potential other actions including these against various types of cancer (albendazole) or virucidal (ivermectin).

2.5.2.3. Safety pharmacology programme

Both, albendazole and ivermectin have been used extensively as separate drugs in adult and paediatric populations and their efficacy and safety are well established. Both, albendazole and ivermectin belong to the WHO Model List of Essential Medicines (WHO 2021).

Safety pharmacology studies revealed that, ivermectin does not normally penetrate the CNS of mammals, and when it does happen, this can result in neurotoxicity. P-gp is considered a protective main factor whose presence prevents the penetration of ivermectin through the blood brain barrier. Various studies conducted on avermectins showed that these drugs induce nephrotoxicity in many animals like mice, bats, rabbits, and rats. Nephrotoxicity is the result of the oxidative damage which has been observed in histopathological changes like interstitial nephritis, glomerular damage, interstitial infiltration areas of round cells, and tubular necrosis as well as elevated levels of serum creatinine, urea, and the uric acid in the blood. On the other hand, albendazole is the only nematocidal drug capable of crossing the blood-brain barrier, therefore suitable for the management of neuroangiostrongyliasis. The potential neurotoxic and nephrotoxic effects of ivermectin are adequately addressed in the SmPC.

2.5.2.4. Pharmacodynamic drug interactions

In-vivo studies demonstrate that ivermectin can enhance the pharmacological actions of diazepam.

2.5.2.5. Resistance data

Resistance to ivermectin

The increasing selection pressure on gastrointestinal nematodes due to the high frequency of the usage of macrocyclic lactones is thought to contribute the development of resistance to these compounds mainly in veterinary medicine. Changes on the GluCl structure and an increased expression of different proteins involved in drug efflux (P-gp) have been postulated as the main mechanism of resistance to the macrocyclic lactones in nematodes. It has been shown that *H. contortus* resistant to ivermectin possess an increased level of P-gp expression and that the co-application of verapamil (an MDR-reversing agent) increased efficacy of ivermectin and moxidectin against resistant strains of *H. contortus*. In addition to a role in ivermectin resistance, a subset of the amphid mutants is resistant to the non-related benzimidazole class of anthelmintics, raising the potential link to a multi-drug resistance mechanism.

Resistance to albendazole

The best understood type of resistance to anthelmintics is the resistance to benzimidazoles, including albendazole. The number of genes involved in resistance and their mode of inheritance (dominant or recessive) are additional factors with an important influence on the rate at which the resistance spreads. Polymorphism in β-tubulin isotype 1 seems to be most important for the resistance to benzimidazoles in *H. contortus*.

2.5.3. Pharmacokinetics

Ivermectin is generally well absorbed after oral or parenteral application. In a mice study, Cmax was 80-100 ng/ml after oral administration between 6 and 12 h. Ivermectin is also well distributed post absorption. Albendazole is poorly absorbed unless administered with high-fat meals. The absorption rate of oral albendazole in mice and rats is 20-30% compared to 1-5% from the human intestine.

The highest residue levels of ivermectin in body tissues in fat, liver, kidney and muscle were observed in rats post-oral administration. In a neonatal rat study, the transfer of drugs via milk is observed. In monkeys, the concentrations of ivermectin in plasma were proportional to the administered dose, but this proportionality was not linear. Albendazole sulfoxide is widely distributed in the body and is 70% bound to plasma proteins.

Metabolism of ivermectin forms a smaller portion of polar metabolites with antiparasitic activity, but more than 70% of the drug remains unchanged. Two major polar metabolites (2-11%) were formed. One metabolite has been identified as the C_{24}-methyl alcohol of the parent compound, and a smaller quantity was identified as the monosaccharide of the C_{24}-alcohol. These two metabolites represented the major fraction of metabolites more polar than the respective parent compound. Similar pathways for albendazole

metabolisation have been observed in rats, mice, humans, cattle and sheep. Albendazole biotransformation is characterised by a first-pass metabolism that results in the rapid oxidation of sulfide groups, the formation of albendazole sulfoxide and their subsequent oxidation into albendazole sulfone. The cleavage of the carbamate group follows this into 2-amino-sulfone. Albendazole sulfoxide is considered the active metabolite responsible for the therapeutic activity of albendazole. Plasma levels of the initially oxidised metabolites (the sulfoxide and sulfone) in all species are much higher than those of the parent drug.

Ivermectin is mainly excreted via urine and faeces. In the rat study, 83% (males) and 91.7% (females) of the administered drug were eliminated five days after administration. Albendazole is mainly excreted via urine and faeces. In rats, albendazole sulfone and sulfoxide metabolites resulted in 73 and 42.7% urinary secretion of the administered doses, respectively.

In humans, it is known that administration of albendazole with a fatty meal markedly increases the levels of its active metabolite. Albendazole should be taken with a meal.

Ivermectin is a substrate of P450 3A enzymes, substrate and inhibitor of P-gp and multidrug resistance protein (MRP), and an inhibitor of Breast Cancer Resistance Protein (BCRP) transporter. Therefore, complex interactions could be expected with this molecule. Ivermectin is extensively metabolised by cytochrome P450 enzymes (P450s, CYP) both in vivo and in vitro. Numerous *in vitro* testings showed that ivermectin was demonstrated as a weak, or medium inhibitor of the reactions catalysed by P450 enzymes. On the level of P450 enzymes, drug-drug interaction might be provoked by co-administration with drugs which are inhibitors of P450 3A enzymes, as these may impede the metabolism and subsequent excretion of ivermectin. Alternatively, potent inducers of P450 3A activity might affect ivermectin systemic exposure lowering its therapeutic effect. On the level of drug transport, by inhibiting P-gp or MRPs, unexpected high plasma concentration and potential toxic effects of ivermectin might be elicited.

Phenytoin, carbamazepine, and phenobarbital appear to induce the oxidative metabolism of albendazole by the cytochrome P450 isoenzyme CYP3A to roughly the same extent, resulting in significantly reduced levels of albendazole sulfoxide, an active metabolite having the similar activity to albendazole. Phenytoin, and to a lesser extent carbamazepine, may also induce the metabolism of albendazole sulfone by CYP2C. Mebendazole is similarly affected. Cimetidine raises serum mebendazole levels, and prolongs the half-life of albendazole sulfoxide, which may increase the effectiveness of these anthelmintics against systemic infection. This interaction is likely caused by the enzyme inhibitory actions of cimetidine, which result in a reduction in the metabolism of albendazole and mebendazole. Conversely, cimetidine may also reduce albendazole absorption and minimise inter-patient variability by reducing gastric acidity, but the reduction in absorption appears to be outweighed by the enzyme- inhibitory effects. Dexamethasone co-administration can raise levels of albendazole sulfoxide by 50%, which might increase its efficacy in systemic worm infections. Dexamethasone is an inducer of the cytochrome P450 isoenzyme CYP3A4 and might therefore be expected to reduce levels of albendazole, so the finding is unexpected. Dexamethasone appears not to alter the rate of formation of albendazole sulfoxide but decreases its elimination.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

No single dose toxicity studies were performed by the applicant. A thorough bibliographic search was provided to support the acute toxicity assessment with concrete literature evidence on non-clinical safety aspects related to the active ingredients.

Ivermectin and albendazole are intended to be orally administered as a fixed dose combination (FDC) containing ivermectin (two strengths: 9 mg for 15-45 kg body weight or 18 mg for >45 kg body weight) and albendazole (400 mg in both weight groups), which would allow the delivery of doses of ivermectin between 200 and 600 µg/kg and doses of albendazole between 8.8 and 26.7 mg/Kg, depending on patient's body weight. The proposed posology consists of one single oral dose administration. In certain cases, the dose can be administered for 3 consecutive days, in line with the SmPC/Posology. Therefore, data from acute toxicity studies is considered relevant to characterise of the safety profile of both active substances in the intended target population/therapeutic indication.

Ivermectin

A set of single dose studies conducted in mice, rats, dogs, and rhesus monkeys were provided by the applicant to characterise the safety profile of ivermectin administered by the oral route. Juvenile animals have also been included in rat and rhesus monkey acute toxicity assessment.

Data from a dedicated study addressing the acute toxicological potential of the individual components of ivermectin (H2B1a, H2B1b, tetrahydroavermectin-B1) in mice has been provided. No significant differences in acute toxicity were observed for the components H2B1a, H2B1b; however, the most abundant potential impurity (Tetrahydroavermectin-B1), was of significantly lower acute oral toxicity, based on the corresponding LD_{50} values.

The main clinical signs of acute toxicity reported in mice, rats (in both strains of adult Sprague-Dawley and Charles River-CD rats), and dogs were central nervous system (CNS) findings such as ataxia, tremors, bradypnoea, decreased activity and loss of righting, paralysis and death. The most sensitive indicator of toxicity in immature rhesus monkey was emesis, pupil dilation and/or decreased constriction, and decreased levels of activity or slight to moderate sedation. The central nervous system toxicity adverse effects were observed within 1 h and up to 7 days following a single oral dose of ivermectin depending on the test species and the applied dose. No toxicokinetics data was provided to calculate the corresponding safety margins in the single dose toxicity studies.

With respect to the acute toxicological profile of ivermectin in neonatal rats, a higher sensitivity was noted for neonatal rats (LD_{50}=2.3 mg/kg) when compared with the LD_{50} values reported for adult animals (LD_{50}=42.8-52.8 mg/kg). The increased toxicity of ivermectin in neonatal rats is likely due to a combination of increased plasma levels resulting from exposure via maternal milk and the increased permeability of the blood-brain barrier during the early postnatal period in this species.

The acute toxicity of ivermectin has also been assessed for other administration routes. No toxicological effects (except local mucosal irritations) were noted in a single inhalation toxicity study conducted in rats. Moreover, only a slight local irritation has been evidenced in the acute ocular toxicity in rabbits. However, signs of systemic toxicity, mainly characterised by CNS symptoms, were noted in the acute percutaneous toxicity assessment in rats and rabbits, and in acute subcutaneous toxicity in beagle dogs.

Albendazole

A low toxicity after acute oral administration was described for albendazole. The available acute oral LD_{50} for mice, rat, hamster, guinea pig and rabbits, showed values between 500 to 10000 mg/kg. Findings in dead rats included urinary staining of abdomen, bloody discharge around nose, red tears (chromodacryorrhoea), and intestinal haemorrhage.

Ivermectin/albendazole

With respect to combination ivermectin/albendazole, no additional studies were conducted in line with the *Guideline on the non-clinical development of fixed combinations of medicinal products* (EMEA/CHMP/SWP/258498/2005), which is acceptable as both albendazole and ivermectin have been used extensively as separate drugs and also in co-administration in adult and paediatric populations and their efficacy and safety has been well established (WHO Model List of Essential Medicines).

2.5.4.2. Repeat dose toxicity

No repeat dose toxicity studies were performed by the applicant.

A thorough bibliographic search was provided to support the acute toxicity assessment with concrete literature evidence on non-clinical safety aspects related to the active ingredients.

The safety profile based on sub-chronic and chronic repeat dose studies has also been established for ivermectin and albendazole as individual active substances:

Ivermectin

Repeat dose toxicity studies up to 14 weeks duration were conducted in rats and dogs. Moreover, 14 days duration studies were conducted in neonatal and immature rhesus monkeys.

The reported findings in rats consisted in increased spleen and reactive hyperplasia of bone marrow (from the intermediate dose tested, 0.8 mg/kg). Central nervous system toxicity was evidenced in dogs dosed up to 14-weeks: mydriasis (at 0.5 mg/Kg and 1.0 mg/Kg over a treatment period of 35 days and 14 weeks, respectively), ataxia, anorexia/dehydration/weight loss, whole-body tremors, and dead (for the highest dose tested in all studies, 2 mg/Kg). No TK data was provided to establish the corresponding safety margins.

Repeat dose toxicity studies 14-days duration were conducted in neonatal rhesus monkeys (7 to 13 days old) and in immature rhesus monkeys (13-21 months old at initiation) to assess the potential significance of neonatal and developmental exposure to ivermectin. Neonatal monkeys were examined for mydriasis,

pupillary light response and adverse reactions. No safety concerns were identified in animals dosed up to 0.1 mg/kg. In addition, the results of the examinations (physical, ophthalmic, haematologic, serum biochemical examination, body weight and necropsy) indicated no treatment-related effects in immature monkeys dosed up to 1.2 mg/kg. These dose levels were chosen to provide a 6-fold safety margin relative to the human clinical dose.

From a non-clinical point of view, the rational to support the ivermectin dose in the FDC for children ≥6 years with a body weight of 15 kg (600 μg/Kg) is based on the repeat dose toxicity study, up to 16 days duration, conducted in rhesus monkeys. No toxicokinetics data was provided in order to establish the corresponding systemic exposure, allowing the calculation of safety margins. Therefore, the applicant discussed safety margins in terms of dose in animal models *vs* planned clinical regime. According to data provided, no treatment-related effects were identified in immature rhesus monkeys (13-21 months old at study initiation) orally dosed with the highest dose tested, 1.2 mg/Kg (HED = 387 μg/Kg), which provides a 2-fold safety margin to the human clinical dose 600 μg/Kg. The applicant also mentioned a set of additional ivermectin doses tested in an acute and repeat dose toxicity studies, ranging from 0.2 to 24 mg/Kg. Based on very scarce data concerning this study design and the corresponding safety assessment, emesis was noted at 2 mg/Kg and adverse effects were observed at 12 and 24 mg/Kg. No toxicological concerns were observed at doses up to 8 mg/Kg [HED: 2580 μg/Kg; a 13-fold dose-based safety margin for the dose under discussion (600 μg/Kg)]. The applicant was asked to provide a thorough description of this study design and the corresponding assessment of the data. Within the scope of the response to this question, the applicant provided an updated Non-clinical Overview. With respect to repeat dose studies, a thorough information focused on PK data has been added for the study conducted in rhesus monkeys dosed up to 1.2 mg/Kg for 7 days.

Albendazole

The toxicological profile of albendazole has also been characterised in a set of repeat dose toxicity studies 3 months duration conducted in mice, and 6-month duration in rats and dogs.

Haematological effects (such as reduced haemoglobin, haematocrit, erythrocyte levels, and decreased leucocyte counts) and liver findings were the main toxicological effects noted in mice, rats and dogs.

In rat, histopathological examination revealed hypoplasia in testes, bone marrow, spleen and lymph nodes at the highest dose tested in the 4-weeks study. Moreover, liver findings (centrilobular cloudy swelling, vacuolation or necrosis) and hypocellularity of lymphoid tissues (such as bone marrow, spleen and thymus) suggestive of atrophy were observed in the rat chronic toxicity assessment. The target organs of toxicity identified in the repeat dose toxicity studies conducted in dogs were the testes and uterus (decreased absolute and relative weights in all doses tested), and the liver and kidney (slight increases in relative weights in the highest dose tested).

No toxicokinetics assessment was included in repeat dose toxicity studies allowing the calculation of safety margins. However, an additional request of toxicokinetics data/safety margins assessment will not be deemed necessary as albendazole and ivermectin have been extensively used as separate drugs and also in

co-administration and their safety profile has been well established in adult and paediatric populations. Moreover, the ivermectin/albendazole FDC has been developed for one single oral dose administration (or at least, to be administered for 3 consecutive days in certain cases), in line with the SmPC/Posology.

2.5.4.3. Genotoxicity

Ivermectin

Ivermectin and each component of ivermectin were tested in the Ames test. Tests were done with and without rat liver metabolic activation systems. None of the agents studied produced any noteworthy increase in revertants to histidine prototrophy (FAO/WHO 1990, FAO/WHO 1992).

Mouse lymphoma tests revealed that ivermectin was detoxified in the presence of rat liver S-9 fraction. The mutagenic assays were done by exposing cells to ivermectin at dose levels of 40, 60, and 80 µg/ml, with and without S-9. The second assay was done with 20, 40 and 60 µg/ml in the presence of S-9 only. The dose levels of ivermectin without S9 activation, were 5, 10, and 20 µg/ml. The results of both tests were negative when compared with appropriate negative controls. The positive control, 3-methylcholanthrene with S-9 produced significant increases in mutation frequency (FAO/WHO 1990, FAO/WHO 1992).

Effects of ivermectin on unscheduled DNA synthesis (UDS) were studied in IMR-90 normal human embryonic lung fibroblasts in the presence and absence of rat liver microsomal activation systems. The drug concentration ranged from 10 to 1000 µg/ml. Ivermectin did not produce any significant increase in background thymidine incorporation. In contrast it produced an unexplained decrease at 10, 100, 300, and 1000 µg/ml but not at 30 µg/ml. The positive controls, methylmethane sulfonate and aflatoxin B-1, both produced significant increases in UDS (FAO/WHO 1990, FAO/WHO 1992).

Albendazole

Albendazole showed a negative performance in *S. Typhimurium* mutation testing on strains TA1530, TA1532, TA1534, TA1537, TA98, TA100, LT2 and on *Salmonella typhimurium* G46. It also did not show genotoxic properties in the test of metaphase analysis cells in Chinese hamster ovarian cells (CHO) or at cell *in vitro* transformation of mouse BALB/3T3. However, albendazole was positive in micronucleus test *in vivo* on mouse bone marrow cells. This may indicate *in vivo* mutagenic properties of albendazole; however, such a claim was not confirmed in other studies (EMA/CVMP 2004).

2.5.4.4. Carcinogenicity

No new studies were conducted by the applicant. This is acceptable. Available information is bibliographical and builds on existing evidence. The negative mutagenicity studies on ivermectin and the negative carcinogenicity studies with abamectin indicate that ivermectin has no carcinogenic potential. Also, no carcinogenic potential was identified in different carcinogenicity studies with albendazole.

Ivermectin

Carcinogenicity studies were performed with abamectin, another mixture of natural avermectins, therefore structurally very close to ivermectin. Abamectin was fed for 94 weeks to Cr1: CD-1 mice at doses of 2, 4 or 8 mg/kg body weight per day. Each treatment group (n=3) and two controls included 74 mice of both sexes. Tremor, that was attributed to the test substance was a common finding in females of all treated groups. Seven females treated with 8 mg/kg and 3 females treated with 4 mg/kg, have died already after single administration of the drug through the feed. Increased level of mortality was noted in mice treated with the highest dose, but only in male animals (the cause of deaths was due to amyloidosis and lymphoma). Treatment has stopped after 90 weeks, when survival rate of the animals in this group declined to 40%. Other mice were treated until the end, (94 weeks) and then sacrificed. Mice treated with the highest dose of abamectin were reported for reduction in body weights (7% and 21% males/ females respectively), while females only had an increase in feed intake and decrease in feed conversion (20%). Changes in haematological and biochemical parameters were not recorded and the same was with ophthalmic disorders, changes in organ weights and with gross or histopathological changes. Abamectin was not found carcinogenic molecule in this study (FAO/WHO 1990).

Carcinogenic potential of abamectin was also studied in Cr1: CD (SD) BR rats. Abamectin was administered in feed to male and female rats for 105 weeks at doses of 0.75, 1.5 or 2mg/kg/day. This study also showed the absence of significant pathological changes or alterations that might have suggested for carcinogenic effects of abamectin (FAO/WHO 1990).

Ivermectin differs from abamectin in that it lacks a double bond in one of the lactone rings at C 22-C23. Several studies, but notably subchronic (13-18 weeks) studies in dogs, teratogenicity studies in mice, rabbits and rats, and multigeneration studies in rats, suggest that abamectin and ivermectin have a similar order of toxicity. In fact, abamectin appears to be marginally more toxic than ivermectin in all these studies. Consequently, the negative mutagenicity studies on ivermectin and the negative carcinogenicity studies with abamectin may indicate that ivermectin has no carcinogenic potential. The main signs of toxicity in the 94-week study in mice with abamectin were tremors; the NOEL was 4 mg/kg b.w./day. In the 105-week study in rats with abamectin, tremors were again the main treatment-related effect. The NOEL was 1.5 mg/kg b.w./day (FAO/WHO 1992).

Albendazole

Groups of 100 male and 100 female Charles River CD-1 mice were fed diets containing albendazole for 25 months. Drug levels were adjusted to provide daily doses of 0, 25, 100 or 400 mg/kg b.w. Additional groups of 25 males and 25 females were given control and high dose treatments and used for haematology measurements. There were no toxic signs or effects on food intake and body weight. Haematology was studied after 3, 6, 12, 18 and 24 months in the main groups and monthly in the ancillary groups. A complete gross post-mortem examination was carried out on all mice. Full histopathology was undertaken on control and high dose mice. In intermediate groups, 6 major organs and grossly abnormal tissues were examined routinely. The NOEL in this study was set was 25 mg/kg b.w./day (FAO/WHO 1987).

Carcinogenic properties of albendazole were also tested in rats. Groups of 100 male and 100 female Sprague Dawley CD rats were fed diets containing albendazole. The initial groups (F0) received doses of 0, 1, 2.5 or 5 mg/kg b.w./d for 60 days and then through mating, gestation and post-natal periods. Similar size groups of

F1 animals received 0, 3.5, 7 or 20 mg/kg b.w./d for 28 months. Additional groups of 25 males and 25 females were given control and high dose treatments and used for haematology measurements. An interim sacrifice of 10 males and females per group was made after 12 months. A complete gross post-mortem examination was carried out on all rats. Full histopathology was undertaken on control and high dose rats. The NOEL for development of endometrial/cervical tumours and skin histiocytic sarcomas was set on 7 mg/kg/d.

2.5.4.5. Reproductive and developmental toxicity

No new reproductive and developmental studies were conducted by the applicant, which is acceptable based on the literature search performed to support the assessment of reproductive and developmental safety aspects related to the individual active ingredients.

Ivermectin

The assessment of potential adverse effects on fertility and early embryofetal development is based on a combined study, in which animals were dosed prior to mating until 20 days post-partum. No fertility and early embryofetal development adverse findings were identified for ivermectin

Potential adverse effects on embryo-foetal development have been addressed in mice (DG6-DG15), in rats (DG6-DG17) and rabbits (DG6-DG18). In addition, a set of multigeneration studies and combined embryo-foetal development and pre- and postnatal development studies in rats were also provided within the scope of the embryo-foetal toxicological assessment.

In studies conducted in mice, rats and rabbits, teratogenicity was evidenced by an increased incidence of cleft palate in a number of pups whose mothers received higher ivermectin doses associated with maternal toxicity.

Data from a fertility and early embryofetal development, in which animals were dosed prior to mating until 20 days post-partum has been provided. Safety concerns were noted in the postnatal developmental assessment, consisting in increased mortality among pups in the highest dose treated group, and a slightly accelerated developmental concerning the eye opening, ear opening, incisor eruption and hair growth. Moreover, a set of multigeneration studies and combined embryo-foetal development and pre- and postnatal development studies in rats were also provided within the scope of embryo-fetal toxicological assessment. Concerning the prenatal development effects, a significant increase in the average gestation length has been noted among females rats in the high-dose treated group. During the lactation period, high offspring mortality occurred up to day 10 post-partum. The most common signs of toxicity in pups that died was lethargy, hypothermia an absence of milk in the stomach. With respect to postnatal development, a significant delay in the appearance of the righting reflex and the auditory startle reflex, and a significant earlier incisor eruption have been reported. Moreover, concerning the F1 sexual maturity, a significantly delayed vaginal opening and a treatment-related delay in testes descent were observed.

Albendazole

Fertility and Early Embryonic Development was assessment in Long Evans rats (for 3 successive generations, starting on the 64th day before the initial mating) and Sprague Dawley rats (from 60 days prior to mating to the end of the breeding period). No adverse findings were identified on fertility and early development endpoints. The reduced testicular size, together with focal testicular hypoplasia had no impact on fertility endpoints. Postnatal growth, physical and behavioural development were unremarkable.

Potential adverse effects on embryo-foetal development have been addressed in studies conducted in rat (DG5-DG15) and rabbit (DG7-DG19). Embryotoxic effects consisting in decreased foetal weight, reduction in implants and increased resorptions were noted in both rats and rabbits. An increased frequency of skeletal abnormalities has also been observed. The major malformations were craniofacial and bone defects: retarded skeletal ossification and increased incidences of micromelia and microfetalis (which included shortened long bones in fore and hind limbs) were reported in the rat, and ectrodactyly in the rabbit study. In additional studies addressing the teratogenic potential of the albendazole active metabolite in rats it was established that albendazole sulfoxide exerted similar teratogenic effects to albendazole.

The assessment of potential effects on peri- and postnatal development, including maternal function, has been supported by the combination studies provided within the scope of the Fertility and Early Embryonic Development conducted in Long Evans rats (for 3 successive generations, from the 64th day before the initial mating). According to study results, pup survival and/or weight gain were depressed during the lactation period.

The non-clinical reproductive and developmental safety findings for ivermectin and albendazole have been summarised in the SmPC/5.3. The corresponding risk mitigation measures have been mentioned in the SmPC/4.6 (and SmPC/4.3).

With respect to studies in which the offspring (juvenile animals) are dosed and/or further evaluated, no new studies were performed by the applicant, which is acceptable based on the provided literature search.

Ivermectin

Studies including juvenile animals have been previously mentioned within the scope of dedicated single and repeat dose toxicity studies.

No toxicological concerns were identified in neonatal (7 to 13 days old) nor in immature rhesus monkeys (13-21 months old at study initiation) orally dosed with ivermectin up to 14-days (*see*: Repeat dose toxicity section).

The assessment of potential acute toxicological effects of ivermectin was also addressed in neonatal rats. A higher sensitivity of neonatal rats was noted when the reported LD_{50}~~DL_{50}~~ values were compared with those reported for adult animals (LD_{50}~~DL_{50}~~=2.3 mg/kg *vs* LD_{50}~~DL_{50}~~=42.8-52.8 mg/kg). The increased toxicity of ivermectin in neonatal rats is likely due to a combination of excessive plasma levels resulting from exposure via maternal milk and the increased permeability of the blood-brain barrier during the early postnatal period in this species (FAO/WHO 1990) (*see*: Single dose toxicity section).

Albendazole

No corresponding juvenile animal study with albendazole was found in the literature.

2.5.4.1. Toxicokinetic data

No toxicokinetics assessment was included in the set of toxicological studies allowing the calculation of safety margins. However, an additional request of toxicokinetics data/safety margins assessment will not be deemed necessary as albendazole and ivermectin have been extensively used as separate drugs and also in co-administration and their safety profile has been well established in adult and paediatric populations. Moreover, the ivermectin/albendazole FDC has been developed for one single oral dose administration (or at least, to be administered for 3 consecutive days in certain cases), in line with the SmPC/Posology.

2.5.4.2. Other toxicity studies

Ivermectin can inhibit the cell viability, induce DNA damage and enhance apoptosis. Apart from the induction of cytotoxicity, ivermectin reduced the phagocytic capacity and significantly increased the mRNA expression levels of proinflammatory cytokines IL-6, IL-1 β and TNF-α. Intracellular biochemical assay indicated that activation of the NF-κB signalling pathway, overproduction of reactive oxygen species (ROS), release of cytochrome C, DNA double strand damage. These results published by Zhang et al. 2022, indicate that ivermectin can induce immunotoxicity through induction of immune dysfunction and cytotoxicity.

Among the avermectins, ivermectin and abamectin are investigated as endocrine disruptors. Ivermectin was also shown to suppress the sexual behaviour in oestradiol treated female rats at therapeutic dose (0.2 mg/kg). In another study after the male albino rats were exposed to sublethal dose of abamectin, there were significant alterations in sex hormones as well as the thyroid hormones were observed. There were reports on disruption of sexual hormones in domestic animals (cattle) after continuous ivermectin administration from birth to puberty. In humans, abamectin is placed under the category which is more likely to cause endocrine disruption (Salman et al., 2022).

Albendazole is not proven as sensitizing agent, neither an acute skin nor eye irritant. Groups of rabbits had 100 mg albendazole powder instilled into the conjunctival sac or 500 mg albendazole applied, under occlusion, to abraded and non-abraded skin. There were no primary irritant effects at any site. However, the main albendazole metabolite albendazole sulfoxide showed to be a potential skin sensitiser in a guinea-pig maximisation test (FAO/WHO 1987, Dayan 2003, EMA/CVMP 2004, PuBChem 2022).

Specific studies of phototoxicity have not been presented nor discussed. However, it is likely that any problem of this nature would have emerged in the pivotal studies already conducted and existing clinical experience.

Due to findings observed in repeat-dose toxicity studies, the potential immunotoxicity for albendazole is supported by haematological changes, alterations in immune system organ weights and/or histology, effects on the liver or kidney. However, as albendazole has a long history of use, no further non-clinical data about immunotoxicity have to be submitted, and potential immunotoxicity is acknowledged.

2.5.5. Ecotoxicity/environmental risk assessment

A bibliographic Environmental Risk Assessment (ERA) based on the scientific literature evidence related to both active ingredients were performed to support this application. As per EMA/CHMP/SWP/44609/2010 rev1, 2016 "Questions and answers on *Guidelines on the environmental risk assessment of medicinal products for human use",* in the case of fixed combination medicinal products, the ERA is performed separately for each compound within the product. Therefore, the environmental risk assessment of albendazole and ivermectin have been evaluated separately.

Relevant endpoints, methods used, and results obtained for albendazole were discussed and study results are summarised in Table 1.

Table 1: Summary of main results – albendazole

Substance (INN/Invented Name): Albendazole					
CAS-number (if available):					
PBT screening		Result			Conclusion
Bioaccumulation potential- log K_{ow}	OECD107	3.83			Potential PBT: Y
PBT-assessment					
Parameter	Result relevant for conclusion				Conclusion
Toxicity	OECD 202 *(Dapnhia magna*) (*Danio rerio)*	NOEC = 48 µg/L NOEC= 0.022 mg/L			Potentially
PBT-statement:	The compound is not considered to be either P or B.				
Phase I					
Calculation	Value			Unit	Conclusion
$PEC_{sw, default}$	0.016			µg/L	≥ 0.01 threshold: Y
Other concerns	Antiparasitics MoA/ toxicity profile				Y
Phase II Physical-chemical properties and fate					
Study type	Test protocol	Results			Remarks
Adsorption-Desorption 5 Sediments 5 Soils	OECD 106	$K_{oc, soil1}$= 2547 L/kg_{oc} $K_{oc, soil2}$=1757 /kg_{oc} $K_{oc, soil3}$=3561 L/kg_{oc} $K_{oc, soil4}$=2411 L/kg_{oc} $K_{oc, soil5}$= 1553 L/kg_{oc} $K_{oc, sediment\ 1}$ = 3177 L/kg_{oc} $K_{oc, sediment\ 2}$ = 3934 L/kg_{oc} $K_{oc, sediment\ 3}$ = 1402 L/kg_{oc} $K_{oc, sediment\ 4}$= 8399 L/kg_{oc} $K_{oc, sediment\ 5}$= 5305 L/kg_{oc}			Koc < the trigger value of 10000 L/kg
Phase IIa Effect studies					
Study type	Test protocol	Result	Value	Unit	Remarks
Algae, Growth Inhibition Test/ *Raphidocelis subcapitata*	OECD 201	EC_{50}	0.0022	µg/L	growth rate

Daphnia magna, Reproduction Test	OECD 202	EC_{50} (48h) EC_{50} (72h) EC_{50} (96h)	67.9 62.9 42.8	µg/L	48h immobilisation Acute toxicity
Fish, Early Life Stage Toxicity Test *Danio rerio*	Not relevant OECD GL	NOEC EC50	0.22 x 10^{-4} 0.42 x 10^{-3}	µg/L	24hpf, 48hpf,144 hpf, mortality, hatching and deformation. 144 hpf Acute toxicity

**Time for recording of embryos has been extended to 144 hpf and sublethal endpoints have been included. Round-bottom 96-well plates were used, containing 250 µL water (instead of 24-well plates with 2.5–5 ml filling capacity). The authors have performed numerous tests and confirmed no difference in development of control embryos up to 144 hpf if grown in 250 µl water.*

Albendazole

The applicant performed an extended scientific literature search to identify albendazole available environmental fate and ecotoxicological data, published in the scientific literature, to perform an ERA phase I and II evaluation according to ERA guidelines.

Phase I

A phase I trial is required to screen albendazole consumption data and experimentally determine its Log Kow value.

The n-octanol/water partition coefficient was determined experimentally following the flask method (OECD 107) and an experimental Log Kow value of 3.83 has been estimated. The result was below 4.5, the guideline Phase I action limit for Persistence, Bioaccumulation, and Toxicity (PBT) assessment. Therefore, no further PBT assessment was required, according to EMA´s Guideline EMEA/CHMP/SWP/4447/00 corr 2, 2006.

The PECSurfacewater (PECsw), determined based on the default Fpen, was 0.016 µg/L above the action limit of 0.01 µg/L defined by EMA, which indicates that a Phase II, environmental fate and effects are required.

Concentrations of albendazole up to 1,330,000 ng/L were found in environmental water samples, according to studies in the reviewed literature (Mutavdzic et al,2019). High-measured environmental concentrations of albendazole were found in WWTPs and hospital effluents (Santos et al, 2013; Sim et al, 2013; Celic et al, 2019) and river (Zrncic et al, 2014). Belew et al (2021) reported a high concentration of albendazole of 280,000 ng/L in WWTP influents in South Africa. These measured concentrations are much higher than the concentration of albendazole which was observed to have toxic effects on aquatic organisms.

Phase II Tier A

Aquatic Environmental Fate

Mutavdzic Pavlovic et al (2018), performed an adsorption-desorption study with albendazole according to the OECD 106 guideline method. The estimated Koc values ranged from 1402 L/ Kg to 8,399 L/Kg for sediment,

and from 1,553 L/ Kg to 3,561 L/Kg for soils. The results obtained are below the action limit of 10,000 L/Kg, indicating a lack of affinity to bind to sewage sludge in the sewage treatment plants (STP) which suggests a lack of effect on the terrestrial compartment.

Aquatic effect studies

The toxicity studies on fish, daphnia and algae published in the scientific literature are proposed to determine Predicted No Effect Concentration PNECwater values to perform risk characterisation, that integrates the results of exposure and toxicity data to evaluate the likelihood of adverse ecological effects.

The lowest EC50 value in aquatic organisms has been identified in the freshwater crustacean Daphnia magna as 42.8 μg/L. The relatively high toxicity for Daphnia magna is expected given its mode of action and therapeutic target. Carlsson et al. (2013) report high toxicity for zebrafish (Danio rerio) with a NOEC value of 0.022 mg/L. In a previous study Carlsson et al. (2011), demonstrated the embryotoxicity of albendazole in zebrafish (Danio rerio) embryos (Carlsson et al., 2011). Note that they are not long-term toxicity studies.

The toxicity studies on fish, daphnia and algae are proposed to determine Predicted No Effect Concentration PNECwater values to perform risk characterisation, that integrates the results of exposure and toxicity data to evaluate the likelihood of adverse ecological effects.

Based on the published toxicity data PEC/PNEC ratios surface and groundwater fall below the action limit, and a Tier B assessment of albendazole is not required. The PECsw/ PNECmicroorganism ratio is also lower than the value of 0.1 specified by the guideline. Hence, further evaluation of the fate and the effects of the drug substance and/or its metabolites on micro-organisms is not required in Tier B.

Labelling and risk mitigation measures

To minimise environmental exposure, it is recommended that practical instructions for disposal of unused medicinal products and waste materials are included in the product information, as appropriate. The applicant is advised to consult with the local authorities where the medicinal product is intended to be authorised to any potential environmental impact, any specific arrangements to limit this impact if needed and ensure that the documentation complies with the applicable national legislation.

Precautionary and safety measures taken to reduce environmental risk by including the general statement on the SmPC and PL have been applied by the applicant, according to the Guideline EMEA/CHMP/SWP/4447/00, corr 2, 2006.

SmPC section 5.3: *Environmental risk assessment studies have shown that albendazole may pose a risk for the aquatic compartment*. (see section 6.6).

SmPC, Section 6.6: *This medicinal product may pose a risk to the environment (see section 5.3). Any unused medicinal product or waste material should be disposed of according to local requirements*.

PL. section 5: *Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.*

Relevant endpoints, methods used, and results obtained for ivermectin were discussed and study results are summarised in Table.

Table 2: Summary of main results – ivermectin

Substance (INN/Invented Name): Ivermectin				
CAS-number (if available):				
PBT screening		Result		Conclusion
Bioaccumulation potential- log K_{ow}	OECD123	5.6		Potential PBT: Y >4.5
PBT-assessment				
Parameter	Result relevant for conclusion			Conclusion
Bioaccumulation	log K_{ow}	5.6		B
	BCF	63–111 L/kgw		Not B < threshold value of 2000
Persistence	DT50 OECD 308	$DT_{50,\ water}$ = 2.9 ±0.4 days $DT_{50,\ water/sediment}$ = 15 d ±2 days		P
Toxicity	OECD 211 *(Dapnhia magna*)	NOEC = 0.0003 ng L^{-1}		T
PBT-statement:	The compound is considered to be P and T			
Phase I				
Calculation	Value		Unit	Conclusion
$PEC_{sw,\ default}$	0.007		µg/L	≥ 0.01 threshold: N
Other concerns	Antiparasitics MoA and toxicity profile			Y
Phase II Physical-chemical properties and fate				
Study type	Test protocol	Results		Remarks
Adsorption-Desorption Soil (13 types) Sediment (7 types) *Heinrich et al 2021* *Liebig et al 2010* *Halley and Jacob, 1989*	OECD 106	$K_{oc,\ soil\ (average)}$=13266 L/Kg $K_{oc,\ sediment\ (average)}$= 4.61 L/kg $K_{oc,artificial\ soil}$ =4000 L/Kg $K_{oc,loamy\ soils\ York}$=25800 L/kg $K_{oc,loamy\ soils\ Madrid}$=12800 L/kg $K_{oc,clay\ loam\ and\ silty\ clay\ loam\ Newton}$=14700 L/kg $K_{oc,clay\ loam\ and\ silty\ clay\ loam\ Fulton}$=15700 L/kg		Koc > the trigger value of 10000 L/kg trigger further studies in soil
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50,\ water}$ = 2.9 ±0.4 days $DT_{50,\ water/sediment}$ = 15 d ±2 days		>10% has shifted to the sediment. Need for further investigation of effects on sediment-dwelling organisms
Phase IIa Effect studies				

Study type	Test protocol	Result	Value	Unit	Remarks
Algae, Growth Inhibition Test/*Pseudokirchneriella Subcapitata*	OECD 201	NOEC	390	µg/L	Growth rate, yield
Daphnia magna, Reproduction Test *Daphnia magna*	OECD 211	NOEC	$3x10^{-7}$	µg/L	Reproduction and growth inhibition
Fish, Early Life Stage Toxicity Test/*Danio rerio*	OECD 203	NOEC	40	µg/L	96 h, survival Acute toxicity
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF_{kgL}	101-111	L/kg	Related to total radioactive residues and normalised to a 5% lipid content < threshold value of 2000
Aerobic and anaerobic transformation in soil *3 topsoils: from York , Madrid and Copenhagen, and 1 artificial soil (70% sand and 20% kaolin clay)* (different sorption strengths) *Krogh et al, 2009*	OECD 307	All DT50 > 120 d Extractable amount remains fairly unchanged between day 14 and 120 2 TP were identified in soil < 10% of the parent compound	for all 4 soils		Not readily transformed under anaerobic conditions Degree of sorption dependents on soil properties
Earthworm, Acute Toxicity Tests/*E. fetida*	OECD 207	EC_{50}	4.7	mg/kg_{dw}	14d
Collembola, Reproduction Test/*Folsomia candida* (springtail)	ISO 11267	NOEC	0.3	mg/kg_{dw}	Reproduction 28 d
Chironomus riparius *(OECD 218)* Lumbriculus variegatus *(OECD 225)*	OECD 218 OECD225	LOEC LOEC	34 500	$µg/kg_{dw}$	*Larval survival (10 days)* *Larval survival (10 days)* Corrected for 10% organic carbon

Ivermectin

The applicant performed an extended search of the scientific literature to identify ivermectin available environmental fate and ecotoxicological data, published in the scientific literature, to perform the ERA, phase I and II evaluation for ivermectin, according to ERA guidelines.

Phase I

A phase I trial is required to screen ivermectin consumption data and experimentally determine its Log Kow value.

PECSurfacewater (PECsw), determined based on the default Fpen, was below the action limit of 0.01 µg/L (0.007 µg/L) defined by EMA, which indicates that a Phase II, environmental fate and effects are not required.

Phase II Tier A

Aquatic Environmental Fate

Organic carbon normalised sorption coefficients (Koc) of ivermectin were assessed by the Adsorption-Desorption Using a Batch Equilibrium Method (OECD 106), according to GLP, published in the scientific literature. The organic carbon normalised adsorption coefficient (Koc) for soil and sediments, showed that ivermectin exhibits adsorption, with Koc values higher than the guideline terrestrial assessment trigger (Koc soil >10,000), which suggests an effect on the terrestrial compartment.

The fate of ivermectin in water–sediment systems was investigated under the OECD 308 method. The dissipation half-life (DT50) values were 2.9±0.4 days in the water phase and 15 days in a water/sediment system, containing natural sediment with 1.4% TOC (Loffler et al. 2005).

Fast partitioning from water to sediment was observed in two studies: an aerobic transformation study (Prasse et al. 2009) and an outdoor aquatic mesocosm study (Sanderson et al. 2007).

DT50 from the water phase was found to be less than 6 h mainly due to the rapid sorption to the sediment. Furthermore, a DT90-value in water of 16.8 d was determined. For the entire system, a DT50 value of 127 d reflects that the transformation of ivermectin into transformation products and bound residues was relatively slow. These values show that ivermectin was rapidly sorbed to the sediment and converted into bound residues (in a total 30.4%) (Prasse et al 2009).

Similar DT50 values (>100 d) were also reported by Mougin et al. (2003) and Davies et al. (1998) for ivermectin in soils. Ivermectin persists in the sediment for months or years (Boxall 2010).

In an outdoor mesocosm study conducted over 265 days with natural water and sediments, a half-life of 4 days for the water phase of ivermectin was determined. However, it was not possible to determine the DT50 for sediment as no dissipation of ivermectin was observed until the end of the study, even after reaching a steady state (Sanderson et al. 2007). The data obtained in the OECD 308 study indicate the persistence of ivermectin in the water/sediment system under aerobic conditions, and that predominately sediment-active organisms can be significantly impacted.

Ivermectin rapidly moved from the water compartment into the sediment, which is due to its high log Pow value and Koc values. The results of the adsorption study with ivermectin indicated that binds to soil and triggers an assessment in soil at Phase II B.

Aquatic effect studies

The toxicity studies on fish, daphnia and algae published in the scientific literature are proposed to determine Predicted No Effect Concentration PNECwater values to perform risk characterisation, which integrates the results of exposure and toxicity data to evaluate the likelihood of adverse ecological effects.

Ivermectin is highly toxic to freshwater aquatic species with the LOEC and NOEC for the reproduction of Daphnia magna by the OECD 211 method, being as low as 0.001 ng L^{-1} and 0.0003 ng L^{-1}, respectively (Garric et al., 2007).

Exposure to low concentrations of ivermectin has been found to induce significant effects on both the physiological and biochemical endpoints in zebrafish (Danio rerio). The mentioned study is not according to the OECD TG 210. Nevertheless, , observed effects include weight loss, as well as changes in feeding and swimming behaviour, and biochemical endpoints in zebrafish. Swimming behaviour is disrupted at concentrations as low as 0.25 mg L^{-1} (Domingues et al, 2016).

Based on the presented studies data PEC/PNEC ratios for surface and groundwater for ivermectin are far above the action limit of 1, an environmental risk of ivermectin to aquatic organisms is identified, and further evaluation in Tier B would be demanded in a Phase II assessment

The PECsw/ PNECMicroorganism ratio is lower than the value of 0.1 specified by the guideline. Hence, further evaluation of the fate and the effects of the drug substance and/or its metabolites on micro-organisms is not required in Tier B.

Phase II Tier B

In studies with zebrafish (Danio rerio) performed according to Guideline OECD 305, using radiolabelled (3H) ivermectin, bioconcentration factors of 63–111 for ivermectin (based on total radio-active residues, normalised to a 5% lipid content) were determined.

These BCF values are clearly below the threshold value of 2000 for the B-criterion. Therefore, an accumulation of ivermectin in aquatic organisms is not expected.

Using the OECD 307 method the dissipation kinetics of ivermectin under both aerobic and anaerobic conditions in four sandy loam soils having different sorption strengths towards ivermectin was determined (Krogh et al, 2009) and the highest DT50 days were reported. The transformation products identified were quantified at levels lower than 10% of the parent compound. The dissipation of ivermectin is relatively slow in many soils even under aerobic conditions.

A bioassay using the sediment-dwelling larvae of *Chironomus riparius* (OECD 218) and *Lumbriculus variegatus* (OECD 225) has been completed using ivermectin. Following the requirements of EMA/CHMP/SWP/44609/2010 Rev. 1, 2016, the NOEC from the study was normalised to a standard sediment organic carbon content of 10%.

Ivermectin has the lowest LOEC of 6.3 µg/Kg*,* 10 days, larvae dry weight, indicating the high toxicity for *Chironomus riparius* and the potential impact on freshwater benthic invertebrates. *L. variegatus* was considerably less sensitive to ivermectin than *C. riparius*, presenting a LOEC of 500 µg/kg dry sediment, derived for effects on survival/reproduction and total biomass.

Labelling and Risk mitigation measures

Risk mitigation measures to reduce the risk to the environment and enhance environmental protection in the SmPC and PL were applied by the applicant:

SmPC section 5.3: *Environmental risk assessment studies have shown that ivermectin may pose a risk for the aquatic compartment*. (see section 6.6).

SmPC, Section 6.6: *This medicinal product may pose a risk to the environment (see section 5.3). Any unused medicinal product or waste material should be disposed of according to local requirements*.

PL. section 5: *Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.*

Conclusion on ERA

Albendazole and Ivermectin are well-known active substances already used in existing marketed products and no significant increase in environmental exposure is anticipated with the authorisation of the fixed-dose combination of Ivermectin/Albendazole, 18 mg/400 mg and 9 mg/400 mg, orodispersible tablets, by Article 58 of Regulation (EC) No 726/2004. Authorisation of the fixed combination will replace treatment with monotherapies containing each active substance.

Albendazole is neither persistent nor bioaccumulates but presents toxicity to Zebrafish (*Danio rerio*) and *Daphnia magna*. Ivermectin is a persistent active substance considered toxic to Zebrafish (*Danio rerio)* and *Daphnia magna.*

As expected for antiparasitics, albendazole and ivermectin have adverse effects, especially on invertebrates Therefore, the SmPC addresses the potential toxicological effects of Ivermectin and Albendazole and applies risk mitigation measures to reduce environmental risk and enhance environmental protection.

It is also recommended that the company contacts the local authorities where the product will be used to ensure that they comply with the local rules that can change from one country to another.

2.5.6. Discussion on non-clinical aspects

Albendazole and ivermectin have been used extensively as separate drugs and also in co-administration in adult and paediatric populations. The applicant therefore did not perform new pre-clinical studies, which is acceptable. A thorough bibliographic search was performed to support the dossier with concrete literature evidence on non-clinical aspects related to the active ingredients.

The current non-clinical overview is mainly based on regulatory documents (e.g., joint FAO/WHO Expert Committee on Food Additives reports) for the single agents. The inclusion of these monographs in the dossier is well-justified, given the long-established use and known toxicological profiles of both APIs. Since both APIs were evaluated by the joint FAO/WHO Expert Committee on Food Additives, these reports serve as crucial references in this NCO. Given that the most recent versions of these reports date back to 1987 and 1992

(FAO/WHO 1987, FAO/WHO 1990, FAO/WHO 1992, Wayne A. and Smith 1992), a literature search was conducted to identify any relevant information published since then, which is considered appropriate.

As stated in the Notice to Applicants volume 2A, Chapter 1, section 5.4, "Scientific monographs *may* offer an overview on published scientific literature", which means that WHO/FAO scientific reports can be considered as supportive, as they are not based on proprietary information from a certain product (e.g., EPAR). In addition, a literature search was conducted by the applicant to identify any relevant information published, confirming that the nonclinical safety profile of ivermectin and albendazole remains unchanged.

The potential neurotoxic and nephrotoxic effects of ivermectin are adequately addressed in the SmPC.

In-vivo studies demonstrate that ivermectin can enhance the pharmacological actions of diazepam.

Pharmacological characterisation shows high efficacy against parasites, but potential neurotoxicity and nephrotoxicity may occur with ivermectin. Ivermectin may enhance diazepam effects in humans. Resistance mechanisms overlap between the two drugs.

Overall, the non-clinical pharmacokinetic data presented provide valuable insights into the behaviour of ivermectin and albendazole across different species, aiding in our understanding of its pharmacological and toxicological dynamics.

Ivermectin is a substrate of P450 3A enzymes, substrate and inhibitor of P-gp and multidrug resistance protein (MRP), and an inhibitor of Breast Cancer Resistance Protein (BCRP) transporter. Therefore, complex interactions could be expected with this molecule.

In humans, it is known that administration of albendazole with a fatty meal markedly increases the levels of its active metabolite. Albendazole should be taken with a meal.

CYP3A, CYP3A4, and CYP2C inducers appear to induce the metabolism of albendazole.

No general toxicity studies were performed by the applicant. A thorough bibliographic search was provided to support the acute and repeat dose toxicity assessment with concrete literature evidence on non-clinical safety aspects related to the active ingredients.

Ivermectin and albendazole are intended to be orally administered as a fixed dose combination (FDC) containing ivermectin (two strengths: 9 mg for 15-45 kg body weight or 18 mg for >45 kg body weight) and albendazole (400 mg in both weight groups). The proposed posology consists of one single oral dose administration. In certain cases, the dose can be administered for 3 consecutive days, in line with the SmPC/Posology. Therefore, data from acute toxicity studies is considered relevant to characterise of the safety profile of both active substances in the intended target population/therapeutic indication.

A set of single dose studies conducted in mice, rats, dogs, and rhesus monkeys were provided by the applicant to characterise the safety profile of ivermectin administered by the oral route. Juvenile animals have also been included in rat and rhesus monkey acute toxicity assessment.

Data from a dedicated study addressing the acute toxicological potential of the individual components of ivermectin (H2B1a, H2B1b, tetrahydroavermectin-B1) in mice has been provided. No significant differences in

acute toxicity were observed for the components H2B1a, H2B1b; however, the most abundant potential impurity (Tetrahydroavermectin-B1), was of significantly lower acute oral toxicity, based on the corresponding LD_{50} values. The main signs of acute toxicity reported in mice, rats, and dogs were central nervous system (CNS) findings such as ataxia, tremors, bradypnoea, decreased activity and loss of righting, paralysis and death. The most sensitive indicator of toxicity in immature rhesus monkey was emesis, pupil dilation and/or decreased constriction, and decreased levels of activity or slight to moderate sedation. The central nervous system adverse effects were observed within 1 h and up to 7 days following a single oral dose of ivermectin depending on the test species and the applied dose. No toxicokinetics data was provided to calculate the corresponding safety margins in the single dose toxicity studies.

A low toxicity after acute oral administration was described for albendazole. The available acute oral LD_{50} for mice, rat, hamster, guinea pig and rabbits, showed values between 500 to 10000 mg/kg in rabbits and hamsters, respectively.

With respect to combination ivermectin/albendazole, no additional studies were conducted in line with the *Guideline on the non-clinical development of fixed combinations of medicinal products* (EMEA/CHMP/SWP/258498/2005), which is acceptable as both albendazole and ivermectin have been used extensively as separate drugs and also in co-administration in adult and paediatric populations and their efficacy and safety has been well established (WHO Model List of Essential Medicines).

Repeat dose toxicity studies up to 14 weeks duration were conducted in rats and dogs to assess the non-clinical safety profile of ivermectin. Moreover, 14 days duration studies were conducted in neonatal and immature rhesus monkeys.

The reported findings in rats consisted in increased spleen and reactive hyperplasia of bone marrow (from the intermediate dose tested, 0.8 mg/kg). Central nervous system toxicity was evidenced in dogs dosed up to 14-weeks: mydriasis (at 0.5 mg/kg and 1.0 mg/kg over a treatment period of 35 days and 14 weeks, respectively), ataxia, anorexia/dehydration/weight loss, whole-body tremors, and dead (for the highest dose tested in all studies, 2 mg/kg). No TK data was provided to establish the corresponding exposure margins. No toxicological concerns were identified in neonatal (7 to 13 days old) nor in immature rhesus monkeys (13-21 months old at study initiation) orally dosed with ivermectin up to 14-days.

From a non-clinical point of view, the rationale to support the ivermectin dose in the FDC for children aged 5 years and older with a body weight of 15 kg (600 µg/Kg) is based on the repeat dose toxicity study, up to 16 days duration, conducted in rhesus monkeys. No toxicokinetics data was provided in order to establish the corresponding systemic exposure, allowing the calculation of safety margins. Therefore, the applicant discussed safety margins in terms of dose in animal models *vs* planned clinical regime. According to the data provided, no treatment-related effects were identified in immature rhesus monkeys (13-21 months old at study initiation) orally dosed with the highest dose tested, 1.2 mg/Kg (HED = 387 µg/Kg), which provides a 2-fold safety margin to the human clinical dose 600 µg/Kg. The applicant also mentioned a set of additional ivermectin doses tested in a repeat dose toxicity study, ranging from 0.2 to 24 mg/Kg. Based on very scarce data concerning this study design and the corresponding safety assessment, emesis was noted at 2 mg/Kg and adverse effects were observed at 12 and 24 mg/Kg. No toxicological concerns were observed at doses up to 8 mg/Kg [HED: 2580 µg/Kg; a 13-fold dose-based safety margin for the dose under discussion (600

µg/Kg)]. The toxicological profile of albendazole has been characterised in a set of repeat dose toxicity studies of 3-month duration conducted in mice, and 6-month duration in rats and dogs.

Haematological effects (such as reduced haemoglobin, haematocrit, erythrocyte levels, and decreased leucocyte counts) and liver findings were the main toxicological effects noted in mice, rats and dogs.

In rat, histopathological examination revealed hypoplasia in testes, bone marrow, spleen and lymph nodes at the highest dose tested in the 4-weeks study. Moreover, liver findings (centrilobular cloudy swelling, vacuolation or necrosis) and hypocellularity of lymphoid tissues (such as bone marrow, spleen and thymus) suggestive of atrophy were observed in the rat chronic toxicity assessment. The target organs of toxicity identified in the repeat dose toxicity studies conducted in dogs were the testes and uterus (decreased absolute and relative weights in all doses tested), and the liver and kidney (slight increases in relative weights in the highest dose tested).

No toxicokinetics assessment was included in repeat dose toxicity studies allowing the calculation of safety margins. However, an additional request of toxicokinetics data/safety margins assessment will not be deemed necessary as albendazole and ivermectin have been extensively used as separate drugs and also in co-administration and their safety profile has been well established in adult and paediatric populations. Moreover, the ivermectin/albendazole FDC has been developed for one single oral dose administration (or at least, to be administered for 3 consecutive days in certain cases), in line with the SmPC/Posology.

No new reproductive and developmental studies were conducted by the applicant. A literature search was performed to support the assessment of reproductive and developmental safety aspects related to the individual active ingredients.

No fertility and early embryofetal development adverse findings were identified for ivermectin in a combined study, in which animals were dosed prior to mating until 20 days post-partum. However, teratogenic effects in mice, rats and rabbits were evidenced by an increased incidence of cleft palate in a number of pups whose mothers received higher ivermectin doses associated with maternal toxicity. Concerning the prenatal development effects, a significant increase in the average gestation length has been noted among females rats in the high-dose treated group. During the lactation period, high offspring mortality occurred up to day 10 post-partum. The most common signs of toxicity in pups that died was lethargy, hypothermia an absence of milk in the stomach. Postnatal safety concerns, consisting in increased mortality among pups, and a slightly accelerated developmental concerning the eye opening, ear opening, incisor eruption and hair growth, were also observed. A significant delay in the appearance of the righting reflex and the auditory startle reflex, and a significant earlier incisor eruption have been reported. Moreover, concerning the F1 sexual maturity, a significantly delayed vaginal opening and a treatment-related delay in testes descent were observed.

No adverse findings were identified for albendazole in fertility and early development endpoints. Embryotoxic effects consisting in decreased foetal weight, reduction in implants and increased resorptions were noted in both rats and rabbits. An increased frequency of skeletal abnormalities has also been observed. The major malformations were craniofacial and bone defects: retarded skeletal ossification and increased incidences of micromelia and microfetalis (which included shortened long bones in fore and hind limbs) were reported in

the rat, and ectrodactyly in the rabbit study. The assessment of postnatal development has shown adverse effects on the pup survival and/or weight gain during the lactation period.

No genotoxicity testing was performed by the applicant. The available information is collected from previous and publicly available knowledge concerning both active substances. Both ivermectin and albendazole showed negative results in a battery of genotoxicity of *in vitro* and *in vivo* assays.

Considering the totality of evidence available and the accumulated experience with these drugs, this is considered acceptable, and no genotoxicity risk is currently identified for both drugs.

No new carcinogenicity studies were conducted by the applicant. This is acceptable. Available information is bibliographical and builds on existing evidence. The negative mutagenicity studies on ivermectin and the negative carcinogenicity studies with abamectin indicate that ivermectin has no carcinogenic potential. Also, no carcinogenic potential was identified in different carcinogenicity studies with albendazole.

The non-clinical reproductive and developmental safety findings for ivermectin and albendazole have been summarised in section 5.3 of the SmPC. The corresponding risk mitigation measures have been mentioned in sections 4.3 and 4.6 of the SmPC.

With respect to studies in which the offspring (juvenile animals) are dosed and/or further evaluated, no new studies were performed by the applicant, which is acceptable based on the provided literature search.

Studies including juvenile animals have been previously mentioned within the scope of dedicated single and repeat dose toxicity studies.

Repeat dose toxicity studies 14-days duration were conducted in neonatal rhesus monkeys (7 to 13 days old) and in immature rhesus monkeys (13-21 months old at initiation) to assess the potential significance of neonatal and developmental exposure to ivermectin. Neonatal monkeys were examined for mydriasis, pupillary light response and adverse reactions. No safety concerns were identified in animals dosed up to 0.1 mg/kg. In addition, the results of the examinations (physical, ophthalmic, haematologic, serum biochemical examination, body weight and necropsy) indicated no treatment-related effects in immature monkeys dosed up to 1.2 mg/kg. These dose levels were chosen to provide a 6-fold safety margin relative to the human clinical dose, as presented in the Repeat dose toxicity section.

The assessment of potential acute toxicological effects of ivermectin was also addressed in neonatal rats. A higher sensitivity of neonatal rats was noted when the reported LD_{50} values were compared with those reported for adult animals (LD_{50}=2.3 mg/kg *vs* LD_{50}=42.8-52.8 mg/kg). The increased toxicity of ivermectin in neonatal rats is likely due to a combination of excessive plasma levels resulting from exposure via maternal milk and the increased permeability of the blood-brain barrier during the early postnatal period in this species, as presented in the Single dose toxicity section.

No corresponding juvenile animal study with albendazole was encountered in literature.

These results published by Zhang et al. 2022, indicate that ivermectin can induce immunotoxicity through induction of immune dysfunction and cytotoxicity.

Among the avermectins, ivermectin and abamectin are investigated as endocrine disruptors. Ivermectin was also shown to suppress the sexual behaviour in oestradiol treated female rats at therapeutic dose (0.2 mg/kg). In humans, abamectin is placed under the category which is more likely to cause endocrine disruption (Salman et al., 2022).

Albendazole is not proven as sensitizing agent, neither an acute skin nor eye irritant. However, the main albendazole metabolite albendazole sulfoxide showed to be a potential skin sensitiser in a guinea-pig maximisation test (FAO/WHO 1987, Dayan 2003, EMA/CVMP 2004, PuBChem 2022).

Specific studies of phototoxicity have not been presented nor discussed. However, it is likely that any problem of this nature would have emerged in the pivotal studies already conducted and existing clinical experience.

The ERA is considered acceptable. Approval of the present application following its prescribed usage does not pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

Overall, the non-clinical data submitted by the applicant provided adequate evidence supporting the clinical use in the applied therapeutic indication.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 3: Summary of clinical studies assessing the efficacy of the fix-dose combination of albendazole plus ivermectin

Study ID	Number of Sites; Country(is)	Design	Objective	Investigational Product(s) and Route of Administration	Study Population	Dose and Duration of Exposure	Efficacy Endpoints
ALIVE Phase II	Single centre Kenia	3-arm, parallel, open-label study. Participants were stratified into 3 weight groups and then randomised with unequal probability (1:2:2) to 1 of the study arms (ALB, FDC-SD, FDCx3) within the 3 body weight groups.	This phase of the study evaluated safety, population pharmacokinetics (PK), and acceptability of the formulation.	<u>Test Product:</u> A/I-FDC dispersible tablet, oral <u>Reference:</u> Eskazole (Albendazole) chewable tablets, oral	Patients aged 5-17 years infected with *T. trichiura*, *A. lumbricoides*, Hookworm, and *S. stercoralis*. 135 subjects randomised: - FDC-SD: 51 - FDCx3: 54 - Eskazole®: 30	<u>FDC:</u> single dose or daily dose for 3 days Albendazole: 400 mg Ivermectin: 9 mg (body weight 15-23 kg and 23-≤30 kg) Or 18 mg (body weight 30-45 kg) <u>Eskazole ®</u> 400 mg single dose	- To evaluate the efficacy of FDC against *T. trichiura* in a paediatric population. - To evaluate the efficacy of FDC against hookworms and *S. stercoralis* in participants co-infected with species concomitantly to their infections with *T. trichiura*.
ALIVE Phase III	Multicentre Kenya, Ethiopia, and Mozambique	Single-blinded, randomised, active-controlled, parallel-group, multi-centre, superiority study. Participants were assigned to 1 of 3 study arms by block randomisation:	To assess FDC-SD or FDCx3 compared with active control (ALB 400 mg single dose) in a paediatric and young adult population.	<u>Test Product:</u> A/I-FDC, dispersible tablet, oral <u>Reference:</u> Eskazole ® (Albendazole) chewable tablets, oral	Patients aged 5-18 years infected with *T. trichiura*, *A. lumbricoides*, Hookworm, and *S. stercoralis*. 866 subjects randomised:	<u>FDC single dose</u> - Body weight ≥45 kg: 400 mg A/18 mg I - Body weight <45 kg: 400 mg A/9 mg I <u>FDC daily dose, 3-days</u>	- To evaluate the efficacy of FDC-SD and FDCx3 compared to the standard single dose regimen of ALB (400 mg) for the treatment of *T. trichiura* in a paediatric and

Study ID	Number of Sites; Country(is)	Design	Objective	Investigational Product(s) and Route of Administration	Study Population	Dose and Duration of Exposure	Efficacy Endpoints
		T. trichiura 1:2:2 hookworms 1:1:1 S. stercoralis 2:5:5 and stratified by species of STH.			- FDC single dose: 330 - FDC daily dose, 3-days: 323 - Eskazole: 213	- Body weight ≥45 kg: 400 mg A/18 mg I - Body weight <45 kg: 400 mg A/9 mg I Eskazole ® 400 mg single dose	young adult population. - To evaluate the efficacy of FDC-SD and FDCx3 for the treatment of hookworm and *S. stercoralis*.
A/I = Albendazole/Ivermectin; ALB = Albendazole; FDC = Fix dose combination; ID = Identification; N = Number of subjects; SD = Single dose.							

Table 4: Summary of published studies assessing the efficacy of a combination of albendazole and ivermectin

Publication	Design	Objective	Investigational Product(s) and Route of Administration	Study Population; Country	Dose and Duration of Exposure	Efficacy Endpoints
Ndyomugyenyi et al., 2008	Randomised, open label, controlled trial with four arms.	To examine the efficacy of ivermectin and albendazole alone and in combination given in the second trimester of pregnancy and record adverse events after treatment.	Group A: Ivermectin Group B: Albendazole. Group C: Combination of A/I Group D: reference group without STHs. All medicaments were orally administered	Adult pregnant women (≥16 weeks of gestation) infected with any intestinal helminth. 832 randomised Group A: 198 Group B: 194 Group C: 199 Group D: 241	Ivermectin 150-200 µg/kg, single dose Albendazole 400 mg, single dose Albendazole 400 mg + Ivermectin 150-	Efficacy (cure rate of STHs) was defined as the proportion of pregnant women who were excreting eggs in their stool before treatment, but who had a negative test result at 21 days follow-up.

Publication	Design	Objective	Investigational Product(s) and Route of Administration	Study Population; Country	Dose and Duration of Exposure	Efficacy Endpoints
				Uganda	200 µg/kg, both single dose	
Knopp et al., 2010	Randomised controlled trial	To assess the efficacy and safety of albendazole plus placebo, albendazole plus ivermectin, mebendazole plus placebo, and mebendazole plus ivermectin in children with parasitologically confirmed *T. trichiura* infection.	Albendazole/Placebo Albendazole/Ivermectin Mebendazole/Placebo Mebendazole/Ivermectin All medicaments were orally administered	Children >5 years old infected with *T. trichiura*, *A. lumbricoides*, and Hookworm 610 randomised, 548 analysed: Albendazole+Placebo: 132 Albendazole+Ivermectin: 140 Mebendazole+Placebo: 138 Mebendazole+Ivermectin : 138 Tanzania	<u>Albendazole</u> 400 mg <u>Ivermectin</u> 200 mg/kg <u>Mebendazole</u> 500 mg All single dose	Cure rate (CR) and egg reduction rate (ERR) achieved by treatment with any drug regimen against *T. trichiura* infections. CR was determined as the percentage of children excreting eggs before treatment who became negative after treatment. The ERR was calculated as the reduction in the group's geometric mean (GM) egg count, including infected and noninfected subjects at follow-up
A/I = Albendazole/Ivermectin; ALB = Albendazole; CR = Cure rate; ERR = Egg reduction rate; GM = Geometric mean; IVM = Ivermectin; qPCR = Real-Time PCR; SD = Single dose; STH = Soil transmitted helminths						

Publication	Design	Objective	Investigational Product(s) and Route of Administration	Study Population; Country	Dose and Duration of Exposure	Efficacy Endpoints
Speich et al., 2015	Randomised controlled trial	To compare the efficacy and safety of ALB plus	Albendazole/Ivermectin	Children aged 6-14 years infected with *T. trichiura*,	<u>Albendazole</u> 400 mg	The primary endpoints were the proportion of children cured and the

Publication	Design	Objective	Investigational Product(s) and Route of Administration	Study Population; Country	Dose and Duration of Exposure	Efficacy Endpoints
		ivermectin, ALB plus mebendazole, and ALB plus oxantel pamoate, with a standard treatment (one-dose mebendazole), to identify the intervention with the greatest potential against *T. trichiura* and concomitant STHs	Albendazole plus Mebendazole Albendazole plus Oxantel pamoate Mebendazole alone All medicaments were orally administered	*A. lumbricoides*, *S. stercoralis*, and Hookworm 440 randomised: 110 assigned to each arm. Tanzania	Ivermectin 200 µg/kg Mebendazole 500 mg Oxantel pamoate 20 mg/kg All single dose	reduction in the number of eggs of *T. trichiura* analysed by available case. Secondary outcomes were the proportion of children cured and the reduction in the number of eggs of concomitant nematode infections and drug safety (assessed at two timepoints) analysed by intention to treat, per protocol, and available case.
Matamoros et al., 2021	Phase II randomised, open-label, controlled, outcome assessor–blinded, clinical trial.	To present safety and efficacy results from comparing experimental multiple-day regimens and high-dose IVM drug combinations against ALB monotherapy for the treatment of *T. trichiura* infections	Arms 1 and 3: Albendazole alone Arms 2 and 4: Albendazole+Ivermectin All medicaments were orally administered	Children aged 2-14 years infected with *T. trichiura* and body weight ≥15 kg. 176 children randomised: Arm1: 38 Arm 2: 56 Arm 3: 23 Arm 4: 58 Honduras	Albendazole 400 mg Ivermectin 600 µg/kg Arm 1: ALB-SD Arm 2: A/I SD Arm 3: ALBx3 Arm 4: A/Ix3	The primary outcome of this clinical trial was CR against *T. trichiura* at 14–21 days after treatment in a single Kato-Katz specimen. The secondary outcome was *T. trichiura* ERR at the same end point.

Publication	Design	Objective	Investigational Product(s) and Route of Administration	Study Population; Country	Dose and Duration of Exposure	Efficacy Endpoints
A/I = Albendazole/Ivermectin; ALB = Albendazole; CR = Cure rate; ERR = Egg reduction rate; GM = Geometric mean; IVM = Ivermectin; qPCR = Real-Time PCR; SD = Single dose; STH = Soil transmitted helminths						
Publication	Design	Objective	Investigational Product(s) and Route of Administration	Study Population; Country	Dose and Duration of Exposure	Efficacy Endpoints
Hürlimann et al., 2022	Phase 3, randomised, controlled, double-blind, parallel group, superiority trial	To demonstrate superiority of co-administered ivermectin–albendazole over albendazole monotherapy in three distinct epidemiological settings.	Albendazole/Ivermectin Albendazole/Placebo All medicaments were orally administered	Patients aged 6-60 years infected with *T. trichiura* and concomitant infections with *A. lumbricoides*, *S. stercoralis*, and Hookworm 1,673 patients randomised: Albendazole + Placebo: 835 A/I: 838 Côte d'Ivoire, Laos, Tanzania	<u>Albendazole</u> 400 mg <u>Ivermectin</u> 200 µg/kg All single dose	The primary outcome was the CR of *T. trichiura*, defined as the proportion of participants with no eggs in their faeces 14–21 days after treatment. Secondary outcomes were the ERR against *T. trichiura*, CR and ERRs against *A. lumbricoides*, hookworm, and *S. stercoralis* as well as infection status assessed by qPCR.
Sprecher et al., 2023	Community-based randomised, placebo-controlled, parallel-group, phase III	To evaluate if moxidectin in combination with ALB yields superior efficacy compared to ALB monotherapy by *T. trichiura* infections and to provide further evidence on	Albendazole Moxidectin Ivermectin Arm 1: ALB alone, Arm 2: ALB+Moxidectin	Adolescents and adults aged 12-60 years infected with *T. trichiura* 255 patients randomised: Arm 1: 84	<u>Albendazole</u> 400 mg <u>Moxidectin</u> 8 mg <u>Ivermectin</u> 200 µg/kg	The primary outcome was the CR against *T. trichiura* between the moxidectin-ALB combination compared to ALB alone. Secondary outcomes were the ERR of *T. trichiura* with

Publication	Design	Objective	Investigational Product(s) and Route of Administration	Study Population; Country	Dose and Duration of Exposure	Efficacy Endpoints
	superiority trial	the previously found low efficacy of A/I combination in the same population.	Arm 3: A/I All medicaments were orally administered	Arm 2: 85 Arm 3: 86 Côte d'Ivoire	All single dose	moxidectin-ALB combination and ALB alone, the CR and ERR of A/I combination compared to ALB alone in *T. trichiura* as well as the CRs and ERRs of the three treatments in *A. lumbricoides* and hookworm

A/I = Albendazole/Ivermectin; ALB = Albendazole; CR = Cure rate; ERR = Egg reduction rate; GM = Geometric mean; IVM = Ivermectin; qPCR = Real-Time PCR; SD = Single dose; STH = Soil transmitted helminths

Publication	Design	Objective	Investigational Product(s) and Route of Administration	Study Population; Country	Dose and Duration of Exposure	Efficacy Endpoints
Welsche et al., 2023	Open-label, non-inferiority, randomised, controlled, phase 2/3 trial	To assess the efficacy and safety of moxidectin and ALB compared with A/I against *T. trichiura*. To measure long-term effects of moxidectin due to its longer half-life (20–35 days vs 18 h for ivermectin).	Albendazole Moxidectin Ivermectin Arm 1: ALB + Moxidectin Arm 2: A/I Arm 3: ALB alone Arm 4: IVM alone Arm 5: Moxidectin alone	Adolescents aged 12-19 years infected with *T. trichiura* and concomitant infections with *A. lumbricoides*, and Hookworm 536 randomised (safety population): Arm 1: 207 Arm 2: 211 Arm 3: 19 Arm 4: 19	Albendazole 400 mg Moxidectin 8 mg Ivermectin 200 µg/kg All single dose Follow-up was conducted at	The primary outcome was ERR of *T. trichiura* 14–21 days after treatment in the available case population. Secondary outcomes were CRs (defined as the proportion of participants converted from egg-positive at baseline to egg-negative after treatment) of combination therapy groups compared with

Publication	Design	Objective	Investigational Product(s) and Route of Administration	Study Population; Country	Dose and Duration of Exposure	Efficacy Endpoints
			All treatments were orally administered	Arm 5: 80 Tanzania	14–21 days, 5–6 weeks, and 3 months after treatment	monotherapy groups for *T. trichiura* 14–21 days after treatment; ERR and CR for *A. lumbricoides* and hookworm assessed at 14–21 days, 5–6 weeks, and 3 months after treatment
Lymphatic filariasis						
Dembele et al., 2010	Randomised controlled trial	To determine the effect of increased dose and frequency of A/I treatment on microfilarial clearance in residents of an area of *W. bancrofti* endemicity in Mali	Albendazole Ivermectin All treatments were orally administered	Males and females aged 14-65 years infected with *W. bancrofti.* 390 screened, 51 randomised: Annual standard dose: 26 Twice-yearly high dose: 25	Standard dose: ALB: 400 mg IVM: 150 µg/kg High dose: ALB: 800 mg IVM: 400 µg/kg	The primary endpoint evaluated the difference in *W. bancrofti* levels between the 2 groups at 12 months by examining parasite clearance rates at baseline and 12 months.
A/I = Albendazole/Ivermectin; ALB = Albendazole; CR = Cure rate; ERR = Egg reduction rate; GM = Geometric mean; IVM = Ivermectin; qPCR = Real-Time PCR; SD = Single dose; STH = Soil transmitted helminths						

2.6.1. Clinical pharmacology

Albendazole

In vitro experiments with larval stages

In a comprehensive *in vitro* study different groups of anthelmintics against *Trichuris muris* (L1 and adults), *A. ceylanicum* L3 larvae and adults), *N. americanus* L3 larvae and adults), *H. polygyrus* L3 larvae and adults), and *S. ratti* (L3 larvae and adults) were tested. In brief, the benzimidazoles showed higher activity against the adult stages when compared to the larval stages. This was attributed to the differences in the tubulin interaction between larval and adult stages and among the different derivatives (the role of tubulin is detailly explained in 4.2.1.2.2).

In more detail, the benzimidazoles showed low to moderate activity against adult *T. muris* with thiabendazole and mebendazole revealing the highest activity (IC50 values of 13.8 and 14.3 µM, respectively). Fenbendazole lacked activity against adult *T. muris*. Except for thiabendazole the benzimidazoles lacked activity against *H. polygyrus* adults and showed variable (absence of activity up to moderate activity) against adult *A. ceylanicum* (IC50 values 40.0 to >100 µM) and *S. ratti* (IC50 values: 21.8 to >100 µM). The highest activity of the benzimidazoles against adult stages was observed against adult *N. americanus*, with flubendazole and oxibendazole revealing IC50 values <5 µM. Absolute *in vitro* efficacy of albendazole was reported for *L. muris* (L1), *A. ceylanicum*, *N. americanus* (L3), *H. polygyrus* (L3 and adult) and *S. ratti* (L3). Poor efficacy of albendazole was seen in adult forms of *T. muris* and *N. americanus* (Table 4) (Keiser and Häberli 2021). This is in correlation with field report from Laos, where both, albendazole and mebendazole showed disappointing CRs efficacy against whipworms and hookworms in school children (Soukhathammavong, Sayasone et al. 2012).

Five different concentrations of albendazole solution (50 µg/ml, 100 µg/ml, 150 µg/ml, 200 µg/ml, and 250 µg/ml) were tested *in vitro* against cultivated hookworm larvae (*A. duodenale* and *N. americanus*) isolated from fresh stool samples or study participants. This examination was done within an open-label, single-arm clinical trial with single dose albendazole in a single treatment arm to assess the efficacy of a single dose of albendazole (400 mg) *in vivo* (Bezie, Aemero et al. 2021).

After the application of different concentrations of albendazole on the larvae stage, the lowest and highest mortality rates were observed at 50 and 250 µg/ml of the drug, respectively. The 50 µg/ml of albendazole results in a 57% mortality rate, while the 250 mg/l of the drug resulted in 93% (65 of 70) of the larval death. The *in vitro* recorded LC99 values against the parasite larva were 573 µg/ml (Table 5) (Bezie, Aemero et al. 2021).

Table 5: In vitro hookworm larva-killing effect of albendazole

Dose response		**% dead larvae**	**Estimated LC values and confidence limits**			
					95%CI	
Conc. (µg/ml)	% of exposed larvae		LC	Mean conc. (µg/ml)	Lower	upper
50	70	44	5	59.9	0.16	111.9
			10	73.4	0.50	126
100	70	49	15	84.4	1.07	137
			20	94.3	1.94	146.5
150	70	57	50	152.3	24.37	201.5
			60	175.9	50.52	229.2
200	70	61	70	205.4	102.00	283.4
			75	223.7	139.20	346.1
250	70	65	80	246.1	176.70	480.1
			90	316.2	241.51	1557
Control	70	0	95	388.9	282.00	4557
			99	573.477	360	55823

(Bezie, Aemero et al. 2021)

This study showed that the larval mortality rate increased with an increasing albendazole concentration (Figure 3.

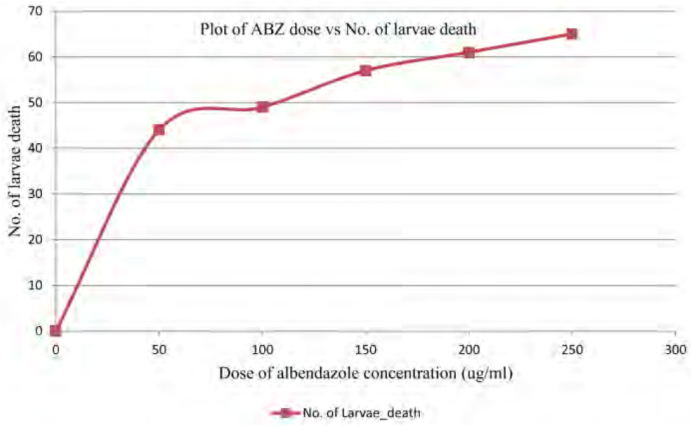


Figure 3: In vitro dose response curve of different albendazole concentration against hookworm larvae death

WHO recommended treatments with a single dose of albendazole or mebendazole against *T. trichiura* in humans are known to exert only moderate improvement of the infection. (Hansen, Friis et al. 2014, Clarke, Doi et al. 2019).

Mixed in vitro/ex vivo experiments with adult and larval stages

Apart from the development of the resistance which is always considered as the main cause of the drug inefficiency, it is obvious that the efficacy of an anthelmintic will dependent on the ability of the active compound to reach the location of the parasite and to enter and bind to specific receptors within the parasite in sufficient and sustained concentrations. Given the similarity in the anatomy with *T. trichiura*, and its sensitivity to benzimidazoles, the investigations on the benzimidazole uptake on *Trichuris (T.) suis*, an important parasite in veterinary pathology, may provide a useful explanatory model to understanding the uptake of benzimidazole drugs in *T. trichiura.*

The results of controlled experiment with domestic pigs indicated the low uptake of fenbendazole observed for *T. suis* in *in vitro* conditions, also takes place *in vivo*.

The high and significant correlations between concentrations of the both metabolites in pig plasma of the pigs and *T. suis* suggests that the metabolites reach the worms via the blood / blood-enterocyte interface, while fenbendazole primarily reaches the worms in the intestinal lumen of the host penetrating the parasite through the cuticle (Hansen, Friis et al. 2014).

Given that albendazole and fenbendazole belong to the same group of benzimidazole drugs (benzimidazole carbamates), their chemical and pharmacokinetic properties are very likely to be close. The whole class is poorly soluble in water, having very limited absorption in monogastric species. Therefore, it is possible to extrapolate the results obtained with one member of the class to another.

This hypothesis was further confirmed in the study where the distribution and uptake of albendazole and its metabolites albendazole sulfoxide, albendazole sulfone were investigated in the hookworm *H. polygyrus* in *in vitro* and in *in vivo* conditions. By investigating the pathways of albendazole uptake, the two still non investigated gastrointestinal nematodes, the study tended to clarify whether the differences in albendazole's efficacy against hookworm and *Trichuris* correlate with the extent of drug uptake (Cowan, Meier et al. 2017).

Four-week-old female NMRI mice n=4 per treatment group) were infected via oral gavage of 200 or 80 *H. polygyrus* L3 stage larvae for *in vitro* or *in vivo* experiments, respectively. Adult *H. polygyrus* were harvested from infected mice by dissection, from ten days post-infection onwards. Four *H. polygyrus* per group were incubated at solutions of albendazole, albendazole sulfoxide and albendazole sulfone at concentration of 200 µM each. For *in vivo* part of the study, *H. polygyrus* infected mice were treated orally with 100 mg/kg albendazole, or with 100 mg/kg albendazole sulfoxide. The same treatments were also applied into the peritoneal cavity to groups of four mice (Cowan, Meier et al. 2017).

Worms recovered from the treated mice revealed albendazole as well as its metabolites. After oral treatment, albendazole sulfoxide was found in highest amounts, which was on average 3.2-fold higher than albendazole and 11-fold higher than albendazole sulfone. Intraperitoneal treatment resulted in albendazole sulfoxide concentration of 204 nmol/10 worms, which was 20-fold higher than albendazole and 5.3-fold higher than albendazole sulfone. There was no correlation between the drug concentrations measured in *T. muris*, compared to the plasma or the large intestinal content. The authors concluded that there was no correlation between drug accumulation in the target parasite and the drug efficacy. Clearly, drug efficacy is not a matter of how much drug accumulates in the worms, but how much drug interacts with the target (Cowan, Meier et al. 2017).

The effects of albendazole on *Strongyloides* sp., were examined *in vitro* and in experimentally infected animals (*in vivo*). Albendazole inhibited the hatching and moulting of *S. ratti* eggs and larvae and prevented the development in vitro of *S. stercoralis* first-stage larvae. Results of experiment are summarised in Table 6;

Table 7 and Table 8 (Grove, Lumsden et al. 1988).

Table 6: Number of first-, second-, and third-stage larvae in faeces in vitro after two days incubation with or without albendazole (n = 6 per group)

S.ratti	L1 mean	L2 mean	L3 mean
Control	1.0±1.7	0.7±1.1	52±12
Albendazole	20±13	2.5±2.8	0

Source: (Grove, Lumsden et al. 1988)

Table 7: Numbers of *S. ratti* larvae in the lungs at various times after infection n mice given a single dose of 4 mg albendazole on the day of infection (n=6 per group)

	Lung larval counts	
Days after infection	Control mice mean	Treated mice
1	13±9	0
2	84±44	1±3
3	31±24	0

Source: (Grove, Lumsden et al. 1988)

Table 8: Effects of albendazole on *S. stercoralis* in mice

Experiment	No of mice	Infective dose (larvae)	Albendazole dose	No larvae in muscles
No I	24	3000	0 mg (controls)	87±53
			2x1mg	68±75
			2 x 4 mg (D0 and D3)	18±30*
No II	14	3000	0 mg (controls)	85±50
			20 mg (5xin 3 days)	4±8
No III	18	3000	0 mg (controls)	85±50
			48 mg (12x in 4 days	0

Table Legend: *- significant finding; Source: (Grove, Lumsden et al. 1988)

Pre-exposure to the drug did not impair the infectivity of either *S. ratti* or *S. stercoralis* third-stage larvae. Albendazole had a dose-dependent inhibitory effect on *S. ratti* migrating larvae in mice when measured in terms of the numbers of larvae recovered from the skin or lungs or the subsequent development of a patent infection. Likewise, killing of adult *S. ratti* in the gut and eradication of *S. stercoralis* third-stage larvae from the muscles of mice were dose-dependent. Albendazole in a dose of 100 mg twice daily for three days given at the time of infection with *S. stercoralis* of immunocompetent dogs prevented completely the subsequent development of patent infection. When the drug was given in the same dosage to immunosuppressed dogs with patent infections, the larvae disappeared from the stools transiently; when the animals were killed seven

weeks after treatment, small numbers of adult worms and rhabditiform larvae were found in the gut. It is concluded that albendazole may be effective treatment for strongyloidiasis if it is given in sufficiently large doses (Grove, Lumsden et al. 1988).

Human studies with ivermectin + albendazole

In a randomised controlled trial, a comparison was made between three drug combinations and one standard drug alone in children aged 6–14 years in two schools on Pemba Island, Tanzania infected with *T. trichiura* and concomitant intestinal nematodes. We assigned children, via a randomisation list with block sizes of either four or eight, to orally receive albendazole (400 mg) plus ivermectin (200 µg/kg); albendazole (400 mg) plus mebendazole (500 mg); albendazole (400 mg) plus oxantel pamoate (20 mg/kg); or mebendazole (500 mg) alone. The primary endpoints were the proportion of children cured of *T. trichiura* infection and the reduction of *T. trichiura* eggs in stool based on geometric means, both analysed by available case.

Albendazole plus oxantel pamoate (74 of 108 children cured [68·5%, 95% CI 59·6–77·4]; egg reduction 99·2%, 98·7–99·6) and albendazole plus ivermectin (30 of 109 cured [27·5%, 19·0–36·0]; egg reduction 94·5%, 91·7–96·3) were significantly more effective against *T. trichiura* than mebendazole alone (nine of 107 cured [8·4%, 3·1–13·8]; egg reduction 58·5%, 45·2–70·9).

A double-blind, parallel-group, phase 3, randomised controlled trial was conducted in community members aged 6–60 years infected with T*. trichiura* in Côte d'Ivoire, Laos, and Pemba Island, Tanzania, between Sept 26, 2018, and June 29, 2020. Participants with at least 100 *T. trichiura* eggs per g of stool at baseline were randomly assigned (1:1) using computer-generated randomisation sequences in varying blocks of four, six, and eight, stratified by baseline *T. trichiura* infection intensity, to orally receive either a single dose of ivermectin (200 µg/kg) plus albendazole (400 mg) or albendazole (400 mg) plus placebo. Patients, field staff, and outcome assessors were masked to treatment assignment. The primary outcome was cure rate against *T. trichiura*, defined as the proportion of participants with no eggs in their faeces 14–21 days after treatment, assessed by Kato-Katz thick smears, and analysed in the available-case population according to intention-to-treat principles.

Cure rates and egg-reduction rates of the available-case population are summarised in Table 9: Efficacy against *T.* trichiura and co-infecting STH by trial country (available case analysis).

Table 9: Efficacy against *T. trichiura* and co-infecting STH by trial country (available case analysis)

	Côte d'Ivoire		Laos		Pemba Island	
	Albendazole (n=235)	Ivermectin–albendazole (n=232)	Albendazole (n=194)	Ivermectin–albendazole (n=213)	Albendazole (n=293)	Ivermectin–albendazole (n=288)
Trichuris trichiura						
Participants positive for infection after treatment	211	200	178	73	275	148
Cure rate, % (95% CI)	10% (7 to 15)	14% (10 to 19)	8% (5 to 13)	66% (59 to 72)	6% (4 to 10)	49% (43 to 55)
Difference in cure rate, percentage points (95% CI)*	..	4 (–2 to 10)	..	58 (50 to 65)	..	43 (36 to 49)
Cure rate by infection intensity, % (n/N)						
Light	13% (22/175)	15% (25/172)	9% (15/164)	74% (131/176)	8% (17/222)	53% (116/219)
Moderate	3% (2/58)	12% (7/57)	3% (1/30)	25% (9/36)	1% (1/71)	36% (24/66)
Heavy	0% (0/2)	0% (0/3)	..	0% (0/1)	..	0% (0/3)
Geometric mean EPG						
Baseline	488·8	475·4	369·8	361·0	462·8	463·2
After treatment	175·7	141·6	115·5	3·0	198·5	8·0
Geometric mean ERR, % (95% CI)	64% (54 to 72)	70% (61 to 77)	69% (61 to 75)	99% (99 to 99)	57% (48 to 65)	98% (98 to 99)
Difference in geometric mean ERR, percentage points (95% CI)*	..	6 (–6 to 18)	..	30 (24 to 38)	..	41 (34 to 50)
Arithmetic mean EPG						
Baseline	1048·8	1110·9	626·1	688·7	848·5	938·0
After treatment	874·6	866·8	403·2	70·8	698·9	105·1
Arithmetic mean ERR, % (95% CI)	17% (–14 to 39)	22% (–14 to 46)	36% (19 to 50)	90% (81 to 96)	18% (4 to 30)	89% (83 to 93)
Moderately or heavily infected participants with no or light infection after treatment, % (95% CI; n/N)	40% (27 to 53; 31/60)	52% (39 to 65; 24/60)	63% (45 to 82; 19/30)	97% (92 to 103; 34/71)	48% (36 to 60; 36/37)	94% (89 to 100; 65/69)
Ascaris lumbricoides						
Participants positive for infection						
Baseline	82	81	77	70	70	86
After treatment	4	5	0	0	2	1
Cure rate, % (95% CI)	95% (90 to 100)	94% (89 to 99)	100% (100 to 100)	100% (100 to 100)	97% (93 to 101)	99% (97 to 101)
Cure rate by infection intensity, % (n/N)						
Light	100% (34/34)	100% (36/36)	100% (44/44)	100% (38/38)	97% (33/34)	100% (50/50)
Moderate	92% (33/36)	86% (30/35)	100% (28/28)	100% (31/31)	97% (34/35)	97% (34/35)
Heavy	92% (11/12)	100% (10/10)	100% (5/5)	100% (1/1)	100% (1/1)	100% (1/1)
Geometric mean EPG						
Baseline	5315·6	4748·2	3458·5	3374·7	4378·8	3173·9
After treatment	0·1	0·2	0	0	0·3	0·1
Geometric mean ERR, % (95% CI)	100% (100 to 100)	100% (100 to 100)	100% (100 to 100)	100% (100 to 100)	100% (100 to 100)	100% (100 to 100)

(Table 2 continues on next page)

	Côte d'Ivoire		Laos		Pemba Island	
	Albendazole (n=235)	Ivermectin–albendazole (n=232)	Albendazole (n=194)	Ivermectin–albendazole (n=213)	Albendazole (n=293)	Ivermectin–albendazole (n=288)
(Continued from previous page)						
Arithmetic mean EPG						
Baseline	22 874·2	19 907·6	12 977·7	9801·6	9525·3	7782·0
After treatment	0·9	5·1	0·0	0·0	101·1	24·4
Arithmetic mean ERR, % (95% CI)	100% (100 to 100)	100% (99·9 to 100)	100% (100 to 100)	100% (100 to 100)	99% (97 to 99)	100% (99 to 100)
Moderately or heavily infected participants with no or light infection after treatment, % (95% CI; n/N)	100% (100 to 100; 48/48)	100% (100 to 100; 45/45)	100% (100 to 100; 32/32)	100% (100 to 100; 33/33)	100% (100 to 100; 36/36)	100% (100 to 100; 36/36)
Hookworm						
Participants positive for infection						
Baseline	28	17	180	194	49	39
After treatment	1	2	80	79	9	11
Cure rate, % (95% CI)	96% (89 to 104)	88% (71 to 105)	56% (48 to 63)	59% (52 to 66)	82% (70 to 93)	72% (57 to 87)
Cure rate by infection intensity, % (n/N)						
Light	96% (27/28)	93% (14/15)	63% (85/136)	67% (95/142)	82% (40/49)	72% (28/39)
Moderate	..	..	36% (10/28)	41% (14/34)	..	..
Heavy	..	50% (1/2)	31% (5/16)	33% (6/18)	..	..
Geometric mean EPG						
Baseline	94·4	108·6	731·4	861·8	100·6	80·5
After treatment	0·1	0·9	7·9	6·5	1·3	2·5
Geometric mean ERR, % (95% CI)	100% (100 to 100)	99% (97 to 100)	99% (98 to 99)	99% (99 to 100)	99% (97 to 100)	97% (93 to 99)
Arithmetic mean EPG						
Baseline	232·9	878·5	1620·6	1678·7	223·0	214·0
After treatment	0·4	89·3	146·6	129·5	30·6	48·0
Arithmetic mean ERR, % (95% CI)	100% (99 to 100)	90% (75 to 100)	91% (87 to 94)	92% (88 to 95)	86% (77 to 95)	78% (64 to 90)
Moderately or heavily infected participants with no or light infection after treatment, % (95% CI; n/N)	ND	100% (100 to 100; 2/2)	95% (89 to 102; 42/44)	98% (94 to 102; 51/52)	ND	ND
***Strongyloides stercoralis*†**						
Participants positive for infection						
Baseline	ND	ND	22	22	ND	ND
After treatment	ND	ND	4	1	ND	ND
Cure rate, % (95% CI)	ND	ND	82% (64 to 99)	96% (86 to 105)	ND	ND

EPG=eggs per g of stool. ERR=egg reduction rate. ND=not determined. *Significant differences are highlighted in bold; for cure rates, significance was defined when the p-value was <0·05 according to the melded binomial test for difference (mid-p version), whereas for ERRs, significance was defined when the 95% CI did not include 0. †*S stercoralis* infection was assessed qualitatively only (positive *vs* negative) in stool samples collected in Laos; 406 participants (193 in the albendazole group and 213 in the ivermectin–albendazole group) in Laos had at least one stool sample examined for *S stercoralis* at baseline and follow-up.

***Table 2*: Efficacy against *T trichiura* and co-infecting soil-transmitted helminths by trial country (available-case analysis)**

In Laos and Pemba Island, treatment with ivermectin–albendazole resulted in significantly higher cure rates and egg reduction rates (ERRs) compared to albendazole alone. In Côte d'Ivoire, ivermectin–albendazole showed similarly low efficacy to albendazole in terms of cure rates and ERRs. Subgroup analysis revealed higher cure rates against *T. trichiura* in participants with light infection intensities, irrespective of treatment group. The cure rate for ivermectin–albendazole in the 6–12 years age group was lower than the cure rate in the 13–60 years age group, but baseline infection intensities were also higher in the younger age group. Both treatment regimens showed high efficacy against *A. lumbricoides*, with cure rates above 93% and ERRs of 99–100% in all trial settings. Cure rates in hookworm-infected participants differed between settings but not between treatment groups, with the highest cure rate against hookworm observed in Côte d'Ivoire. Hookworm infections were well reduced in terms of ERRs in all settings. In Laos, participants infected with *S. stercoralis* showed high cure rates with both treatment regimens, with slightly better efficacy observed with ivermectin–albendazole.

To determine the efficacy of single doses of albendazole, ivermectin and diethylcarbamazine, and of the combinations albendazole + ivermectin and albendazole + diethylcarbamazine against common intestinal helminthiases caused by *Ascaris* and *Trichuris* spp, a randomised, placebo-controlled trial was performed, with infected children being randomly assigned to treatment with albendazole + placebo, ivermectin + placebo, diethylcarbamazine + placebo, albendazole + ivermectin, or albendazole + diethylcarbamazine.

Albendazole, ivermectin and the drug combinations gave significantly higher cure and egg reduction rates for ascariasis than diethylcarbamazine. For trichuriasis, albendazole + ivermectin gave significantly higher cure and egg reduction rates than the other treatments: the infection rates were lower 180 and 360 days after treatment.

Resistance

In the publication from Hürlimann et al (2022), regarding efficacy and safety assessment of co-administered ivermectin and albendazole in school-aged children and adults infected with *Trichuris trichiura*, the authors attribute to acquired drug resistance an explanation for treatment failure. Differences in parasite genetics, causing variance in parasite defence systems (e.g., drug efflux pumps and detoxification enzymes), among *T. trichiura* strains might have a role in reduced treatment efficacy.

Ivermectin

The increasing selection pressure on gastrointestinal nematodes due to the high frequency of the usage of macrocyclic lactones is thought to contribute the development of resistance to these compounds mainly in veterinary medicine. Changes on the GluCl structure and an increased expression of different proteins involved in drug efflux (P-gp) have been postulated as the main mechanism of resistance to the macrocyclic lactones in nematodes. It has been shown that *H. contortus* resistant to ivermectin possess an increased level of P-gp expression and that the co- application of verapamil (an MDR-reversing agent) increased efficacy of ivermectin and moxidectin against resistant strains of *H. contortus*. In addition to a role in ivermectin resistance (see 4.2.1.1.2), a subset of the amphid mutants is resistant to the non-related benzimidazole class of anthelmintics, raising the potential link to a multi-drug resistance mechanism (Lanusse C.; Lifschitz A. 2009, Page 2018).

Albendazole

The mechanism of resistance to benzimidazoles is most likely due to changes in β-tubulin protein, which decreases the binding to β-tubulin (Thakur and Patel, 2022).

The number of genes involved in resistance and their mode of inheritance (dominant or recessive) are additional factors with an important influence on the rate at which the resistance spreads. Polymorphism in β-tubulin isotype 1 seems to be most important for the resistance to benzimidazoles in *H. contortus* (Vercruysse, Albonico et al. 2011).

Effect on coagulation

According to the literature (reviewed by Canga et al, 2008), haematomatous swellings were reported in 2 out of 28 onchocerciasis patients treated with ivermectin (150 µg/kg), and prothrombin times were significantly above baseline by one week to one month after drug ingestion, suggesting an antagonist effect against vitamin K. Nevertheless, in other 20 subjects, no changes were observed in prothrombin nor in thromboplastin times compared with baseline results, during 13 days after the ingestion of 220–420 µg/kg of ivermectin; bleeding disorders were not found in 15,000 patients treated with ivermectin (150 µg/kg). Moreover, prolonged prothrombin ratios were observed in 148 subjects given ivermectin orally. Although no patients suffered bleeding complications, factor II and VII levels were reduced in most of them, suggesting interference with vitamin K metabolism. Ivermectin has a minimal effect on coagulation and concern about mass treatment for this reason appears to be unjustified. Finally, a man that had been on long-term oral anticoagulant therapy with acenocoumarol showed a persistent, excessive hypocoagulability while using insecticides (ivermectin and metidation).

Prolongation of QTc interval

In Study BLCL-IVA-EU-01, all subjects who received at least one dose of Test or Reference product constitute the safety population. Safety was evaluated through the assessment of AEs, electrocardiograms (ECGs), vital signs, and clinical laboratory tests.

In Study BLCL-IVA-EU-01, vital signs (blood pressure, pulse rate, respiratory rate and body temperature) and ECG recordings were collected. One subject presented low abnormal values of diastolic blood pressure (DBP) during Period 3. These abnormal results were considered clinically relevant by the Investigator and reported as TEAE (“Hypotension”). One subject presented high abnormal values of body temperature at admission of Period 3. These abnormal results were considered clinically relevant by the Investigator and reported as TEAE (“Hyperthermia”). No further out of range vital signs were judged to be clinically relevant by the Investigator, and no abnormality in the 12-lead ECG recordings was considered of clinical relevance by the Investigator.

In Suzuki et al, 2023, the authors evaluated the cardiovascular safety pharmacology of ivermectin using isoflurane-anesthetised beagle dogs (n=4). Ivermectin in doses of 0.1 followed by 1 mg/kg was intravenously infused over 10 min with an interval of 20 min, attaining peak plasma concentrations of 0.94 ± 0.04 and 8.82 ± 1.25 µg/mL, which were 29-31 and 276-288 times higher than those observed after its antiparasitic oral dose of 12 mg/body, respectively. The latter peak concentration was > 2 times greater than those inhibiting proliferation of dengue virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and hepatitis B

virus *in vitro*. Ivermectin decreased heart rate without altering mean blood pressure, suggesting that ivermectin does not cause hypotension or tachycardia directly. Ivermectin hardly altered atrioventricular nodal or intraventricular conduction, indicating a lack of inhibitory action on Ca2+ or Na+ channel *in vivo*. Ivermectin prolonged QT interval/QTcV in a dose-related manner and tended to slow the repolarisation speed in a reverse frequency-dependent manner, supporting previously described its IKr inhibition, which would explain Tpeak-Tend prolongation and heart-rate reduction in this study. Meanwhile, ivermectin did not significantly prolong J-Tpeakc or terminal repolarisation period, indicating torsadogenic potential of ivermectin leading to the onset of cardiopulmonary arrest would be small.

The authors suggest a hypothesis that ivermectin could be accumulated in the heart to increase its local tissue concentration, partly explaining the slow onset of the negative chronotropic effect and ventricular repolarisation delay. In order to test the validity of that hypothesis, the authors initially evaluated the relationship between the plasma ivermectin concentration and the change in QTcV (AQTcV) using all data points as depicted in Figure 4 below. No significant correlation was found between them. Next, to verify the presence of hysteresis, a diagram showing the time course of relationship between the plasma concentration and the AQTcV was depicted. After the low and high doses administration, a counterclockwise hysteresis was observed in the time course of relationship with further increase of the AQTcV even after max. Thus, these findings support the hypothesis that ivermectin may accumulate in the heart.

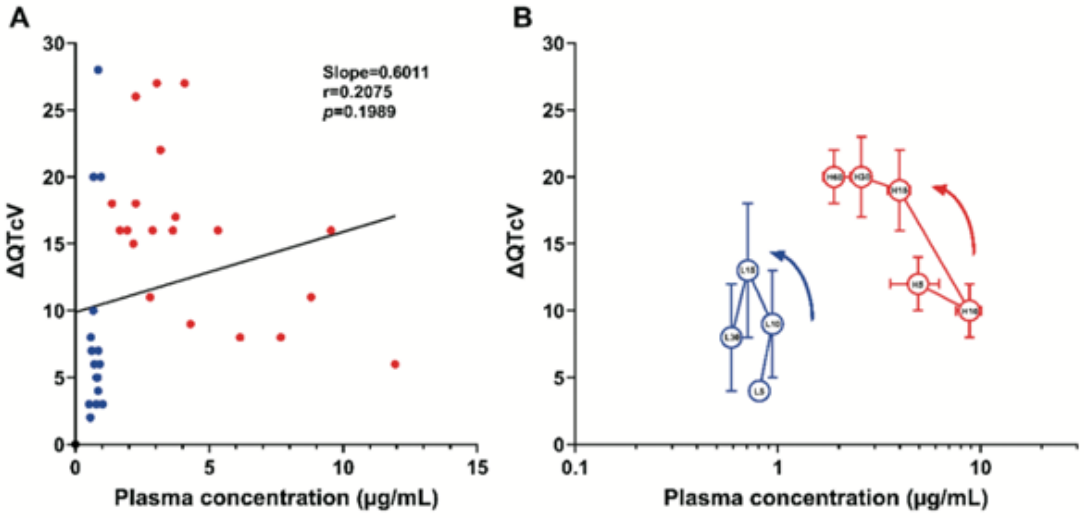


Fig. 6. The relationship between the plasma concentrations of ivermectin and the changes in QTcV from basal control value (ΔQTcV) after its 0.1 (blue) and 1 mg/kg (red) administration. (A) The individual ΔQTcV values were plotted versus the plasma concentration, which was evaluated by linear regression and correlation analyses. The slope value of linear regression line was 0.6011, and the correlation r-value was 0.2075 (p=0.1989). (B) The mean ΔQTcV values at each time point after the low and high doses administration were plotted versus the logarithmic plasma concentrations. The numbers in the symbols indicate elapsed time (min) after the start of administration of low (L, blue) and high doses (H, red). Data are presented as mean ± S.E. Note that ivermectin-induced prolongation of QTcV was enhanced despite a decline in the plasma drug concentration.

Figure 4 Plasma ivermectin concentration and the change in QTcV (AQTcV)

Effect on $GABA_A$ receptor

Ivermectin supressed convulsions that were artificially induced in mice (by pentylenetetrazole or electroshock). Intraperitoneally administered, ivermectin at doses of 0.5 mg/kg, 1 mg/kg, 5 mg/kg, and 10 mg/kg increased the clonic seizure threshold considerably. However, at doses of 0.05 mg/kg and 0.2 mg/kg ivermectin had no significant anticonvulsive effects. It is thought that this effect of ivermectin might be mediated by $GABA_A$ receptors and KATP channels (Manavi, Mohammad Jafari et al. 2022).

2.6.2. Discussion on clinical pharmacology

Pharmacokinetics

The present application concerns the development of a fixed dose combination with the purpose of an initial combination treatment (as defined in the guideline EMA/CHMP/158268/2017). Regarding the clinical pharmacology development and following the recommendations of the guideline EMA/CHMP/158268/2017, the PK of the individual active substances should be well understood and a DDI study between the active substances in the fixed combination product should be evaluated. Also, a popPK analysis should be developed for evaluating the potential impact of combined PK in vulnerable subgroups. Overall, this approach was followed by the applicant that basically conducted 2 clinical trials:

- Comparative bioavailability trial (BLCL-IVA-EU-01) – the 18/400 mg FDC was compared with administration of ivermectin (Stromectol 6x3 mg) and albendazole (Eskazole 1x400 mg) in adults under light meal conditions to demonstrate similar exposure based on geometric least-square mean ratios (GMRs) but not on 90% confidence interval (CI) that fall within 80-125%.
- Efficacy and safety trial (ALIVE) – to demonstrate superior efficacy of a single dose of the FDC vs. a single dose of 400 mg albendazole given alone and superior efficacy of a 3-day FDC regimen vs. a single dose of 400 mg albendazole given alone for treatment of each of whipworm, hookworm and strongyloidiasis. The efficacy of 1 vs. 3 FDC doses was also be compared.

Methods

Analytical methods were developed for the determination of albendazole, albendazole sulfoxide, ivermectin B1a and ivermectin B1b in plasma. The validations were overall well-made and resulted in acceptable expected performances. In study analysis were generally acceptable. For the BA study, there was a need for method optimisation during study due to insufficient analytical sensitivity. Although unusual, this allowed for a better characterisation of the PK data. The general performance and the ISR analysis confirmed the adequacy of the method. Regarding the analytical determination of the phase II/III study, no ISR analysis was provided. This was justified due to the low sample volume available that rendered impossible to perform such analysis. This is acceptable.

Data from the BA/BE study was analysed based on non-compartmental approaches and comparisons based on ANOVA and GMR CI90. This data was also evaluated, together with the data from the phase II study, in a popPK analysis.

The applicant developed two popPK models with the data from the phase I BA/BE study with adult healthy volunteers and the phase II study with paediatric and young adults with STH infection. The first model focused on the Albendazole sulfoxide PK and the second on the ivermectin (H2B1a) PK. The modelling procedure was similar for both models. Data exclusion considered only a few samples (<3% for ALB and < 6% for IVR) that were either missing or showing post-dose BLQ. The model building procedure was following general approaches, starting with a structural model evaluation, random effects and residual errors, followed by a covariate effect. This latter was done by univariate screening followed by a stepwise backward elimination process. This seems appropriate as the shrinkage in the model random parameters was low (ALB) to medium (IVR). The final model parameters seemed acceptable and confirmed in a bootstrap approach. Also, Cl/F and V/F were found to be correlated with the subject's weight in an allometric scaling way. The predicted exponents were far from the theoretical ones but resulted in significantly better fittings to the data. In fact, standard allometric exponents using exponents of 0.75 for CL and 1 for V could potentially underpredict the clearance and volume of the paediatric participants with lower body weight, resulting in a under prediction of the doses needed to achieve the target albendazole and ivermectin exposure. The IVR model seems to show some relevant underprediction on the early time points, visible on the GOF plots and on the vPCs of the phase II (ALIVE) data. However, the comparison of geometric means between observed and model predicted Cmax resulted in a geometric mean ratio (GMR) of 1.04 with a 90% confidence interval (CI) of 0.91 to 1.19.

Bioavailability of ivermectin was 16% higher for the FDC compared to administration of Stromectol. As exposure-response analysis showed a flat relationship and the FDC regimen was well tolerated in children and adolescents this is regarded as acceptable.

Absorption

This application concerns a FDC of albendazole and ivermectin which was developed as an orodispersible tablet with the strengths 9 mg ivermectin/400 mg albendazole and 18 mg ivermectin/ 400 mg albendazole. Since ivermectin and albendazole are well known substances, ADME data of the single active substances have been very briefly summarised by the applicant based on literature data.

No new data was presented regarding the absorption of both ivermectin and albendazole. According to the known behaviour of these drugs, their absorption is relatively fast with t_{max} values at around 4 h. No new studies were presented regarding the bioavailability of both active substances. The absolute bioavailability is unknown for both active substances, but due to their low aqueous solubility, their BCS class is predicted to be either II or IV.

In clinical studies, an increase of ivermectin bioavailability up to 2.5 times has been reported. However, based on a recent population-based PK analyses, the food effect on relative bioavailability of ivermectin is minimal and the recommendations for administration of ivermectin has been changed accordingly for ivermectin products in the EU. Albendazole, on the contrary, has a clear increase in bioavailability due to the presence of food in the GI track and should be administered with a meal. In line with that, it is recommended to administer the FDC with or after a meal, as reflected in sections 4.2 and 5.2 of the SmPC.

The only PK study conducted with the FDC was study BLCL-IVA-EU-01, a single-centre, single-dose, open-label, randomised, six-sequence, three treatment, three-period cross-over study to compare the bioavailability of the FDC with the reference products Stromectol (ivermectin) and Eskazole (albendazole) under light meal conditions in adult healthy subjects. Based on the results the major ivermectin component H2B1, can be considered bioequivalent between the FDC and the reference formulation. The bioavailability of albendazole and its metabolite is lower in the FDC formulation than in the reference formulation. However, efficacy of the FDC was shown in the pivotal phase III study and thus the difference in bioavailability is not considered clinically relevant. No biowaiver for the lower dose FDC formulation was provided, but both strengths products were used in clinical studies.

Distribution

Both active components of the FDC, albendazole and ivermectin, have been on the market for treatment of helminthiasis for many years. Thus, information on their pharmacokinetic characteristics, including distribution characteristics, is available in published scientific literature.

As albendazole rapidly undergoes extensive first-pass metabolism in the liver prior to reaching the systemic circulation, albendazole concentrations are negligible or undetectable in plasma. The systemic anthelmintic activity has been attributed to the primary metabolite, albendazole sulfoxide. The primary metabolite albendazole sulfoxide is 70% bound to plasma protein. It is widely distributed throughout the body, as is evident by its detection in urine, bile, liver, cyst wall, cyst fluid, and cerebrospinal fluid. Concentrations in plasma are 3- to 10-foldand two-fold higher than in the cyst fluid and cerebrospinal fluid (simultaneously determined), respectively.

Due to the high lipid solubility of ivermectin, this compound is widely distributed within the body. In healthy men, the volume of distribution in the central compartment, Vc, was 3.1 and 3.5 L/kg, after ingesting 6 and 12 mg of ivermectin, respectively. In onchocerciasis patients, with 6 mg (tablet), the volume of distribution of the area (Vλ) was 9.9 L/kg. Distribution of ivermectin in tissues was evaluated after a single oral dose of 150 µg/kg in 10 onchocerciasis patients. Ivermectin could be detected in all tissues sampled. Fat showed the highest and most persistent levels, whilst values for skin, nodular tissues, and worms were comparable. Subcutaneous fascia contained the lowest concentrations. The high concentration of ivermectin in fat is a function of the lipid solubility of the drug, and fat acts as a reservoir for ivermectin.

Elimination

Only simple descriptions on the elimination and metabolism were provided. For ivermectin, it is clear that it is mostly eliminated as metabolites. Its metabolism seems to be mainly by CYP3A4, although other CYP may also be involved. Regarding Albendazole, it is also eliminated by both CYP3A4 and FMO. Since these are old drugs and their use generally known, this level of knowledge, although not quite clear, is acceptable.

Regarding albendazole sulfoxide, the main active metabolite and circulating species after administration of albendazole, only vague information was provided referring that it is metabolised and mainly eliminated in the urine with a plasma half-life of 8.5 h. Based on literature, after a single oral dose of 400 mg albendazole was rapidly metabolised, with albendazole sulfoxide and albendazole sulphone measured in the bloodstream at the first sampling time (2 h post treatment). The pharmacologically active albendazole sulfoxide

metabolite was the analyte recovered at the highest concentrations which rapidly increased to reach its peak concentration (C_{max}=1.20±0.44 µg/mL) at 4.75 h (t_{max}). The systemic drug exposure, estimated as the albendazole sulfoxide $AUC_{0\text{-}LOQ}$ value, was 21.4±1.19 µg·h/mL. This analyte was measured in the bloodstream up to 72 h after albendazole oral administration in seven volunteers. Albendazole sulfoxide was rapidly excreted in urine following the albendazole treatment and was the main albendazole metabolite recovered between 4 h (first sampling time) and 72 h post treatment. Albendazole sulfoxide peak urine concentration (3.24±1.51 µg/mL) was reached at 6.50 h (t_{max}). Low concentrations of albendazole sulphone were quantified in urine between 4 and 8 h post treatment, mostly under the LOQ which precluded any pharmacokinetic analysis. Albendazole concentrations in urine were under the limit of detection at all sampling times.

Research with human liver microsomes identified albendazole as a high-clearance medication (hepatic clearance [CLH] = 18.2 mL/min/kg) with metabolism primarily through CYP1A2 and CYP3A4, with some involvement from CYP1A1. It is also known that other flavin-containing oxidases are involved in metabolism, in addition to the CYP oxidases, and that repeated exposure alters kinetics likely through induction of the CYP enzymes involved.

Published information indicates that there is dose linearity for ivermectin and dose-dependent PK for albendazole. In this last case, it should be due to solubility issues. The FDC considers a single dose for albendazole (400 mg) and two dosage strengths for ivermectin (9 mg and 18 mg). These two different doses are not for obtaining higher exposures during treatment but for obtaining similar exposures in different subpopulations.

No information was provided regarding the possibility of time-dependency. Based on the concentrations observed on 24 h and 48 h on the BA/BE study, the potential for accumulation is low and less than about 25% in a daily administration regime. Moreover, the popPK model that included data of multiple administrations did not require any non-linearity in its structural model. In any case, the drug is to be administered in a single dose administration or, in some situations, in a once-a-day administration for only 3 days. As such, the risk of time-dependent PK issues is low.

The estimated intrasubject variability (based on the residual variability of the ANOVA) observed in the BA/BE study for the C_{max} and AUC was low for H2B1a, average for H2B1b and albendazole sulfoxide and high for albendazole.

Pharmacokinetics in the target population

The applicant is proposing a weight-based posology according to the following:

Adults, children (≥5 years) and adolescents with a body weight of:

- 15 kg to <45 kg: one single oral dose of 9 mg/400 mg ivermectin/albendazole orodispersible tablet
- ≥45 kg: one single oral dose of 18 mg/400 mg ivermectin/albendazole orodispersible tablet

This was based on the initial results observed in the phase II part and were later confirmed in the phase III part of the ALIVE study.

It should be mentioned that, regarding albendazole, the group taking the reference product presented a higher AUC than the groups taking the FDC formulation, confirming the reduced bioavailability observed in the BA/BE study. Another relevant fact is that, in the phase II part, only one subject had a weight above 45 kg questioning the extrapolation of the observed results for the adult population, were the weights are expectably higher. In published literature, reported values for C_{max} ranged from 0.288 µg/mL (288 ng/mL) to 1.20 µg/mL (1,200 ng/mL) after a dose of 400 mg, a range that comprises the values of ALIVE (see Table 7). Similarly, reported values for AUC ranged from 3.418 µg·h/mL (3.418 ng·h/mL) to 22.4 µg·h/mL (22,400 µg·h/mL). These values contained the Expected exposures to albendazole calculated using the PPK model by different weight bands (15-23 kg, 23-30 kg, 30-45 kg, 45-70 kg, 70-100 kg).

Regarding ivermectin, it should be mentioned that the values proposed for dose/weight are frequently higher than the ones in use in the reference formulation (200 ug/kg). The applicant referred that, in the recent years, new data on the safety and PK of ivermectin have been published by other groups, showing the adequate safety profile of the drug in small groups of children and adults when given at doses of up to 600 µg/kg.

In order to clarify some of these previous issues, the applicant provided a discussion on the therapeutic window of these two drugs. Regarding ivermectin several published studies showed that, for doses as high as 800 mg/kg, an overall comparable safety to standard doses. Moreover, trials exploring the safety of combination therapy (high dose IVM plus albendazole) in comparison with albendazole (ALB) monotherapy or with diethylcarbamazine containing dual or triple chemotherapy did not report significant differences in the frequency or severity of AEs both in children and adults, indicating a better safety profile of IVM-ALB combination chemotherapy. Regarding albendazole efficacy, since a dose of 200 mg has been shown to be effective, the efficacy of the combination product should not be jeopardised by a decrease in bioavailability of ALB.

Special populations

No clinical studies were provided regarding the consequences of impaired renal function or impaired hepatic function on the PK of both drugs. Based on the lack of renal elimination and the major elimination by metabolism, warning was made on the use of these drugs in hepatic impairment subjects.

Gender does not seem to influence the Ivermectin PK, however, regarding albendazole sulfoxide, females seem to present a CL/F with a 10% reduction when compared to males. This should not be clinically relevant. Race do not seem to influence the PK of both drugs. Weight is a significant variable in the PK of both drugs. As in the reference product, albendazole is administered in a fixed-dose regime of 400 mg. Regarding ivermectin, the applicant proposes a two-strength regime based on two weight bands. Apparently, there is limited data of patients above 65 years old published in the literature and no single subject was included in the presented clinical studies performed with the FDC formulation in this age band. As such, it is acceptable to follow the current information provided in the SmPC of the two individual drugs. Regarding paediatrics, besides the information assessed in the popPK model, the decision on safety and efficacy of the current FDC mainly relies on the phase II/III study performed in children and young adults.

Pharmacokinetic interactions

Several *in vitro* DDI were described for ivermectin, due to the fact that this drug is a substrate of P450 3A enzymes, substrate and inhibitor of P-gp and multidrug resistance protein (MRP), and an inhibitor of Breast Cancer Resistance Protein (BCRP) transporter. Several consequences are expected by these known characteristics, but no *in vivo* data exist to support these.

Regarding albendazole, no relevant pre-clinical data was provided and the DDI profile will be defined based on published *in vivo* studies. In this regard, there are already several DDI described in the literature with complex behaviours. For example, the effect of inhibitors or inducers of CYP3A can result in a decrease exposure of albendazole sulfoxide probably by a mixed effect at its production and elimination. These known DDI are well described in the SmPC.

The CHMP considered that the main risk regarding the drug-drug interactions is for the fixed-dose combination to be the “victim”, since it will be administered either in a single dose or in a 3-day regime and both active substances have relatively small elimination half-lives.

No interaction between ivermectin and albendazole was observed in the study by Awadzi et al. (2003).

Pharmacodynamics

Ivermectin’s mode of action involves its effect on ion channels in cell membranes, leading to muscle paralysis. While initially it was believed ivermectin targets gamma-amino butyric acid (GABA)-regulated chloride channels, later evidence suggested that it induces an influx of chloride through channels not regulated by GABA. Specifically, GABA-linked chloride channels in parasitic nematodes are less sensitive to ivermectin compared to other channels.

Benzimidazoles, including albendazole, disrupt microtubule function, inhibiting polymerisation of tubulin and affecting nematode feeding and egg production. This action is more pronounced in parasites due to slower dissociation from parasite tubulin compared to mammalian tubulin. Albendazole’s gradual effect is attributed to interference with microtubule formation and cellular mitotic activity. This mechanism leads to starvation and death of nematodes by affecting intestinal cells. Additionally, albendazole inhibits axoplasmic transport, impacting parasite neuronal activities. Its therapeutic usage extends to flatworms, particularly trematodes and cestodes.

The applicant has supported the primary pharmacodynamics mainly on non-clinical data, with characterisation on the spectrum of activity of both individual active substances. In the literature, clinical trials characterising the effect of this combination have been performed, either with isolated active substances or other combinations, in which a support for the primary pharmacodynamics can be found, by the establishment of a correlation between cure rates of infected patients and egg number reduction in stools, providing a biomarker for the pharmacodynamic effect of the combination.

Although some information was provided on the resistance profile to albendazole, mainly to support the clinical rationale of the ivermectin combination, the possible resistance development for the combination proposed was also further discussed. Although it can be agreed that combination therapy with 2 medicines of different mechanisms of action has been the core recommendation to prevent the emergence of resistance, with albendazole and ivermectin being the most cited example for the case of STH, nevertheless, the absence

of results of the resistance analysis of isolates from STH species collected in the ALIVE trial prevents the definite establishment of a resistance profile for this combination, pending new data from exposed individuals. The CHMP noted the applicant´s commitment to submit these data post-authorisation, as soon as they become available.

Regarding secondary pharmacology, the applicant has not presented dedicated data on this topic form human studies. However, in the non-clinical development, a possible allosteric modulation of $GABA_A$ was observed in mice. The applicant stated that avermectin B1A acts on a modulatory binding site of benzodiazepine receptor and could stimulate it. That can be an indicator that ivermectin can act as a positive allosteric modulator of the $GABA_A$ receptor. Given the possible effect of ivermectin on $GABA_A$ receptors, the applicant was asked to discuss possible pharmacodynamic interactions with other $GABA_A$ allosteric modulators. The applicant has agreed that the modulating effect of ivermectin on GABA receptors may be related to interactions with other GABA modulators like benzodiazepines, sodium oxybate and valproic acid. Besides the warning of not treating an ivermectin overdose with GABA agonists (in section 4.9 of the SmPC), the applicant has additionally included these potential interactions in section 4.5.

In some patients treated in the clinical trials provided by the applicant, increased bleeding times were reported. Although not leading to bleeding events, there is data that suggests an effect on the clotting factors II and VII. The applicant has reported no ECG alterations that were found to be correlated to the active substances administration in the two major clinical trials provided.

Taking into consideration the secondary pharmacology of ivermectin, the potential for pharmacodynamic interactions with anticoagulants, particularly anti-vitamin K (warfarin), was further discussed by the applicant and a text regarding co-administration of ivermectin and warfarin was included in section 4.5 of the SmPC.

The applicant has not presented any data regarding the dose-effect relationship or data that could support a PK/PD correlation or dose chosen. Published data on the dose relationship effect of ivermectin on several species can be used as support for the doses chosen. The use of this combination of specific doses is based on the accumulating individual evidence for each active substance and recent Phase 3 clinical trials (BLCL-IVA-EU-01 and ALIVE) have used already the proposed posology in this application without PK/PD data. Provided that efficacy of the proposed combination is established, absence of PK/PD support could be justified.

2.6.3. Conclusions on clinical pharmacology

The clinical pharmacokinetics was mainly based on bibliographic literature, and data from the Phase 1 BE and Phase 2/3 studies on the combination. The clinical pharmacodynamics was mainly based on bibliographic literature and non-clinical information, further complemented during the assessment with information from study BLCL-IVA-EU-01 (phase I) and study ALIVE (phase II/III) on the combination. This was accepted by the CHMP.

The CHMP recommends the following measures necessary to address the issues related to pharmacology:

Pending new data from exposed individuals, the definite establishment of a resistance profile for the ivermectin and albendazole combination is prevented by the absence of results of the resistance analysis of isolates from soil-transmitted helminth species collected in the ALIVE trial. Therefore, these resistance data should be submitted as soon as they become available.

2.6.4. Clinical efficacy

2.6.4.1. Dose response studies

The applicant did not initially address this topic. Ivermectin and albendazole are extensively used and the rationale for a fixed-dose combination is explained in other sections of the assessment report. There are some groups where a higher than approved dose of ivermectin is used, e.g. the approved dose in some indications can go up to 400 µg/kg).

The CHMP noted that in this FDC, the dose can achieve >600 µg/kg in some children weight groups and asked the applicant to further elaborate on the rationale for the use of doses up to 600 µg/kg of ivermectin.

The applicant supported the higher ivermectin dose (up to 600 µg/kg) mainly by demonstration of no significant safety issues from the use of high doses in the treatment of parasitic infections or when ivermectin was tested for the treatment of patients with COVID-19.

2.6.4.2. Main study

An Adaptive Phase II/III Single-Blinded, Randomised, Multi-Center, Parallel-Group, Active-Controlled, Superiority Study to Evaluate the Safety and Efficacy of a Single Day or 3-day Single Dose of an ALBENDAZOLE-IVERMECTIN Co-formulation vs ALBENDAZOLE for the Treatment of Soil-Transmitted Helminth Infections (*Trichuris trichiura*, hookworm, *Strongyloides stercoralis*) in Paediatric and Young Adult *Population*

Methods

- Study Participants

Inclusion Criteria

To be eligible to participate in the study, an individual must have met the following criteria:

Phase II candidates: Positive infection test by microscopy for *T. trichiura.*

Phase III candidates: Positive infection test by microscopy for at least 1 of the following STH:

T. trichiura, hookworms, and/or larvae of *S. stercoralis*.

All candidates (Phase II/III):

1. Weight ≥ 15 kg (for Phase II/III) and ≤ 45 kg (Phase II only).

2. Male or female, aged 5 to 18 years.

3. Female participants who were ≥ 12 years old (or any female who was post-menarche) was required to have a negative urine pregnancy test at Screening or at the time of randomisation.

4. Ability to take oral medication and willingness to comply with all study procedures.

Main Exclusion Criteria

1. Intake of ALB, mebendazole, and/or IVM within the previous 3 months before Screening.

2. Currently receiving warfarin.

4. Epidemiological risk of *Loa loa* infection.

5. Serious medical illness, per investigator's criteria.

8. Positive urine test, pregnant, or first week post-partum.

Note: Individuals infected by the STH parasites (*T. trichiura* in Phase II; *T. trichiura*, hookworm, and/or *S. stercoralis* in Phase III) were eligible to participate. Individuals with a single infection due to *A. lumbricoides* were not enrolled since no extra benefit is expected to be achieved with the FDC for this population due to the high efficacy of the standard of care ALB.

- Treatments

Dosing – Phase II

Phase II participants were enrolled sequentially into 3 body weight-based groups, with the IVM dose starting at 300-391 µg/kg, and stratified into the different weight groups:

- Group 1 (body weight: 23 ≤ 30 kg): FDC as ALB 400 mg/IVM 9 mg (corresponding to an IVM dose of 300-391 µg/kg) or ALB 400 mg

- Group 2 (body weight: 30-45 kg): FDC as ALB 400 mg/IVM 18 mg (corresponding to an IVM dose of 400-600 µg/kg) or ALB 400 mg

- Group 3 (body weight: 15-23 kg): FDC as ALB 400 mg/IVM 9 mg (corresponding to an IVM dose of 391-600 µg/kg) or ALB 400 mg

Participants were then randomly allocated with unequal probability (1:2:2) to receive 1 of 3 treatments within each weight group, please see study schema in Figure 5 bellow:

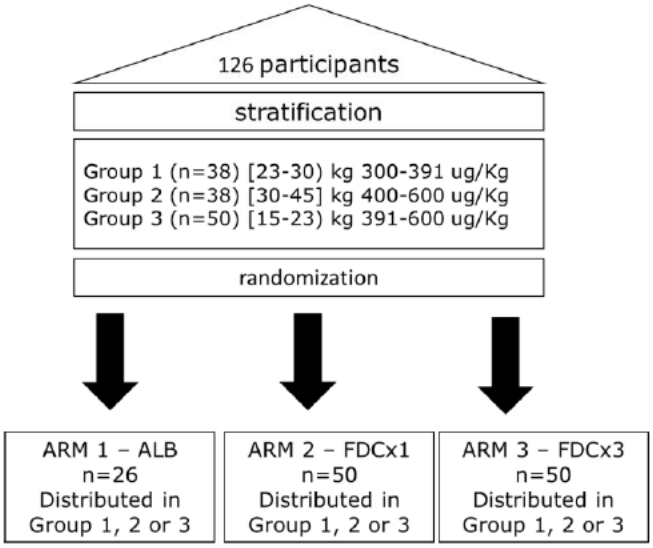


Figure 5: Phase II study schema

Dosing – Phase III

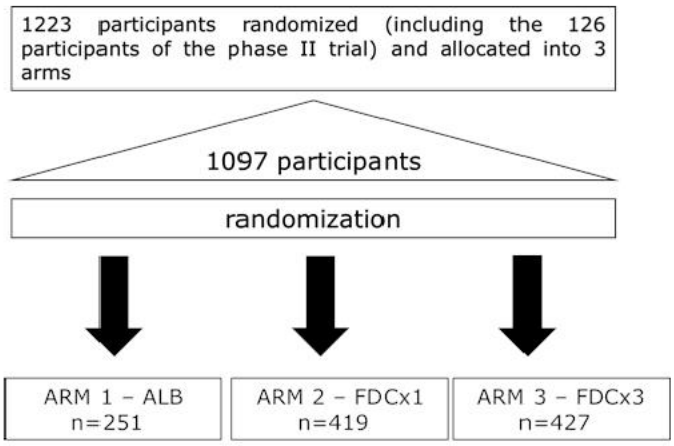
Participants were assigned to 1 of 3 study arms by block randomisation (1:1:1) and stratified by species of STH, please see study schema in Figure 6 bellow:

- Arm 1: ALB 400 mg single dose (active control arm)

- Arm 2: FDC single dose (doses based on body weight)

- Arm 3: FDC daily dose x3 days (doses based on body weight):

(Body weight ≥ 45 kg: ALB 400 mg/IVM 18 mg; Body weight < 45 kg: ALB 400 mg/IVM 9 mg)



Abbreviations: ALB=albendazole; FDC=fixed-dose co-formulation (ALB/IVM); FDC x1=FDC single dose; FDC x3=FDC single dose x3 days.

Figure 6 Phase III study schema

Bioavailability of albendazole is poor and it is recommended to take albendazole with a high-fat meal, while ivermectin should be administered in the fasted state. As a compromise, light fat conditions were chosen during the Phase 2/3 study.

Criteria for treatment rescue

All participants with a positive STH infection by microscopy on the last study visit were provided with rescue treatment:

-*S. stercoralis* infection were offered IVM 3 mg tablets at the currently standard regimen (200 µg/kg). *A. lumbricoides*, hookworms and/or *T. trichiura* were offered ALB through their local health centres.

- Objectives and endpoints

Phase II and III objectives and endpoints are presented in Table 10 and Table 11: Phase III objectives and endpoints respectively.

Table 10: Phase II objectives and endpoints

Objectives	Endpoints
Primary	
To evaluate the safety of FDC as a single dose or FDC daily dose x3 days (FDC x3) for the treatment of *T. trichiura* in pediatric and young adult population.	Frequency, type, severity and relationship to study drug for all AEs and SAEs for FDC single dose and FDC x3.
Secondary	
To evaluate the efficacy of FDC against *T. trichiura* in a pediatric population.	Measurement of cure rate (CR) for *T. trichiura* in the different treatment arms.
	Measurement of the egg reduction rate (ERR) for *T. trichiura* in the different treatment arms.
To evaluate the efficacy of FDC against hookworms and *S. stercoralis* in participants co-infected with species concomitantly to their infections with *T. trichiura*.	Measurement of CR for hookworm and *S. stercoralis* in those co-infected with species concomitantly to their infections with *T. trichiura*.
	Measurement of ERR for hookworm in those co-infected with species concomitantly to their infections with *T. trichiura*.
To describe the extent of IVM exposure in different weight strata	Measurement of the rate of absorption (Cmax), time to reach maximum concentration (Tmax) and extent of absorption (i.e., AUC) of FDC single dose and FDC x3.
To evaluate the acceptability and palatability of the FDC 400 mg/18 mg and 400 mg/9 mg.	Participant acceptability and palatability evaluation of the FDC 400 mg/18 mg and 400 mg/9 mg using the 5-point Likert numeric rating scale.

Abbreviations: AE=adverse event; ALB=albendazole; AUC=area under the concentration time curve; Cmax=maximum concentration; CR=cure rate; ERR=egg reduction rate; FDC=fixed-dose co-formulation (ALB/IVM); FDC x3=FDC daily dose x3 days; SAE=serious adverse event; Tmax=time to reach maximum concentration.

Table 11: Phase III objectives and endpoints

Objectives	Endpoints
Primary	
To evaluate the efficacy of FDC as a single dose and FDC daily dose x3 days (FDC x3) compared to the standard single dose regimen of ALB (400 mg) for the treatment of *T. trichiura* in a pediatric and young adult population.	CR for *T. trichiura* 21 days after treatment, as determined by microscopy (i.e., efficacy for *T. trichiura*).
Secondary	
To evaluate the efficacy of FDC as a single dose and FDC x3 for the treatment of hookworm and *S. stercoralis*.	CR for hookworm and *S. stercoralis* 21 days after treatment, as determined by microscopy (i.e., efficacy for hookworm and *S. stercoralis*). ERR for *T. trichiura* 21 days after treatment by microscopy.
To evaluate the safety of FDC as a single dose and FDC x3 for the treatment of *T. trichiura*, hookworm and *S. stercoralis*.	Frequency, type, severity and relationship to study drug for all AEs and SAEs for ALB, FDC single dose, and FDC x3 (safety).
To evaluate the performance of qPCR in calculating the primary outcome measurement (efficacy) compared to an egg counting method (Kato-Katz).	CR for *T. trichiura*, hookworm, and *S. stercoralis* using qPCR. Change in parasite burden for hookworm, *T. trichiura*, and *S. stercoralis* by qPCR.
To evaluate the frequency of known ALB-resistant alleles in hookworm and *T. trichiura* in the 3 treatment arms before and after treatment.	Evaluation of genotypic ALB resistance in the 3 arms.

Abbreviations: AE=adverse event; ALB=albendazole; CR=cure rate; ERR=egg reduction rate; FDC=fixed-dose coformulation (ALB/FDC); qPCR=quantitative polymerase chain reaction; SAE=serious adverse event; FDC x3=FDC daily dose x3 days.

The evaluation of albendazole-resistant alleles in hookworm and *T. trichiura* is listed as secondary objective. According to the CSR, analysis methods were not validated at the time of the report and results will be reported in a subsequent report. The applicant clarified that new methods were needed to thoroughly evaluate resistant variants. Results from the genomics analyses on resistance are expected by the end of 2025.

- Sample size

Sample size was calculated estimating the efficacy of the different experimental drug or combinations for each of the STH of interest [Chow 2008; StataCorp 2017] and gathering the individual samples sizes for the study. The sample size was calculated for pairwise comparisons of the expected CRs for the 3 study arms with an overall significance level of 5% adjusted for multiple tests by Bonferroni's correction, 80% power and inflated for 10% lost-to-follow-up.

The estimated total number of participants for the adaptive design is 1223 (625 for *T. trichiura*, 286 for *S. stercoralis*, and 312 for hookworm). The sample size for the Phase II component is 20% of the total participants positive for *T. trichiura* (126 participants). The remaining 80% of the participants positive for *T.*

trichiura were randomised in the Phase III component. The total sample size is powered to be able to measure efficacy for all 3 species in the Phase III component.

The sample size calculations according to the expected CR for each drug and STH species of interest, and the resulting sample size inflated by 10% due to the estimated lost-to-follow-up are detailed in the SAP

- Randomisation and Blinding (masking)

Randomisation

Participants were randomised to 3 study arms to minimise bias in IMP assignment, to increase the likelihood that known and unknown subject attributes (e.g., demographic and baseline characteristics) were evenly balanced between groups, and to enhance the validity of statistical comparisons across study arms.

Blinding

In the Phase II component, participants were stratified into 3 body weight groups and then allocated by simple randomisation to 1 of 3 treatment arms with unequal probability (1:1:2, ALB, FDC single dose, FDC x3). The randomisation for each participant detailed the assigned study arm and pharmacokinetic (PK) group, indicating the timepoints for blood collection for the PPK analysis.

In Phase III, allocation of participants to study arms was done by block randomisation and stratified by STH species. Randomisation was conducted separately at each of the 3 study sites.

Computer-generated randomisation lists were prepared before the study start by the statistician and under the supervision of the Sponsor.

- Statistical methods

Primary Efficacy Analyses

The primary efficacy endpoint for the Phase III component was the CR for *T. trichiura* at 21 days after treatment using microscopy. The analysis pooled the ITT populations from Phase II and Phase III. Sensitivity analyses were conducted on the Phase II and Phase III efficacy per-protocol population. The Cochran–Mantel–Haenszel (CMH) test was used to compare the CRs for the 3 treatment arms, controlling the effect of site if that was appropriate (sufficient participants).

Secondary Efficacy Analyses

The secondary efficacy endpoint analyses were conducted using the Phase II and Phase III ITT population (i.e., pooled analyses), the Phase II ITT population alone, the Phase III ITT population alone, and the corresponding efficacy per-protocol populations. The CR for *T. trichiura,* hookworm, and *S. stercoralis* as well as the ERR for *T. trichiura* and hookworm at 21 days after treatment were determined by microscopy.

Results

- Participant flow

Subject disposition in phase II and phase III is presented in Table 12 and Table 13 below.

Table 12: Subject disposition in phase in phase II (ITT population)

Parameter	ALB 400 mg Single Dose (N = 30)	FDC of 400 mg ALB – 18/9 mg IVM			Overall (N = 135)
		Single Dose (N = 51)	Daily Dose x3 Days (N = 54)	FDC Pooled (N = 105)	
Screened, n	-	-	-	-	441
Screen failure	-	-	-	-	307
Screen failure but randomized	-	-	-	-	1
Eligible but not randomized	-	-	-	-	0
Randomized, n	30	51	54	105	135
Randomized but did not receive study drug, n (%)	3 (10.0)	1 (2.0)	3 (5.6)	4 (3.8)	7 (5.2)
Received any study drug after randomization, n (%)	27 (90.0)	50 (98.0)	51 (94.4)	101 (96.2)	128 (94.8)
Completed study, n (%)	24 (80.0)	48 (94.1)	51 (94.4)	99 (94.3)	123 (91.1)
Discontinued study, n (%)	6 (20.0)	3 (5.9)	3 (5.6)	6 (5.7)	12 (8.9)
Primary reason for study discontinuation					
Other	6 (20.0)	1 (2.0)	3 (5.6)	4 (3.8)	10 (7.4)
Eligibility criteria (either newly developed or not previously recognized)	0	0	0	0	1 (0.7)
Missing	0	1 (2.0)	0	1 (1.0)	1 (0.7)

Table 13: Subject disposition in phase in phase III (ITT population)

Disposition, n (%)	ALB 400 mg Single Dose (N = 213)	FDC of 400 mg ALB – 18/9 mg IVM			Overall (N = 866)
		Single Dose (N = 330)	Daily Dose x3 Days (N = 323)	FDC Pooled (N = 653)	
Screened	-	-	-	-	3912
Screen failure	-	-	-	-	3051
Screen failure but randomized	-	-	-	-	6
Eligible but not randomized	-	-	-	-	1
Randomized	213	330	323	653	866
Randomized but did not receive study drug	0	0	0	0	0
Received any study drug after randomization	213 (100.0)	330 (100.0)	323 (100.0)	653 (100.0)	866 (100.0)
Completed study	206 (96.7)	326 (98.8)	319 (98.8)	645 (98.8)	851 (98.3)
Discontinued study	7 (3.3)	4 (1.2)	4 (1.2)	8 (1.2)	15 (1.7)
Primary reason for study discontinuation					
Lost to follow-up	1 (0.5)	0	0	0	1 (0.1)
Eligibility criteria[a]	3 (1.4)	2 (0.6)	1 (0.3)	3 (0.5)	6 (0.7)
Other	3 (1.4)	2 (0.6)	3 (0.9)	5 (0.8)	8 (0.9)

- Conduct of the study

According to the statement in the ALIVE protocol:

Each study site performed internal quality management of study conduct, data and biological specimen collection, documentation, and completion. An individualised quality management plan was developed to describe a site's quality management.

Quality control procedures were implemented which included checks of the data entry system and the database. Any missing data or data anomalies were communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors verified that the clinical study was conducted, data generated and, biological specimens collected, documented (recorded), and reported in compliance with the protocol, SOPs, the International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices, Good Manufacturing Practices).

Each investigational site was required to provide direct access to all study-related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

No major amendments were made to the protocol.

- Baseline data

Baseline characteristics are presented in Table 14, Table 15, Table 16 and

Table 17 below.

Table 14: Demographic and other baseline characteristics (phase II ITT population)

Parameter	ALB 400 mg Single Dose (N = 30)	FDC of 400 mg ALB – 18/9 mg IVM			Overall (N = 135)
		Single Dose (N = 51)	Daily Dose x3 Days (N = 54)	FDC Pooled (N = 105)	
Age					
Median	9.0	8.0	8.5	8.0	9.0
Min, Max	5, 13	5, 15	5, 17	5, 17	5, 17
p-value vs. ALB 400 mg Single Dose	-	0.8788	0.8038	-	-
Age group, n (%)					
5 to 14 years	30 (100.0)	48 (94.1)	52 (96.3)	100 (95.2)	130 (96.3)
15 to 18 years	0	3 (5.9)	2 (3.7)	5 (4.8)	5 (3.7)
p-value vs. ALB 400 mg Single Dose	-	0.2917	0.5353	-	-
Sex, n (%)					
Male	20 (66.7)	28 (54.9)	31 (57.4)	59 (56.2)	79 (58.5)
Female	10 (33.3)	23 (45.1)	23 (42.6)	46 (43.8)	56 (41.5)
p-value vs. ALB 400 mg Single Dose	-	0.3537	0.4874	-	-
Weight group, n (%)					
< 45 kg	30 (100.0)	51 (100.0)	53 (98.1)	104 (99.0)	134 (99.3)
≥ 45 kg	0	0	1 (1.9)	1 (1.0)	1 (0.7)
p-value vs. ALB 400 mg Single Dose	-	NE	1.0000	-	-
BMI					
Median	14.0	14.0	14.0	14.0	14.0
Min, Max	12, 21	12, 31	12, 18	12, 31	12, 31
p-value vs. ALB 400 mg Single Dose	-	0.6034	0.3913	-	-

Abbreviations: ALB=albendazole; BMI=body mass index; FDC=fixed-dose co-formulation (ALB/IVM); ITT=intent-to-treat; IVM=ivermectin; NE=not evaluable.
Notes: P-value for continuous variables from t-test. P-value for categorical variables from Fisher's exact test.

Table 15: Baseline disease characteristics (phase II ITT population)

	ALB 400 mg Single Dose (N = 30)	FDC of 400 mg ALB – 18/9 mg IVM			Overall (N = 135)
Parameter, n (%)		**Single Dose (N = 51)**	**Daily Dose x3 Days (N = 54)**	**FDC Pooled (N = 105)**	
Positive for *T. trichiura*	30 (100.0)	51 (100.0)	54 (100.0)	105 (100.0)	135 (100.0)
p-value vs. ALB 400 mg Single Dose	-	NE	NE	-	-
Positive for *A. lumbricoides*	0	2 (3.9)	1 (1.9)	3 (2.9)	3 (2.2)
p-value vs. ALB 400 mg Single Dose	-	0.5278	1.0000	-	-
Positive for hookworm	2 (6.7)	4 (7.8)	4 (7.4)	8 (7.6)	10 (7.4)
p-value vs. ALB 400 mg Single Dose	-	1.0000	1.0000	-	-
Positive for *S. stercoralis*	0	4 (7.8)	3 (5.6)	7 (6.7)	7 (5.2)
p-value vs. ALB 400 mg Single Dose	-	0.2909	0.5483	-	-

Abbreviations: ALB=albendazole; FDC=fixed-dose co-formulation (ALB/IVM); ITT=intent-to-treat; IVM=ivermectin; NE=not evaluable.
Notes: P-value for continuous variables from t-test. P-value for categorical variables from Fisher's exact test

Analyses of demographic characteristics for the randomised participants compared with the screen failure participants showed no clinically relevant differences between the groups.

Table 16: Demographic and other baseline characteristics (phase II ITT population)

Parameter	ALB 400 mg Single Dose (N=213)	FDC of 400 mg ALB – 18/9 mg IVM			Overall (N=866)
		Single Dose (N=330)	Daily Dose x3 Days (N=323)	FDC Pooled (N=653)	
Age					
Median	11.0	11.0	11.0	11.0	11.0
Min, Max	5, 18	5, 18	5, 18	5, 18	5, 18
p-value vs. ALB 400 mg Single Dose	-	0.4086	0.6681	-	-
Age group, n (%)					
5 to 14 years	186 (87.3)	285 (86.4)	269 (83.3)	554 (84.8)	740 (85.5)
15 to 18 years	27 (12.7)	45 (13.6)	54 (16.7)	99 (15.2)	126 (14.5)
p-value vs. ALB 400 mg Single Dose	-	0.7964	0.2193	-	-
Sex, n (%)					
Male	113 (53.1)	165 (50.0)	179 (55.4)	344 (52.7)	457 (52.8)
Female	100 (46.9)	165 (50.0)	144 (44.6)	309 (47.3)	409 (47.2)

Parameter	ALB 400 mg Single Dose (N=213)	FDC of 400 mg ALB – 18/9 mg IVM			Overall (N=866)
		Single Dose (N=330)	Daily Dose x3 Days (N=323)	FDC Pooled (N=653)	
p-value vs. ALB 400 mg Single Dose	-	0.5383	0.5962	-	-
Country					
Ethiopia	96 (45.1)	107 (32.4)	104 (32.2)	211 (32.3)	307 (35.5)
Kenya	84 (39.4)	158 (47.9)	155 (48.0)	313 (47.9)	397 (45.8)
Mozambique	33 (15.5)	65 (19.7)	64 (19.8)	129 (19.8)	162 (18.7)
p-value vs. ALB 400 mg Single Dose	-	0.0122	0.0112	-	-
Weight group					
< 45 kg	185 (86.9)	277 (83.9)	271 (83.9)	548 (83.9)	733 (84.6)
≥ 45 kg	28 (13.1)	53 (16.1)	52 (16.1)	105 (16.1)	133 (15.4)
p-value vs. ALB 400 mg Single Dose	-	0.3891	0.3870	-	-
BMI					
Median	16.0	16.0	15.0	15.0	16.0
Min, Max	11, 31	12, 25	10, 25	10, 25	10, 31
p-value vs. ALB 400 mg Single Dose	-	0.7514	0.3544	-	-

Serum HIV test (Mozambique only)					
Positive	1 (0.5)	2 (0.6)	0	2 (0.3)	3 (0.3)
Negative	1 (0.5)	6 (1.8)	6 (1.9)	12 (1.8)	13 (1.5)
p-value vs. ALB 400 mg Single Dose	-	1.0000	0.2500	-	-
Missing	211 (99.1)	322 (97.6)	317 (98.1)	639 (97.9)	850 (98.2)

Abbreviations: ALB=albendazole; FDC=fixed-dose co-formulation (ALB/IVM); HIV=human immunodeficiency virus; ITT=intent-to-treat; IVM=ivermectin; NE=not evaluable.

Notes: P-value for continuous variables from t-test. P-value for categorical variables from Fisher's exact test.

Table 17: Baseline disease characteristics (phase III ITT population)

Parameter	ALB 400 mg Single Dose (N=213)	FDC of 400 mg ALB – 18/9 mg IVM			Overall (N=866)
		Single Dose (N=330)	Daily Dose x3 Days (N=323)	FDC Pooled (N=653)	
Positive for *T. trichiura*	101 (47.4)	200 (60.6)	200 (61.9)	400 (61.3)	501 (57.9)
p-value vs. ALB 400 mg Single Dose	-	0.0027	0.0010	-	-
Positive for *A. lumbricoides*	15 (7.0)	19 (5.8)	24 (7.4)	43 (6.6)	58 (6.7)
p-value vs. ALB 400 mg Single Dose	-	0.5883	1.0000	-	-
Positive for hookworm	106 (49.8)	124 (37.6)	120 (37.2)	244 (37.4)	350 (40.4)
p-value vs. ALB 400 mg Single Dose	-	0.0058	0.0043	-	-
Positive for *S. stercoralis*	16 (7.5)	40 (12.1)	41 (12.7)	81 (12.4)	97 (11.2)
p-value vs. ALB 400 mg Single Dose	-	0.1112	0.0631	-	-

Analyses of demographic characteristics for the randomised participants compared with the screen failure participants showed no clinically relevant differences between the groups. However, about 85% of participants had a weight <45 kg. This is considered a limiting factor, since efficacy data for the higher ivermectin dose (18 mg) for patients ≥45 kg allowing to extrapolate efficacy for the adult patient population are limited. No patients >18 years old were included.

- Numbers analysed, Outcomes and estimation

Primary Efficacy Analysis: Cure Rate for *T. trichiura* – Phase II and III Pooled

Result of the primary efficacy analysis and the subgroup analysis results are presented in and Table 19.

Table 18: Cure rate for participants infected with *T. trichiura* at 21 days after treatment as assessed by microscopy (Phase II and Phase III ITT Population)

	ALB 400 mg Single Dose (N = 243)	FDC 400 mg ALB – 18/9 mg IVM	
		Single Dose (N = 381)	Daily Dose x3 Days (N = 377)
Phase II and Phase III Pooled			
Number of participants positive for infection with *T. trichiura* at pre-treatment, n	131	251	254
Number of participants cured at post-treatment, n	47	208	247
Cure rate (CR), % (95% CI)	35.9 (27.7, 44.1)	82.9 (78.2, 87.5)	97.2 (95.2, 99.3)
Difference in CR (vs. ALB 400 mg Single Dose)			
Difference[a]	-	47.2	61.3
P-value[b]	-	< 0.0001	< 0.0001

Abbreviations: ALB=albendazole; CR=cure rate; FDC=fixed-dose co-formulation (ALB/IVM); ITT=intent-to-treat; IVM=ivermectin.

a. Difference in cure rates, expressed in percentages, and based on Mantel Haenszel methods to account for stratification by site.

b. P-values are based on the Cochran-Mantel-Haenszel test, controlling for the effect of site.

Notes: A participant with multiple infections was included in the analysis of each target species that the participant was infected with.

Participants missing the post-treatment stool sample were considered as not cured.

Participants withdrawn before Visit 6 (21 days after treatment) with stool sample were included in the analysis.

Table 19: Subgroup analysis of cure rate for subjects infected with *T. trichiura* at 21 days after treatment by microscopy (phase II and phase III ITT population)

Subgroup Parameters	ALB 400 mg Single Dose	FDC 400 mg ALB – 18/9 mg IVM	
		Single Dose	Daily Dose x3 Days
IVM drug exposure > 400 µg/kg			
Number positive at pre-treatment, n	131	78	85
Number cured at post-treatment, n	47	63	81
Cure rate (CR), % (95% CI)	35.9 (27.7, 44.1)	80.8 (72.0, 89.5)	95.3 (90.8, 99.8)
Difference in CR (vs. ALB)[a]	-	44.3	58.1
P-value[b]	-	< 0.0001	< 0.0001
IVM drug exposure ≤ 400 µg/kg			
Number positive at pre-treatment, n	131	173	169
Number cured at post-treatment, n	47	145	166
Cure rate (CR), % (95% CI)	35.9 (27.7, 44.1)	83.8 (78.3, 89.3)	98.2 (96.2, 100.0)
Difference in CR (vs. ALB)[a]	-	48.4	62.6
P-value[b]	-	< 0.0001	< 0.0001
Age 5 – 14 years			
Number positive at pre-treatment, n	126	237	235
Number cured at post-treatment, n	45	195	228
Cure rate (CR), % (95% CI)	35.7 (27.3, 44.1)	82.3 (77.4, 87.1)	97.0 (94.8, 99.2)
Difference in CR (vs. ALB)[a]	-	46.6	61.0
P-value[b]	-	< 0.0001	< 0.0001

Subgroup Parameters	ALB 400 mg Single Dose	FDC 400 mg ALB – 18/9 mg IVM	
		Single Dose	Daily Dose x3 Days
Age 15 – 18 years			
Number positive at pre-treatment, n	5	14	19
Number cured at post-treatment, n	2	13	19
Cure rate (CR), % (95% CI)	40.0 (0.0, 82.9)	92.9 (79.4, 100.0)	100.0 (100.0, 100.0)
Difference in CR (vs. ALB)[a]	-	57.9	65.1
P-value[b]	-	0.0071	0.0001
Mono-infected			
Number positive at pre-treatment, n	111	204	212
Number cured at post-treatment, n	34	174	206
Cure rate (CR), % (95% CI)	30.6 (22.1, 39.2)	85.3 (80.4, 90.2)	97.2 (94.9, 99.4)
Difference in CR (vs. ALB)[a]	-	54.3	66.1
P-value[b]	-	< 0.0001	< 0.0001
Co-infected			
Number positive at pre-treatment, n	20	47	42
Number cured at post-treatment, n	13	34	41
Cure rate (CR), % (95% CI)	65.0 (44.1, 85.9)	72.3 (59.6, 85.1)	97.6 (93.0, 100.0)
Difference in CR (vs. ALB)[a]	-	14.8	35.6
P-value[b]	-	0.2096	0.0001
Worm burden: light			
Number positive at pre-treatment, n	121	229	229
Number cured at post-treatment, n	45	191	222
Cure rate (CR), % (95% CI)	37.2 (28.6, 45.8)	83.4 (78.6, 88.2)	96.9 (94.7, 99.2)
Difference in CR (vs. ALB)[a]	-	46.2	59.8
P-value[b]	-	< 0.0001	< 0.0001
Worm burden: moderate			
Number positive at pre-treatment, n	10	20	24
Number cured at post-treatment, n	2	16	24
Cure rate (CR), % (95% CI)	20.0 (0.0, 44.8)	80.0 (62.5, 97.5)	100.0 (100.0, 100.0)
Difference in CR (vs. ALB)[a]	-	63.0	80.0
P-value[b]	-	0.0014	< 0.0001

Source: Table 14.2.1.2.1

Abbreviations: ALB=albendazole; CR=cure rate; FDC=fixed-dose co-formulation (ALB/IVM); ITT=intent-to-treat; IVM=ivermectin.

[a]. Difference in cure rates, expressed in percentages, and based on Mantel Haenszel methods to account for stratification by site.

[b]. P-values are based on the Cochran-Mantel-Haenszel test, controlling for the effect of site.

Notes: A participant with multiple infections was included in the analysis of each target species that the participant was infected with.

Participants missing the post-treatment stool sample were considered not cured
Participants withdrawn before Visti 6 (21 days after treatment) with stool sample were included in the analysis.

Superiority of the primary endpoint (cure rate for *T. trichiura*) was shown for both the FDC single dose and the FDCx3 regimen in all subgroups (except for co-infected patients treated with the FDC single dose).

A subgroup analysis for the cut-off weight (<45 kg, ≥45 kg) of the ivermectin dose showed that the cure rate of the FDC single dose arm was lower in patients ≥45 kg compared to patients <45 kg (76% vs 87%).

Results on secondary objectives considered key to the assessment are presented in Table 20, Table 21, Table 22 and Table 23.

Table 20: Cure rate for participants infected with hookworm at 21 days after treatment as assessed by microscopy (phase II and phase III ITT population)

	ALB 400 mg Single Dose (N = 243)	FDC 400 mg ALB – 18/9 mg IVM	
		Single Dose (N = 381)	Daily Dose x3 Days (N = 377)
Phase II and Phase III Pooled			
Number of participants positive for infection with hookworm at pre-treatment, n	108	128	124
Number of participants cured at post-treatment, n	70	99	117
Cure rate (CR), % (95% CI)	64.8 (55.8, 73.8)	77.3 (70.1, 84.6)	94.4 (90.3, 98.4)
Difference in CR (vs. ALB 400 mg Single Dose)			
Difference[a]		12.7	29.3
P-value[b]		0.0321	< 0.0001

Abbreviations: ALB=albendazole; FDC=fixed-dose co-formulation (ALB/IVM); ITT=intent-to-treat; IVM=ivermectin

a. Differences in cure rates are expressed in percentages, and are based on Mantel Haenszel methods to account for stratification by site.
b. The p-values are based on the Cochran-Mantel-Haenszel test, controlling for the effect of site.
Notes: A participant with multiple infections was included in the analysis of each target species that the participant was infected with.
Participants missing the post-treatment stool sample were considered as not cured.
Participants withdrawn before Visit 6 (21 days after treatment) with stool sample were included in the analysis.

Table 21: Cure rate for participants infected with *S. stercoralis* at 21 days after treatment as assessed by microscopy (phase II and phase III ITT population)

	ALB 400 mg Single Dose (N = 243)	FDC 400 mg ALB – 18/9 mg IVM	
		Single Dose (N = 381)	Daily Dose x3 Days (N = 377)
Phase II and Phase III Pooled			
Number of participants positive for infection with *S. stercoralis* at pre-treatment, n	16	44	44
Number of participants cured at post-treatment, n	13	40	43
Cure rate (CR), % (95% CI)	81.3 (62.1, 100.0)	90.9 (82.4, 99.4)	97.7 (93.3, 100.0)

Abbreviations: ALB=albendazole; FDC=fixed-dose co-formulation (ALB/IVM); ITT=intent-to-treat; IVM=ivermectin
Notes: A participant with multiple infections was included in the analysis of each target species that the participant was infected with.
Participants missing the post-treatment stool sample were considered as not cured.
Participants withdrawn before Visit 6 (21 days after treatment) with stool sample were included in the analysis.

The sample size was not reached for the analysis of CR for *S. stercoralis*. Therefore, CR data are presented for informational purposes only.

Table 22: ERR for *T. trichiura* and hookworm 21 days after treatment as assessed by microscopy

Phase 2 and Phase 3 Pooled	ALB 400 mg Single Dose (N=243)	FDC ALB 400 mg – IVM 18/9 mg	
		Single Dose (N=381)	FDC x3 (N=377)
T. trichiura			
Geometric mean ERR for *T. trichiura* (%)	83.4	99.2	99.9
Difference in logarithm of EPG at post-treatment (vs ALB 400 mg single dose)			
LS mean difference	-	-2.4	-2.9
p-value	-	<0.0001	<0.0001
Hookworm			
Geometric mean ERR for hookworm (%)	97.8	98.8	99.7
Difference in logarithm of EPG at post-treatment (vs ALB 400 mg singe dose)			
LS mean difference	-	-0.4	-1.0
p-value	-	0.0460	<0.0001

Notes: A participant with multiple infections was included in the analysis of each target species that the participant was infected with. Participants missing the post-treatment stool sample were considered as not cured. Participants withdrawn before Visit 6 (21 days after treatment) with stool sample were included in the analysis.
ALB=albendazole; CI=confidence interval; CR=cure rate; FDC=fixed-dose combination; ITT=intention-to-treat

population; IVM=ivermectin

Table 23: Cure rate for subjects infected with STH species at 21 days after treatment as assessed by PCR – Phase III (ITT population)

Infection Type Statistics	ALB 400 mg Single Dose (N=213)	FDC of 400 mg ALB - 18/9 mg IVM Single Dose (N=330)	FDC of 400 mg ALB - 18/9 mg IVM Daily Dose x 3 Days (N=323)
Subjects infected with any of STH species			
Number of subjects positive for infection at pre - treatment, n	97	188	190
Number of subjects cured for any STH species at post - treatment, n	50	133	153
Cure rate (CR) %(95% CI)	51.5 (41.6, 61.5)	70.7 (64.2, 77.2)	80.5 (74.9, 86.2)
Difference in CR (vs. ALB 400 mg Single Dose)			
Difference		20.1	29.1
P-value		0.0007	<0.0001
Subjects infected with Trichuris trichiura			
Number of subjects positive for infection at pre - treatment, n	97	188	190
Number of subjects cured at post - treatment, n	50	133	153
Cure rate (CR) %(95% CI)	51.5 (41.6, 61.5)	70.7 (64.2, 77.2)	80.5 (74.9, 86.2)
Difference in CR (vs. ALB 400 mg Single Dose)			
Difference		20.1	29.1
P-value		0.0007	<0.0001

ALB = Albendazole; FDC = Fixed Dose Co-formulation; IVM = Ivermectin.
CI = confidence interval; n = number of subjects in the specified group; N = number of subjects in the specified analysis set under each treatment group; NE = Not Evaluable.
Cure rate (CR) is defined as the proportion of individuals cured (mean Ct-values are less or equal than 50 at baseline, and greater than 50 after treatment) to the total of those infected at baseline with each particular species of soil transmitted helminths (STH).
When there are non-detectable levels of DNA in the sample, it will be categorized with a Ct-value equal to 50.
Difference in cure rates, expressed in percentages, and based on Mantel Haenszel methods to account for stratification by site. P-value based on the Cochran-Mantel-Haenszel test, controlling for the effect of site.
Subjects missing the post-treatment stool sample are considered not cured. Patient withdrawn before visit 6 (21 days after treatment) with stool sample will be included in the analysis

- Ancillary analyses

Table 24: Agreement calculation with Cohen's kappa between *T. trichiura* positivity based on Kato-Katz and qPCR (phase II and phase III ITT population)

Visit Statistic	ALB 400 mg Single Dose (N = 243)	FDC 400 mg ALB – 18/9 mg IVM	
		Single Dose (N = 381)	Daily Dose x3 Days (N = 377)
Pre-treatment, N1			
Positive by qPCR, n/N1 (%)	126/243 (51.9)	237/381 (62.2)	244/377 (64.7)
Positive by Kato-Katz, n/N1 (%)	131/243 (53.9)	251/381 (65.9)	254/377 (67.4)
Positive by both qPCR and Kato-Katz, n/N1 (%)	120/243 (49.4)	227/381 (59.6)	235/377 (62.3)
Cohen's Kappa Coefficient (95% CI)	0.860 (0.795, 0.924)	0.807 (0.745, 0.868)	0.835 (0.776, 0.893)
Post-treatment, N1			
Positive by qPCR, n/N1 (%)	75/243 (30.9)	87/381 (22.8)	52/377 (13.8)
Positive by Kato-Katz, n/N1 (%)	84/243 (34.6)	42/381 (11.0)	7/377 (1.9)
Positive by both qPCR and Kato-Katz, n/N1 (%)	50/243 (20.6)	27/381 (7.1)	5/377 (1.3)
Cohen's Kappa Coefficient (95% CI)	0.449 (0.330, 0.568)	0.329 (0.216, 0.443)	0.141 (0.022, 0.261)

ALB=albendazole; FDC=fixed-dose co-formulation; ITT=intent-to-treat; IVM=ivermectin; N1=number of participants tested with both qPCR and Kato-Katz methods in the specified analysis set by treatment arm.

Notes: When there were non-detectable levels of DNA in the sample, it was categorised with a Ct-value equal to 50. For all participants without baseline PCR results, the median baseline Ct value of the entire population was used. For all participants without post-treatment PCR results, the baseline value of the participant was used as the Ct value. Participants missing the post-treatment stool sample were considered. The EPG value at Day 21 was the baseline value.
Participants withdrawn before Visit 6 (21 days after treatment) with stool sample were included in the analysis.

- Summary of main efficacy results

Table 25 summarises the efficacy results from the main study supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 25: Summary of efficacy for trial ALIVE

Title: An Adaptive Phase II/III Single-Blinded, Randomized, Multi-Center, Parallel-Group, Active-Controlled, Superiority Study to Evaluate the Safety and Efficacy of a Single Day or 3-day Single Dose of an ALBENDAZOLE-IVERMECTIN Co-formulation vs ALBENDAZOLE for the Treatment of Soil-Transmitted Helminth Infections (*Trichuris trichiura, hookworm*, *Strongyloides stercoralis*) in Paediatric and Young Adult *Population*		
Design	PHASE II The Phase II component was a 3-arm, parallel, and open-label study conducted in a paediatric population at a single study site in Kenya. This phase of the study evaluated safety, population pharmacokinetics (PPK), and the acceptability of the formulation. Eligible participants were positive for *T. trichiura* infection (confirmed by Kato-Katz technique in a fresh stool sample). PHASE III The Phase III component was single-blinded, randomised, active-controlled, parallel-group, multi-center (Kenya, Ethiopia, and Mozambique), superiority study to assess FDC single dose or FDC x3 compared with active control (i.e., ALB single dose) in a paediatric and young adult population. Blinded operators conducted the laboratory-based measurements of efficacy for the single blinding of the primary efficacy endpoint. Eligible participants were positive by microscopy infection test for at least 1 of the STH species under study. Eligible participants were positive for STH infection (confirmed by microscopy) with at least 1 of the following: *T. trichiura, S. stercoralis*, or hookworms.	
	Duration of pre-screening period: Duration of screening: Duration of treatment: Post treatment follow up	* Up to 3 months 1 week 1 to 3 days depending on arm of the study 21 days
Hypothesis	The main hypothesis in Phase III is that FDC (either as a single dose or daily dose x3 days) is more effective (superior) against STH than the current strategy (ALB single dose).	
Phase II (N=126)		
ARM1	Alb 400 mg	Albendazole 400 mgx1, control group: N=26

Title: An Adaptive Phase II/III Single-Blinded, Randomized, Multi-Center, Parallel-Group, Active-Controlled, Superiority Study to Evaluate the Safety and Efficacy of a Single Day or 3-day Single Dose of an ALBENDAZOLE-IVERMECTIN Co-formulation vs ALBENDAZOLE for the Treatment of Soil-Transmitted Helminth Infections (*Trichuris trichiura, hookworm*, *Strongyloides stercoralis*) in Paediatric and Young Adult *Population*		
ARM 2	FDC single dose (doses based on body weight): -Body weight ≥ 45 kg: IVM/ALB 18 mg/400 mg -Body weight < 45 kg: IVM/ALB 9 mg/400 mg	FDC single dose (doses based on body weight): -Body weight ≥ 45 kg: IVM/ALB 18 mg/400 mg -Body weight < 45 kg: IVM/ALB 9 mg/400 mg N=50
ARM 3	FDC x3 (doses based on body weight): -Body weight ≥ 45 kg: IVM/ALB 18 mg/400 mg -Body weight < 45 kg: IVM/ALB 9 mg/400 mg	FDC x3 (doses based on body weight): -Body weight ≥ 45 kg: IVM/ALB 18 mg/400 mg -Body weight < 45 kg: IVM/ALB 9 mg/400 mg N=50
Phase III (N=1097)		
ARM1	Alb 400 mg	Albendazole 400 mgx1, control group: N=251
ARM2	FDC single dose (doses based on body weight): -Body weight ≥ 45 kg: IVM/ALB 18 mg/400 mg -Body weight < 45 kg: IVM/ALB 9 mg/400 mg	FDCx1 N=419
ARM3	FDC single dose (doses based on body weight): -Body weight ≥ 45 kg: IVM/ALB 18 mg/400 mg -Body weight < 45 kg: IVM/ALB 9 mg/400 mg	FDCx1 N=427

Title: An Adaptive Phase II/III Single-Blinded, Randomized, Multi-Center, Parallel-Group, Active-Controlled, Superiority Study to Evaluate the Safety and Efficacy of a Single Day or 3-day Single Dose of an ALBENDAZOLE-IVERMECTIN Co-formulation vs ALBENDAZOLE for the Treatment of Soil-Transmitted Helminth Infections (*Trichuris trichiura, hookworm*, *Strongyloides stercoralis*) in Paediatric and Young Adult *Population*			
Endpoints and definitions The primary efficacy endpoint for the Phase III component was the CR for *T. trichiura* at 21 days after treatment using microscopy. The analysis included both Phase II and Phase III participants (i.e., pooled analysis) and was conducted on the ITT population (i.e., Phase II and Phase III ITT population).	The analysis included both Phase II and Phase III participants (i.e., pooled analysis) and was conducted on the ITT population (i.e., Phase II and Phase III ITT population).	ITT population (pooled analysis)	A participant was considered cured if the baseline egg count or larval count was not 0, and the post-treatment egg count or larval count was 0. Similarly, a participant was considered to have treatment failure if the baseline egg or larval count is not 0, and the egg or larval count after treatment is not 0. A total of 2 stool samples (1 pre-treatment and 1 post-treatment) were obtained from each participant. Stool sample collected pre-treatment was used for the baseline information, and stool sample collected post-treatment was used for the post-treatment information in the statistical analysis. A participant with multiple infections was included in the analysis of each target species that the participant was infected with. Efficacy for each type of infection was analysed separately.
	Secondary: -CR for T. trichiura at 21 days after treatment, as determined by microscopy (Phase II only; The corresponding Phase III endpoint was the primary efficacy analysis -CR for hookworm at 21 days after treatment, as determined by microscopy. -CR for S. stercoralis at 21 days after treatment, as determined by microscopy. -ERR for T. trichiura at 21 days after treatment, by microscopy. -ERR for hookworm at 21 days after treatment, by microscopy.		
Results and Analysis			
Analysis description	Primary Analysis		
Analysis population and time point description	Cure Rate for Participants Infected with T. trichiura at 21 Days after Treatment by Microscopy (Phase 2 and Phase 3 ITT Population, ALIVE)		

Title: An Adaptive Phase II/III Single-Blinded, Randomized, Multi-Center, Parallel-Group, Active-Controlled, Superiority Study to Evaluate the Safety and Efficacy of a Single Day or 3-day Single Dose of an ALBENDAZOLE-IVERMECTIN Co-formulation vs ALBENDAZOLE for the Treatment of Soil-Transmitted Helminth Infections (*Trichuris trichiura, hookworm*, *Strongyloides stercoralis*) in Paediatric and Young Adult *Population*				
Descriptive statistics and estimate variability	Treatment group	Alb 400 mg ARM1	FDC single dose (doses based on body weight): -Body weight ≥ 45 kg: IVM/ALB 18 mg/400 mg -Body weight < 45 kg: IVM/ALB 9 mg/400 mg ARM2	FDC x3 (doses based on body weight): -Body weight ≥ 45 kg: IVM/ALB 18 mg/400 mg -Body weight < 45 kg: IVM/ALB 9 mg/400 mg ARM3
	Number of subjects	243	381	377
	Number of participants positive for infection with T. trichiura at pre-treatment/ Number of participants cured at post-treatment	131/47	251/208	254/247
	Cure Rate %(95%CI)	35.9 (27.7-44.1)	82.9 (78.2-87.5)	97.2 (95.2- 99.3)
	Difference in CR (vs ALB 400 mg single dose)			
	Diference[a]	-	47.2	61.3
	P value #		<0.001	<0.001
	Secondary endpoint	Cure Rate for Hookworm and *S. stercoralis* by Microscopy	ARM1 Vs ARM2 Vs ARM3	

Title: An Adaptive Phase II/III Single-Blinded, Randomized, Multi-Center, Parallel-Group, Active-Controlled, Superiority Study to Evaluate the Safety and Efficacy of a Single Day or 3-day Single Dose of an ALBENDAZOLE-IVERMECTIN Co-formulation vs ALBENDAZOLE for the Treatment of Soil-Transmitted Helminth Infections (*Trichuris trichiura, hookworm*, *Strongyloides stercoralis*) in Paediatric and Young Adult *Population*			
		Number of participants positive for infection with hookworm at pre-treatment/ Number of participants cured at post-treatment, n	108/70 vs 128/99 vs 124/117
		Cure rate (CR), % (95% CI)	64.8 (55.8, 73.8) vs 77.3 (70.1, 84.6) vs 94.4 (90.3, 98.4)
		P-value#	-vs 0.03 vs <0.001

*First participant enrolled 19/Jan/2022 (Phase II); 05/May/2022 (Phase III); Last participant completed 24/Mar/2023

a Difference in cure rates is expressed in percentages and are based on Mantel Haenszel methods to account for stratification by site.

P-values are based on the Cochran-Mantel-Haenszel test, controlling for the effect of site.

2.6.4.3. Clinical studies in special populations

No specific information on clinical studies in special populations was provided in addition to what is already described in this AR. Due to the special population involved in the clinical study ALIVE, information related to children > 5 years and above 15 kg is not repeated here. Children not meeting these criteria were not included.

HIV test was performed in the Mozambique site, but due to the low number of patients included no conclusion could be made.

2.6.4.4. Supportive study(ies)

The applicant provided eight studies in support of the indications claimed, as summarised in Table 26.

All of these support the indications claimed, with the exception of the study by Dembele et al. 2010 in which the primary efficacy endpoint was the difference in *W. bancrofti* levels between the 2 groups at 12 months by examining parasite clearance rates at baseline and 12 months after treatment. No other study for treatment of lymphatic filariasis was submitted. This study only supported the indication for treatment of lymphatic filariasis caused by *W. bancrofti*.

Table 26: Summary of published studies submitted by the applicant to support the claimed indication

Publication	Design	Objective	Investigational Product(s) and Route of Administration	Study Population; Country	Dose and Duration of Exposure	Efficacy Endpoints
Ndyomugyenyi et al., 2008	Randomised, open label, controlled trial with four arms.	To examine the efficacy of ivermectin and albendazole alone and in combination given in the second trimester of pregnancy and record adverse events after treatment.	**Group A:** Ivermectin **Group B:** Albendazole. **Group C:** Combination of A/I **Group D:** reference group without STHs. All medicaments were orally administered	Adult pregnant women (≥16 weeks of gestation) infected with any intestinal helminth. 832 randomised Group A: 198 Group B: 194 Group C: 199 Group D: 241 Uganda	Ivermectin 150-200 µg/kg, single dose Albendazole 400 mg, single dose Albendazole 400 mg + Ivermectin 150-200 µg/kg, both single dose	Efficacy (cure rate of STHs) was defined as the proportion of pregnant women who were excreting eggs in their stool before treatment, but who had a negative test result at 21 days follow-up.
Knopp et al., 2010	Randomised controlled trial	To assess the efficacy and safety of albendazole plus placebo, albendazole plus ivermectin, mebendazole plus placebo, and mebendazole plus ivermectin in children with parasitologically confirmed *T. trichiura* infection.	Albendazole/Placebo Albendazole/Ivermectin Mebendazole/Placebo Mebendazole/Ivermectin All medicaments were orally administered	Children >5 years old infected with *T. trichiura*, *A. lumbricoides*, and Hookworm 610 randomised, 548 analysed: Albendazole+Placebo: 132 Albendazole+Ivermectin: 140 Mebendazole+Placebo: 138 Mebendazole+Ivermectin: 138 Tanzania	Albendazole 400 mg Ivermectin 200 mg/kg Mebendazole 500 mg All single dose	Cure rate (CR) and egg reduction rate (ERR) achieved by treatment with any drug regimen against *T. trichiura* infections. CR was determined as the percentage of children excreting eggs before treatment who became negative after treatment. The ERR was calculated as the reduction in the group's geometric mean (GM) egg count, including infected and noninfected subjects at follow-up
Speich et al., 2015	Randomised controlled trial	To compare the efficacy and safety of ALB plus ivermectin, ALB plus mebendazole, and ALB plus oxantel pamoate, with a standard treatment (one-dose mebendazole), to identify the intervention with the greatest potential against *T. trichiura* and concomitant STHs	Albendazole/Ivermectin Albendazole plus Mebendazole Albendazole plus Oxantel pamoate Mebendazole alone All medicaments were orally administered	Children aged 6-14 years infected with *T. trichiura*, *A. lumbricoides*, *S. stercoralis*, and Hookworm 440 randomised: 110 assigned to each arm. Tanzania	Albendazole 400 mg Ivermectin 200 µg/kg Mebendazole 500 mg Oxantel pamoate 20 mg/kg All single dose	The primary endpoints were the proportion of children cured and the reduction in the number of eggs of *T. trichiura* analysed by available case. Secondary outcomes were the proportion of children cured and the reduction in the number of eggs of concomitant nematode infections and drug safety (assessed at two timepoints) analysed by intention to treat, per protocol, and available case.
Matamoros et al., 2021	Phase II randomised, open-label, controlled, outcome assessor–blinded, clinical trial.	To present safety and efficacy results from comparing experimental multiple-day regimens and high-dose IVM drug combinations against ALB monotherapy for the treatment of *T. trichiura* infections	**Arms 1 and 3:** Albendazole alone **Arms 2 and 4:** Albendazole+Ivermectin All medicaments were orally administered	Children aged 2-14 years infected with *T. trichiura* and body weight ≥15 kg. 176 children randomised: Arm1: 38 Arm 2: 56 Arm 3: 23 Arm 4: 58 Honduras	Albendazole 400 mg Ivermectin 600 µg/kg **Arm 1:** ALB-SD **Arm 2:** A/I SD **Arm 3:** ALBx3 **Arm 4:** A/Ix3	The primary outcome of this clinical trial was CR against *T. trichiura* at 14–21 days after treatment in a single Kato-Katz specimen. The secondary outcome was *T. trichiura* ERR at the same end point.

Hürlimann et al., 2022	Phase 3, randomised, controlled, double-blind, parallel group, superiority trial	To demonstrate superiority of co-administered ivermectin–albendazole over albendazole monotherapy in three distinct epidemiological settings.	Albendazole/Ivermectin Albendazole/Placebo All medicaments were orally administered	Patients aged 6-60 years infected with *T. trichiura* and concomitant infections with *A. lumbricoides*, *S. stercoralis*, and Hookworm 1,673 patients randomised: Albendazole + Placebo: 835 A/I: 838 Côte d'Ivoire, Laos, Tanzania	Albendazole 400 mg Ivermectin 200 µg/kg All single dose	The primary outcome was the CR of *T. trichiura*, defined as the proportion of participants with no eggs in their faeces 14–21 days after treatment. Secondary outcomes were the ERR against *T. trichiura*, CR and ERRs against *A. lumbricoides*, hookworm, and *S. stercoralis* as well as infection status assessed by qPCR.
Sprecher et al., 2023	Community-based randomised, placebo-controlled, parallel-group, phase III superiority trial	To evaluate if moxidectin in combination with ALB yields superior efficacy compared to ALB monotherapy by *T. trichiura* infections and to provide further evidence on the previously found low efficacy of A/I combination in the same population.	Albendazole Moxidectin Ivermectin **Arm 1:** ALB alone, **Arm 2:** ALB+Moxidectin **Arm 3:** A/I All medicaments were orally administered	Adolescents and adults aged 12-60 years infected with *T. trichiura* 255 patients randomised: Arm 1: 84 Arm 2: 85 Arm 3: 86 Côte d'Ivoire	Albendazole 400 mg Moxidectin 8 mg Ivermectin 200 µg/kg All single dose	The primary outcome was the CR against *T. trichiura* between the moxidectin-ALB combination compared to ALB alone. Secondary outcomes were the ERR of *T. trichiura* with moxidectin-ALB combination and ALB alone, the CR and ERR of A/I combination compared to ALB alone in *T. trichiura* as well as the CRs and ERRs of the three treatments in *A. lumbricoides* and hookworm
Welsche et al., 2023	Open-label, non-inferiority, randomised, controlled, phase 2/3 trial	To assess the efficacy and safety of moxidectin and ALB compared with A/I against *T. trichiura*. To measure long-term effects of moxidectin due to its longer half-life (20–35 days vs 18 h for ivermectin).	Albendazole Moxidectin Ivermectin **Arm 1:** ALB + Moxidectin **Arm 2:** A/I **Arm 3:** ALB alone **Arm 4:** IVM alone **Arm 5:** Moxidectin alone All treatments were orally administered	Adolescents aged 12-19 years infected with *T. trichiura* and concomitant infections with *A. lumbricoides*, and Hookworm 536 randomised (safety population): Arm 1: 207 Arm 2: 211 Arm 3: 19 Arm 4: 19 Arm 5: 80 Tanzania	Albendazole 400 mg Moxidectin 8 mg Ivermectin 200 µg/kg All single dose Follow-up was conducted at 14–21 days, 5–6 weeks, and 3 months after treatment	The primary outcome was ERR of *T. trichiura* 14–21 days after treatment in the available case population. Secondary outcomes were CRs (defined as the proportion of participants converted from egg-positive at baseline to egg-negative after treatment) of combination therapy groups compared with monotherapy groups for *T. trichiura* 14–21 days after treatment; ERR and CR for *A. lumbricoides* and hookworm assessed at 14–21 days, 5–6 weeks, and 3 months after treatment
Lymphatic filariasis						
Dembele et al., 2010	Randomised controlled trial	To determine the effect of increased dose and frequency of A/I treatment on microfilarial clearance in residents of an area of *W. bancrofti* endemicity in Mali	Albendazole Ivermectin All treatments were orally administered	Males and females aged 14-65 years infected with *W. bancrofti*. 390 screened, 51 randomised: Annual standard dose: 26 Twice-yearly high dose: 25	Standard dose: ALB: 400 mg IVM: 150 µg/kg High dose: ALB: 800 mg IVM: 400 µg/kg	The primary endpoint evaluated the difference in *W. bancrofti* levels between the 2 groups at 12 months by examining parasite clearance rates at baseline and 12 months.

A/I = Albendazole/Ivermectin; ALB = Albendazole; CR = Cure rate; ERR = Egg reduction rate; GM = Geometric mean; IVM = Ivermectin; qPCR = Real-Time PCR; SD = Single dose; STH = Soil transmitted helminths

2.6.5. Discussion on clinical efficacy

The applicant developed an adaptive phase II/III, single-blinded, randomised, multi-centre, parallel group, active-controlled, superiority study to evaluate the safety and efficacy of a single day or three-day single dose of an albendazole/ivermectin co-formulation versus albendazole for the treatment of STH infections in paediatric and young adult population (Study ALIVE).

Design and conduct of clinical studies

The design of the Phase 2/3 study ALIVE has been discussed in three EMA SA procedures and most recommendations were followed. The aim of the study was to show superiority of the FDC against whipworm (*T. trichiura*), hookworm (*A. duodenale*, *N. americanus*) and *S. stercoralis* infections in patients 5-18 years compared to a single dose of 400 mg albendazole. Individuals with a single infection due to *A. lumbricoides* were not enrolled since no extra benefit was expected to be achieved with the FDC, considering that efficacy of standard of care (albendazole) is high. A second control group treated with ivermectin was not included due to the lack of efficacy of ivermectin against all species under evaluation except for *S. stercoralis*.

The open-label design of the study is acceptable since otherwise multiple placebo tablets over 3 days would have to be administered, increasing the risk of choking particularly in young children.

PK samples were only collected in the Phase II part of the study, but the weight cut-off for the higher ivermectin dose (18 mg) was increased from 30 to 45 kg in the Phase III part (based on results of the Phase II part).

The number of included patients weighing more than 45 kg and treated with 18 mg ivermectin is low (about 15%) and thus data to conclude on efficacy in adults is limited.

Taste, smell and texture of the orodispersible tablets was rated during the Phase II part of the study to conclude on acceptability of this new formulation in the paediatric population.

No specific dose response studies were submitted. It is possible to infer from the data provided that the chosen dosages were based on the current approved posology of the two components: albendazole and ivermectin. Further to the request from the CHMP, the applicant provided a justification for the use of the >600 µg/kg ivermectin dose in some weight groups, which was mainly based on demonstration of no significant safety issues when using high doses in the treatment of parasitic infections or when ivermectin was tested for the treatment of patients with COVID-19.

Efficacy data and additional analyses

T. trichiura (whipworm):

The primary endpoint of the ALIVE study was the cure rate (CR) for *T. trichiura*. Superiority was shown for both the FDC single dose and the FDCx3 regimen in all subgroups (except for co-infected patients treated with the FDC single dose). Consistently, the egg reduction rate (ERR) was significantly higher for the FDC (1x and 3x) compared to the albendazole arm.

A. duodenale, N. americanus (hookworm):

The CR and ERR for hookworm infections (pooled data, Phase 3 data) were significantly higher for the FDC given as 3-day regimen compared to albendazole alone. FDC single dose showed also efficacy, but the difference to the albendazole arm was not significant.

S. stercoralis:

For *S. stercoralis*, the sample size for statistical analysis was not reached. However, since ivermectin alone has been shown to be very efficacious against *S. stercoralis*, the FDC could be used to replace ivermectin for treatment of *S. stercoralis* (particular in the MDA setting) provided that the safety profile of the FDC is considered acceptable.

A. lumbricoides (roundworm):

Exploratory efficacy analyses of CR and ERR for *A. lumbricoides* were considered inconclusive due to the small sample size of participants who were co-infected with this soil-transmitted helminth infection (STH) at pre-treatment (ALB arm n = 15; FDC Single Dose arm n = 21; FDC x3 arm n = 25). However, since efficacy of albendazole alone against *A. lumbricoides* is very high, the FDC could be used to replace albendazole for treatment of A*. lumbricoides* (particular in the MDA setting) provided that the safety profile of the FDC is considered acceptable. However, the CHMP noted that the EU reference product Eskazole is not authorised for treatment of *A. lumbricoides*.

Overall, the FDC could be considered efficacious against the STH species described above. However, efficacy of the 3-day regimen was generally higher compared to the single dose and thus, the two dosing regimens cannot be considered equally effective particularly in case of co-infection and patients weighing ≥ 45 kg. In this context, dosing recommendations for both regimens (3-day regimen for individual therapy and 1-day regimen for MDA) were included in the Product Information to offer the most effective and feasible therapeutic option to all patients in the different settings.

In addition to the STH infections studied in the ALIVE study, the indication lymphatic filariasis (LF) is applied for. Efficacy of ivermectin against microfilaria has been well studied and the reference product Stromectol is authorised for treatment of suspected or diagnosed microfilaraemia in patients with LF due to *Wuchereria bancrofti*. In consistence with the above rationale on treatment of *S. stercoralis* and *A. lumbricoides*, the FDC could be used to replace ivermectin for treatment of LF, caused by *Wuchereria bancrofti*, which is the causative agent of LF in Africa.

The evaluation of albendazole-resistant alleles in hookworm and *T. trichiura* was listed as a secondary objective of the Phase 3 part of the ALIVE study. According to the CSR, analysis methods were not validated at the time of the report and results will be reported in a subsequent report. The applicant clarified that new methods were needed to thoroughly evaluate resistant variants. Results from the genomics analyses on resistance are expected by the end of 2025.

Key published studies

The informative value of key published studies is limited for the final conclusion on clinical efficacy of FDC in STH infections. Within ALIVE study, no subjects > 18 years were included and the number of subjects with *S. stercoralis* and *A. lumbricoides* was very limited. 4 publications were identified where subjects > 18 years were enrolled (Ndyomugyenyi et al., 2008; Hürlimann et al., 2022; Sprecher et al., 2023; and Welsche et al., 2023) and only Matamoros et al., 2021 applied doses of IVM (600 µg/kg)/ALB (400 mg) over three days. After thorough review of supportive literature, it became evident that studies were conducted in different regions in Africa with diverging prevalence of STH mono-and polyinfections. Mostly, the WHO standard dose regimen of IVM (150-200 µg/kg) /ALB (400 mg) was applied as a single dose. However, CR for STH infections showed clear differences. Hence, no conclusion on clinical efficacy of the new FDC as SD or SDx3 can be drawn based on the submitted literature.

Statistics

The global protocol-v4 for the Study ALIVE is available. It was created in order to standardise the changes to be implemented in the country specific protocols. It was internally by usage of standard operating procedures approved, which is considered acceptable. The country-specific protocols comply with local regulations and were approved by ethics committees and regulatory authorities. Regarding the Kenya protocol, version 1.8 was in force during the recruitment of the participants.

The provided tabular oversight of differences of the finalised country-specific protocols was provided and enabled a deeper understanding of the evolving of the country-specific protocols as well as the master protocol.

A statistical analysis stratified by country for the primary and secondary endpoints as well as the baseline values show that there are differences among the countries related to the contribution of infected patients with the different species of interest. In addition, separate statistical analysis one for each country for the primary and secondary endpoints as well as the baseline values were provided enabling deeper insights in the data and supplementing and supporting the primary analyses

The interim analyses were conducted only based on safety data and not on efficacy data.

Supportive analysis of the primary endpoint such that ALB missing values are considered a treatment success and FDCx2 and FDCx3 missing values are considered as failures were provided and the results supported the outcome of the primary analyses.

2.6.6. Conclusions on the clinical efficacy

The CHMP concluded that the data submitted by the applicant support efficacy of the fixed-dose combination in the treatment of adults, adolescents and children ≥ 5 years of age for the treatment of:

- Soil-transmitted helminth infections, caused by one or more of the following parasites (see section 5.1): hookworm (*Ancylostoma duodenale, Necator americanus*), roundworm (*Ascaris lumbricoides*), whipworm (*Trichuris trichiura*) and *Strongyloides stercoralis*.
- Proven or suspected microfilaraemia in patients with lymphatic filariasis caused by *Wuchereria bancrofti*.

2.6.7. Clinical safety

2.6.7.1. Patient exposure

Clinical studies conducted by the applicant

Overall Extent of Exposure

During the clinical development of the FDC, a total of 829 subjects received at least one dose of the FDC test product.

Table 27: Overall extent of exposure to the albendazole/ivermectin FDC

Study ID	Study Population	Investigational Product(s) and Route of Administration	Dose and Duration of Exposure	Exposed Patients (N)
BLCL-IVA-EU-01	Healthy volunteers aged 19-59 years. Portugal	Test Product: FDC albendazole/ivermectin, dispersible tablet, oral References: Eskazole tablets (albendazole), oral Stromectol tablets (ivermectin), oral	FDC (A/I) 400 mg/18 mg Eskazole 400 mg Stromectol®18 mg (6x 3 mg) 3 periods each with single dose of test FDC or reference product. Periods separated by ≥28 day wash out interval	78 subjects received at least one dose of investigational or reference product: - FDC: 75 - Eskazole: 74 - Stromectol: 73
ALIVE Phase II	Patients aged 5-17 years infected with *T. trichiura* Kenia	Test Product: FDC albendazole/ivermectin, dispersible tablet, oral Reference: Eskazole (Albendazole) chewable tablets, oral	FDC: single dose or daily dose for 3 days Albendazole: 400 mg Ivermectin: 9 mg (body weight 15-23 kg and 23-≤30 kg) Or 18 mg (body weight 30-45 kg) Eskazole® 400 mg single dose	128 subjects receive any study drug after randomisation: - FDC single dose: 50 - FDC daily dose: 51 - Eskazole: 27
ALIVE Phase III	Patients aged 5-18 years infected with	Test Product: FDC albendazole/ivermect	FDC single dose	866 subjects randomised:

Study ID	Study Population	Investigational Product(s) and Route of Administration	Dose and Duration of Exposure	Exposed Patients (N)
	T. trichiura, *A. lumbricoides*, Hookworms, or *S. stercoralis*. Kenya, Ethiopia, and Mozambique	in, dispersible tablet, oral Reference: Eskazole (Albendazole) chewable tablets, oral	- Body weight ≥45 kg: 400 mg A/18 mg I - Body weight <45 kg: 400 mg A/9 mg I FDC daily dose, 3-days - Body weight ≥45 kg: 400 mg A/18 mg I - Body weight <45 kg: 400 mg A/9 mg I Eskazole 400 mg single dose	- FDC single dose: 330 - FDC daily dose, 3-days: 323 - Eskazole: 213
A/I = Albendazole/Ivermectin; FDC = Fix dose combination; ID = Identifier; N = Number of subjects				

Key publications presented by the applicant

Overall extent of exposure

According to published data, approximately 15,000 persons infected with STH (including children <6 years old and pregnant women) and 9,700 persons infected with lymphatic filariasis were exposed to an A/I combination. The applicant presented 8 supportive key publications evaluating a combination of ivermectin and albendazole in STH and 2 studies evaluating the efficacy and safety of a combination of ivermectin and albendazole against lymphatic filariasis.

2.6.7.2. Adverse events

Clinical studies conducted by the applicant

- *Study BLCL-IVA-EU-01*

Table 28: Causality and intensity of TEAEs in study BLCL-IVA-EU-01 (SAP)

	FDC (n=75)	Stromectol® (n=73)	Eskazole® (n=72)
Number of patients with TEAEs (n [%])	13 (17)	21 (29)	13 (18)
Number of TEAEs symptoms according to MedDRA code	18	26	18

Causality assessment to study medication by investigator (n)	Reasonable possible	9	17	11
	Not reasonable possible	9	9	7
Severity (n)	Mild	17	20	14
	Moderate	1	6	4
	Severe	0	0	0
Source: Source: CSR Study BLCL-IVA-EU-01, Tables AG.1, AG.2, AG.3, and AG.4. MedDRA = Medical Dictionary for Regulatory Activities; n = Number; TEAE = Treatment-emergent adverse event.				

The summary of TEAEs by system organ class (SOC) and preferred term (PT) by MedDRA (version 23.1) is presented in the Table 29 below.

Table 29: Summary of TEAE by SOC and PT in study BLCL-IVA-EU-01 (SAP)

System Organ Class (SOC) Preferred Term (PT)	Safety Population (n=78)	FDC (n=75)	Stromectol® (n=73)	Eskazole® (n=72)
Number of subjects (%)/Number of TEAEs	37 (47)/62	13 (17)/18	21 (29)/26	13 (18)/18
Cardiovascular disorders				
Supraventricular tachycardia	1 (1.3)/1	0	0	1 (1.4)/1
Eye disorders				
Vision blurred	1 (1.3)/1	0	1 (1.4)/1	0
Gastrointestinal disorders	9 (12)/9	1(1.3)/1	5 (6.8)/5	3 (4.2)/3
Abdominal pain	3 (3.8)/3	0	3 (4.1)/3	0
Diarrhoea	2 (2.6)/2	0	1 (1.4)/1	1 (1.4)/1
Flatulence	1 (1.3)/1	1 (1.3)/1	0	0
Nausea	3 (3.8)/3	0	1 (1.4)/1	2 (2.8)/2
General disorders and administration site conditions				
Hyperthermia	1 (1.3)/1	1 (1.3)/1	0	0
Immune system disorders				
Hypersensitivity	1 (1.3)/1	0	1 (1.4)/1	0
Infections and infestations	4 (5.1)/4	01 (1.3)/1	2 (2.7)/2	1 (1.4)/1
Conjunctivitis	1 (1.3)/1	0	1 (1.4)/1	0
Hordeolum	1 (1.3)/1	01 (1.3)/1	0	0
Urinary tract infection	1 (1.3)/1	0	1 (1.4)/1	0
Vulvovaginal candidiasis	1 (1.3)/1	0	0	1 (1.4)/1
Investigations				
Blood CK increased	2 (2.6)/2	1 (1.3)/1	1 (1.4)/1	0

Musculoskeletal and connective tissue disorders	6 (7.7) / 6	2 (2.7) / 2	3 (4.1) / 3	1 (1.4) / 1
Back pain	2 (2.6)/2	0	1 (1.4)/1	1 (1.4)/1
Myalgia	1 (1.3)/1	0	1 (1.4)/1	0
Pain in extremity	1 (1.3)/1	0	1 (1.4)/1	0
Tendon Pain	1 (1.3)/1	1 (1.3)/1	0	0
Torticollis	1 (1.3)/1	1 (1.3)/1	0	0
Nervous system disorders	21 (27) / 26	5 (6.7) / 6	10 (14) / 10	7 (9.7) / 9
Dizziness	1 (1.3)/1	1 (1.3)/1	0	0
Headache	19 (24)/22	4(5.3)/5	9 (12)/9	6 (8.3)/6
Presyncope	1 (1.3)/1	0	0	1 (1.4)/1
Somnolence	2 (2.6)/2	1 (1.3)/1	1 (1.4)/1	0
Psychiatric disorders				
Anxiety	1 (1.3)/1	0	0	1 (1.4)/1
Reproductive system and breast disorders				
Dysmenorrhoea	5 (6.4)/5	3 (4.0)/3	1 (1.4)/1	1 (1.4)/1
Respiratory, thoracic, and mediastinal disorders				
Nasal congestion	1 (1.3)/1	1 (1.3)/1	0	0
Skin and subcutaneous tissue disorders	3 (3.8) / 3		2 (2.7) / 2	1 (1.4) / 1
Acne	2 (2.6)/2	0	2 (2.7)/2	0
Pruritus	1 (1.3)/1	0	0	1 (1.4)/1
Vascular disorders				
Hypotension	1 (1.3)/1	1 (1.3)/1	0	0

Source: CSR Study BLCL-IVA-EU-01, Tables AG.1, AG.2, AG.3, and AG.4.

CK = Creatinine kinase; FDC = Fixed dose combination; MedDRA = Medical Dictionary for Regulatory Activities; n = Number of subjects; TEAE = Treatment-emergent adverse event.

Table 30: Summary of drug-related TEAEs by SOC and PT (study BLCL-IVA-EU-01)

	Test Product N=75	Stromectol N=73	Eskazole N=72	Safety Population Total N=78
	Drug-related TEAEs	Drug-related TEAEs	Drug-related TEAEs	Total
	n {E} (%)	n {E} (%)	n {E} (%)	n {E} (%)
Any AE	7 {9} (9.3%)	15 {17} (21%)	11 {11} (15%)	30 {37} (38%)
Eye disorders	0	1 {1} (1.4%)	0	1 {1} (1.3%)

	Test Product N=75	Stromectol N=73	Eskazole N=72	Safety Population Total N=78
	Drug-related TEAEs	Drug-related TEAEs	Drug-related TEAEs	Total
	n {E} (%)	n {E} (%)	n {E} (%)	n {E} (%)
Vision blurred	0	1 {1} (1.4%)	0	1 {1} (1.3%)
Gastrointestinal disorders	1 {1} (1.3%)	4 {4} (5.5%)	3 {3} (4.2%)	8 {8} (10%)
Abdominal pain	0	3 {3} (4.1%)	0	3 {3} (3.8%)
Diarrhoea	0	1 {1} (1.4%)	1 {1} (1.4%)	2 {2} (2.6%)
Flatulence	1 {1} (1.3%)	0	0	1 {1} (1.3%)
Nausea	0	0	2 {2} (2.8%)	2 {2} (2.6%)
Infections and infestations	0	1 {1} (1.4%)	0	1 {1} (1.3%)
Conjunctivitis	0	1 {1} (1.4%)	0	1 {1} (1.3%)
Investigations	1 {1} (1.3%)	1 {1} (1.4%)	0	2 {2} (2.6%)
Blood creatine phosphokinase increased	1 {1} (1.3%)	1 {1} (1.4%)	0	2 {2} (2.6%)
Nervous system disorders	4 {6} (5.3%)	8 {8} (11%)	7 {7} (9.7%)	18 {21} (23%)
Dizziness	1 {1} (1.3%)	0	0	1 {1} (1.3%)
Headache	3 {4} (4.0%)	7 {7} (9.6%)	6 {6} (8.3%)	16 {17} (21%)
Presyncope	0	0	1 {1} (1.4%)	1 {1} (1.3%)
Somnolence	1 {1} (1.3%)	1 {1} (1.4%)	0	2 {2} (2.6%)
Skin and subcutaneous tissue disorders	0	2 {2} (2.7%)	1 {1} (1.4%)	3 {3} (3.8%)
Acne	0	2 {2} (2.7%)	0	2 {2} (2.6%)
Pruritus	0	0	1 {1} (1.4%)	1 {1} (1.3%)
Vascular disorders	1 {1} (1.3%)	0	0	1 {1} (1.3%)
Hypotension	1 {1} (1.3%)	0	0	1 {1} (1.3%)

Source: CSR BLCL-IVA-EU-01, Table AG.1, Table AG.2, Table AG.3 and Table AG.4. AE=adverse event; {E}=number of adverse events; n=number of subjects with event; N=number of subjects in cohort; PT=preferred term; SOC=system organ class; TEAE=treatment emergent adverse event

– *Study ALIVE*

Phase II

During this part of the study, the ITT population included 135 participants, and the safety per-protocol (SAP) population included 128 subjects (94.8%) that were randomised and received at least one dose of medication. Overall, 27 participants experienced 35 TEAEs, all mild in severity (22 subjects in the pooled FDC arms (FDC-SD and FDCx3) and 5 subjects in the Albendazole arm). 21 participants reported study-drug related TEAEs (18 in the pooled FDC and 3 in the Albendazole arm).

Table 31: Causality and intensity of TEAEs in the phase II of study ALIVE (ITT and SAP)

		ALB (n=30)	FDC-SD (n=51)	FDCx3 (n=54)
Number of participants with TEAEs (n [%])		5 (16.7)	10 (19.6)	12 (22.2)
Number of TEAEs symptoms according to MedDRA code		5	12	18
Causality assessment to study medication by investigator (n)	Reasonable possible	3	9	13
	Not reasonable possible	2	3	5
Severity (n)	Mild	5	12	18
	Moderate	0	0	0
	Severe	0	0	0
Number of participants with drug-related TEAEs by severity (n [%])	Absent	27 (90.0)	43 (84.3)	45 (83.3)
	Mild	3 (10.0)	8 (15.7)	9 (16.7)
	Moderate	0	0	0
	Severe	0	0	0

Source: CSR Study ALIVE, Table 14.3.1.1A.
ALB = Albendazole; FDC = Fix dose combination; MedDRA = Medical Dictionary for Regulatory Activities; n = Number; SD = Single dose; TEAE = Treatment-emergent adverse event.

Table 32: Summary of TEAEs by SOC and PT by MedDRA (version 26.0) in the phase II of the study ALIVE (ITT population)

System Organ Class (SOC) Preferred Term (PT)	ITT population (n=135)	ALB (n=30)	FDC-SD (n=51)	FDCx3 (n=54)
Subjects with at least one TEAE (n [%])	27 (20.0)	5 (16.7)	10 (19.6)	12 (22.2)
Gastrointestinal disorders				
Abdominal pain	12 (8.9)	1 (3.3)	4 (7.8)	7 (13.0)
Diarrhoea	7 (5.2)	1 (3.3)	2 (3.9)	4 (7.4)
Nausea	4 (3.0)	1 (3.3)	1 (2.0)	2 (3.7)
Vomiting	2 (1.5)	0	1 (2.0)	1 (1.9)

Toothache	1 (0.7)	1 (3.3)	0	0
Respiratory, thoracic, and mediastinal disorders				
Nasal congestion	1 (0.7)	0	1 (2.0)	0
Rhinitis	2 (1.5)	1 (3.3)	0	1 (1.9)
Upper respiratory tract infection	1 (0.7)	0	1 (2.0)	0
General disorders and administration site conditions				
Pyrexia	1 (0.7)	0	1 (2.0)	0

Source: CSR Study ALIVE, Table 14.3.1.2.1A.
Subjects who experienced multiple events within a SOC or PT were counted once for each SOC and once for each PT.
CK = creatinine phosphokinase; FDC = Fixed dose combination; MedDRA = Medical Dictionary for Regulatory Activities; n = Number of subjects; TEAE = Treatment-emergent adverse event.

Study-drug related TEAEs (>10%) in the pooled FDC included abdominal pain (4 participants in the FDC-SD arm and 7 participants in the FDCx3 arm), diarrhoea, nausea, vomiting, and pyrexia. In the Albendazole arm, study-drug related TEAEs were abdominal pain, diarrhoea, and nausea, each reported in 1 participant.

Phase III

In this phase, the ITT population included 866 subjects. A total of 229 participants (26.4% overall) experienced 325 TEAEs (267 TEAEs from 184 participants in the pooled FDC group and 58 TEAEs from 45 participants in the Albendazole group).

Table 33: Causality and intensity of TEAEs in the phase III of study ALIVE (ITT population)

		ALB (n=213)	FDC-SD (n=330)	FDCx3 (n=323)
Number of patients with TEAEs (n [%])		45 (21.1)	89 (27.0)	95 (29.4)
Number of TEAEs symptoms according to MedDRA code		58	127	140
Causality assessment to study medication by investigator (n)	Reasonable possible	33	86	98
	Not reasonable possible	25	41	32
Severity (n)	Mild	54	119	132
	Moderate	3	4	8
	Severe	1	0	0
Number of participants with drug-related TEAEs by severity (n [%])	Absent	182 (85.4)	266 (80.6)	246 (76.2)
	Mild	29 (13.6)	61 (18.5)	71 (22.0)
	Moderate	2 (0.9)	3 (0.9)	6 (1.9)

	Severe	0	0	0

Source: CSR Study ALIVE, Table 14.3.1.1B.
ALB = Albendazole; FDC = Fixed dose combination; MedDRA = Medical Dictionary for Regulatory Activities; n = Number of participants; SD = Single dose; TEAE = Treatment-emergent adverse event.

Table 34: Summary of TEAE by SOC and PT by MedDRA (version 26.0) in the phase III of the study ALIVE (ITT population)

System Organ Class (SOC) Preferred Term (PT)	ITT Population (n=866)	ALB (n=213)	FDC-SD (n=330)	FDCx3 (n=323)
Number of subjects with at least one TEAE	229	45	89	95
Eye disorders				
Lacrimation increased	1 (0.1)	0	0	1 (0.3)
Gastrointestinal disorders				
Abdominal pain	110 (12.7)	22 (10.3)	48 (14.5)	40 (12.4)
Diarrhoea	27 (3.1)	4 (1.9)	15 (4.5)	8 (2.5)
Nausea	21 (2.4)	1 (0.5)	5 (1.5)	15 (4.6)
Vomiting	24 (2.8)	4 (1.9)	9 (2.7)	11 (3.4)
Parasitic gastroenteritis	10 (1.2)	3 (1.4)	3 (0.9)	4 (1.2)
Abdominal distension	2 (0.2)	0	1 (0.3)	1 (0.3)
Abdominal cramp	1 (0.1)	0	0	1 (0.3)
Constipation	1 (0.1)	0	0	1 (0.3)
Gastroenteritis	1 (0.1)	0	1 (0.3)	0
Odynophagia	1 (0.1)	0	0	1 (0.3)
Dyspepsia	1 (0.1)	1 (0.5)	0	0
Stomatitis	1 (0.1)	1 (0.5)	0	0
Toothache	1 (0.1)	1 (0.5)	0	0
Respiratory, thoracic, and mediastinal disorders				
Cough	15 (1.7)	1 (0.5)	4 (1.2)	10 (3.1)
Rhinorrhoea	11 (1.3)	4 (1.9)	2 (0.6)	5 (1.5)
Upper respiratory tract infection	7 (0.8)	2 (0.9)	3 (0.9)	2 (0.6)
Exacerbation of asthma	1 (0.1)	0	1 (0.3)	0
Pneumonia	1 (0.1)	1 (0.5)	0	0
General disorders and administration site conditions				
Pyrexia	5 (0.6)	1 (0.5)	0	4 (1.2)
Decreased appetite	2 (0.2)	0	0	2 (0.6)
Face oedema				

	1 (0.1)	0	0	1 (0.3)
Skin and subcutaneous tissue disorders				
Pruritus	5 (0.6)	1 (0.5)	1 (0.3)	3 (0.9)
Rash	2 (0.2)	0	1 (0.3)	1 (0.3)
Dermatitis contact	1 (0.1)	0	1 (0.3)	0
Rash pruritic	1 (0.1)	0	1 (0.3)	0
Musculoskeletal and connective tissue disorders				
Arthralgia	1 (0.1)	0	1 (0.3)	0
Nervous system disorders				
Headache	41 (4.7)	7 (3.3)	20 (6.1)	14 (4.3)
Dizziness	1 (0.1)	0	0	1 (0.3)
Infections and Infestations				
Malaria	1 (0.1)	0	1 (0.3)	0
Tinea capitis	1 (0.1)	0	1 (0.3)	0
Cellulitis	1 (0.1)	1 (0.5)	0	0
Injury, poisoning, and procedural complications				
Face injury	1 (0.1)	0	0	1 (0.3)
Source: CSR Study ALIVE, Table 14.3.1.2.1B. ALB = Albendazole; CK = creatinine phosphokinase; FDC = Fixed dose combination; ITT = Intention-to-treat population; n = Number of subjects; SD = Single dose; TEAE = Treatment-emergent adverse event.				

The most frequently reported study-drug related TEAEs in the pooled FDC included abdominal pain, headache, diarrhoea, nausea, and vomiting. In the Albendazole arm, the most reported study-drug related TEAEs were abdominal pain, headache, vomiting, parasitic gastroenteritis, and diarrhoea.

Table 35: Summary of drug-related TEAEs by SOC and PT (phase III - study ALIVE)

Table 14.3.1.2.7B
Study Drug-Related Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Treatment Group – Phase III
Intention-to-Treat (ITT) Population

System Organ Class Preferred Term	ALB 400 mg Single Dose (N=213) n (%)	FDC of 400 mg ALB - 18/9 mg IVM Daily Dose Single Dose (N=330) n (%)	FDC of 400 mg ALB - 18/9 mg IVM Daily Dose x 3 Days (N=323) n (%)	FDC of 400 mg ALB - 18/9 mg IVM Daily Dose Pooled (N=653) n (%)	Overall (N=866) n (%)
Subjects with at Least One Study Drug-Related TEAE	31 (14.6)	67 (20.3)	78 (24.1)	145 (22.2)	176 (20.3)
Gastrointestinal disorders	25 (11.7)	60 (18.2)	65 (20.1)	125 (19.1)	150 (17.3)
Abdominal pain	16 (7.5)	41 (12.4)	37 (11.5)	78 (11.9)	94 (10.9)
Diarrhoea	2 (0.9)	14 (4.2)	8 (2.5)	22 (3.4)	24 (2.8)
Nausea	1 (0.5)	4 (1.2)	15 (4.6)	19 (2.9)	20 (2.3)
Vomiting	3 (1.4)	8 (2.4)	10 (3.1)	18 (2.8)	21 (2.4)
Parasitic gastroenteritis	3 (1.4)	3 (0.9)	4 (1.2)	7 (1.1)	10 (1.2)
Abdominal distension	0	1 (0.3)	1 (0.3)	2 (0.3)	2 (0.2)
Abdominal cramp	0	0	1 (0.3)	1 (0.2)	1 (0.1)
Constipation	0	0	1 (0.3)	1 (0.2)	1 (0.1)
Odynophagia	0	0	1 (0.3)	1 (0.2)	1 (0.1)
Dyspepsia	1 (0.5)	0	0	0	1 (0.1)
Stomatitis	1 (0.5)	0	0	0	1 (0.1)
Nervous system disorders	5 (2.3)	13 (3.9)	14 (4.3)	27 (4.1)	32 (3.7)
Headache	5 (2.3)	13 (3.9)	13 (4.0)	26 (4.0)	31 (3.6)
Dizziness	0	0	1 (0.3)	1 (0.2)	1 (0.1)
General disorders and administration site conditions	1 (0.5)	0	4 (1.2)	4 (0.6)	5 (0.6)
Pyrexia	1 (0.5)	0	3 (0.9)	3 (0.5)	4 (0.5)
Decreased appetite	0	0	2 (0.6)	2 (0.3)	2 (0.2)
Skin and subcutaneous tissue disorders	0	2 (0.6)	1 (0.3)	3 (0.5)	3 (0.3)
Pruritus	0	0	1 (0.3)	1 (0.2)	1 (0.1)
Rash	0	1 (0.3)	0	1 (0.2)	1 (0.1)
Rash pruritic	0	1 (0.3)	0	1 (0.2)	1 (0.1)

ALB = Albendazole; FDC = Fixed Dose Co-formulation; IVM = Ivermectin.
n (%) = number and percent of subjects in the specified group; N = number of subjects in the specified analysis set under each treatment group; TEAE = treatment-emergent adverse event.
A TEAE is defined as an adverse event that occur or worsen on or after the first dose of study treatment.
Subjects who experienced multiple events within a System Organ Class (SOC) or Preferred Term (PT) were counted once for each SOC and once for each PT.
MedDRA Version 26.0 was used.
The table was sorted by the incidence of SOC in descending order and then by the incidence of PT in descending order within SOC (same incidence in alphabetical order) for Pooled.
Listing Source: Listing 16.2.7.1B

Key studies publications presented by the applicant

Safety summaries provided by the applicant per each publication in STH are presented below.

- Publication: *Efficacy of ivermectin and albendazole alone and in combination for treatment of soil-transmitted helminths in pregnancy and adverse events: a randomized open label-controlled intervention trial in Masindi District, Western Uganda* (Ndyomugyenyi et al., 2008).

  Safety Summary: In pregnant women after administration of an A/I combination, 8 participants (17%) reported only mild and short-lived AEs. Post-treatment 3 of the women (1.8%) had a premature delivery, 3 (1.8%) had stillbirths, and 2 babies (1.4%) die at one-month post-partum. However, when compared with the reference group (no intervention) there were no significant differences in mean birth weight, low birth weight, premature deliveries, stillbirths, or neonatal mortality. The commonly reported adverse events after administration of ivermectin or albendazole and a combination of both drugs were abdominal pain, fever, and body rashes, and they were all mild. No severe adverse events were reported. In this study, administration of ivermectin or

albendazole or the drugs combined during the second trimester of pregnancy showed no severe adverse effects.

- Publication: *Albendazole and mebendazole administered alone or in combination with ivermectin against Trichuris trichiura: a randomized controlled trial* (Knopp et al., 2010).

  Safety Summary: The different treatments investigated were safe, and AEs were transient and mostly mild. The frequency of AEs in this study may be overestimated because pretreatment conditions were not assessed, preventing to distinguish between treatment-related and treatment-unrelated AEs.

- Publication: *Efficacy and safety of albendazole plus ivermectin, albendazole plus mebendazole, albendazole plus oxantel pamoate, and mebendazole alone against Trichuris trichiura and concomitant soil-transmitted helminth infections: a four-arm, randomised controlled trial* (Speich et al., 2015)

  Safety Summary: Adverse events that occurred 3 hours and 24 hours after treatment were assessed in all 435 treated children. Before treatment, 60 children (14%) reported clinical symptoms including seven moderate episodes (five episodes of diarrhoea, one child with headache, and one child with an allergy). Abdominal cramps and headache were the most common adverse events after treatment. About 20% of children had adverse events after treatment during at least one assessed timepoint. Eight children had moderate adverse events 24 h after treatment; (5 treated with albendazole plus oxantel pamoate).

- Publication: *Efficacy and safety of albendazole and high-dose ivermectin coadministration in school-aged children infected with Trichuris trichiura in Honduras: a randomised controlled trial* (Matamoros et al., 2021).

  Safety Summary: No SAEs were noted in this study. The most common AEs were headache and abdominal pain, both with similar frequencies in the experimental arms. Overall, 85.4% of the AEs were mild and all AEs resolved without medical intervention within 48 hours post-treatment. The results of this study are consistent with the already known safety profiles of albendazole and ivermectin and suggested that combination therapy with a high dose of ivermectin could be safely administered to children. There was no correlation between AEs and mean ivermectin systemic concentrations, but a significant association between albendazole blood levels and AEs, regardless of coadministration of ivermectin.

- Publication: *Efficacy and safety of co-administered ivermectin and albendazole in school-aged children and adults infected with Trichuris trichiura in Côte d'Ivoire, Laos, and Pemba Island, Tanzania: a double-blind, parallel-group, phase 3, randomised controlled trial* (Hürlimann et al., 2022).

  Safety Summary: No SAEs were observed in any of the three countries. AEs reporting was similar between treatment groups. The most frequently reported AEs in both groups were headache, abdominal pain, and itching. AEs were mostly transient and resolved within 24 hours. All assessed AEs were classified as possibly treatment related.

- Publication: *Efficacy and safety of moxidectin-albendazole and ivermectin-albendazole combination therapy compared to albendazole monotherapy in adolescents and adults infected with Trichuris trichiura: a randomised controlled superiority trial* (Sprecher et al., 2023).

  Safety Summary: MOX-ALB showed a slightly better safety profile with 40% of participants experiencing an adverse event compared to 43% with IVM-ALB. However, since symptoms like abdominal pain, diarrhoea, and nausea, are related to the infection itself, differentiation between the symptoms caused by a treatment effect and those caused by its absence is challenging.

- Publication: *Efficacy and safety of moxidectin and albendazole compared with ivermectin and albendazole coadministration in adolescents infected with Trichuris trichiura in Tanzania: an open-label, non-inferiority, randomised, controlled, phase 2/3 trial* (Welsche et al., 2023).

  Safety Summary: No SAEs of grade 3–5 were reported in all five treatment groups during the study. AEs were predominantly mild (83%), and a few were moderate (17%). Before treatment, reported symptoms were mainly headache, nausea, or rash. The most reported AEs were headache, abdominal pain, itching, and dizziness.

- Publication: *Open-label, non-inferiority cluster-randomised trial comparing the frequency of adverse events in communities receiving co-administered ivermectin, albendazole, and azithromycin to that in communities given albendazole and ivermectin followed by azithromycin mass drug administration (MDA) after a two-week interval* (McPherson et al., 2023a).

  Safety Summary: Combined administration of albendazole and ivermectin, together or 2 weeks prior to a dose of azithromycin, was safe and well tolerated. Overall, adverse events were reported by 197 (1.2%) of individuals. The most commonly reported adverse events included headache, gastrointestinal disturbance and dizziness. There were no serious adverse events in either arm. The risk of adverse events was the same in individuals who received combined MDA, and individuals who received ivermectin-albendazole alone (aOR 1.28, 95% CI 0.6-2.8, p=0.5). Similarly, the risk of adverse events was the same in individuals who received combined MDA and those who received azithromycin alone (aOR, 1.2 95% CI 0.6-2.3, p=0.6). Neither age nor gender were associated with frequency of adverse events.

The applicant also presented other published studies, evaluating the efficacy and safety of a combination of ivermectin and albendazole against lymphatic filariasis. Overall, in populations being treated with an A/I combination against lymphatic filariasis, more AEs were observed during the first 24 hours post-treatment (day one) and decreased progressively until day seven. Most of the reported post-treatment AEs were mild (83.3%) and moderate (15.9%), with few severe (0.3%). Pre-existing clinical symptoms, chronic manifestations of lymphatic filariasis, chronic illness, and female sex were significant risk factors associated with AEs following MDA of A/I preventive chemotherapy (Dembele et al., 2010; Fimbo et al., 2022).

2.6.7.3. Serious adverse event/deaths/other significant events

- Deaths

Clinical studies conducted by the applicant

- Study BLCL-IVA-EU-01 and Study ALIVE

There were no deaths nor serious adverse events (SAEs) leading to death in these studies.

Key studies publications presented by the applicant

There were no TEAEs leading to death. Only one publication reported two deaths: one from anaphylactic shock after an injection of procaine penicillin and one shortly after a caesarean section. Both events were not related with the study drug (Ndyomugyenyi et al., 2008).

- Other Serious Adverse Events

Clinical Studies

- Study BLCL-IVA-EU-01 and Study ALIVE

There were no SAEs reported in these studies.

Key studies publications presented by the applicant

No SAEs were reported in any of the published studies.

- Other Significant Adverse Events

Clinical Studies

- Study BLCL-IVA-EU-01

Four (4) subjects were discontinued due to TEAEs (hyperthermia, nausea and myalgia, hypersensitivity, and urinary tract infection), which were all considered not drug related. There were no treatment-related SAEs or TEAEs leading to study drug discontinuation.

- Study ALIVE

There were no TEAEs leading to discontinuation in the study.

Key studies publications presented by the applicant

There were no events leading to discontinuation in any of the key published studies.

2.6.7.4. Laboratory findings

In Study BLCL-IVA-EU-01, results for each laboratory analytes were in the normal ranges, excepting two participants that presented high abnormal value of creatinine phosphokinase at the end-of-study (one received Stromectol-FDC-Eskazole and the other received FDC-Eskazole-Stromectol). Both results were considered clinically relevant by the Investigator and reported as drug related TEAE (“Blood creatine phosphokinase increased”). No further abnormality with respect to the clinical laboratory evaluation was

considered of clinical relevance by the Investigator. No subject discontinued the study early due to TEAEs related to a laboratory abnormality.

2.6.7.5. Safety in special populations

Children

Use of A/I orodispersible tablets in children <5 years of age is not recommended due to limited experience. For all indications, safety of the FDC in paediatric patients with body weight <15 kg has not been established.

Elderly population

Experience with albendazole and ivermectin in elderly patients ≥65 years is limited. In general, treatment of elderly patients should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Experience with albendazole in elderly patients ≥65 years is limited. Reports show that no dose adjustment is required. Clinical studies with ivermectin did not include enough subjects ≥65 years to determine whether they respond differently from younger subjects. Nevertheless, reported clinical experience has not identified differences in responses between the elderly and younger patients.

Pregnant women

Benzimidazole derivatives like albendazole are associated with teratogenic properties. Data on a limited number of pregnant women exposed to ivermectin in MDA campaigns indicated no adverse effects neonatal deaths, maternal morbidity, preterm births, or low birthweight. However, in this meta-analysis it remained unclear whether exposure to ivermectin during pregnancy increases the risk of spontaneous abortions and stillbirths (Nicolas et al., 2020). Efficacy and adverse events of ivermectin, albendazole, or the combination of both were evaluated in a randomised open-label trial, including 834 pregnant women with STH infection in the second trimester of pregnancy. One abortion occurred in the albendazole group and 10 stillbirths in the ivermectin (n=1), albendazole (n=5), combination (n=3) and control group with no intervention (n=1). Two babies were born with congenital abnormalities (1 in the ivermectin group and 1 in the control group). The prevalence of anaemia at first antenatal care visit was 20.6% (23.7% [ivermectin], 21.1% [albendazole], 22.2% [combination], and 16.1% [control]). Anaemia was reduced to 8.5% at 36 weeks of gestation with 10.9% (ivermectin), 11.5% (albendazole), 7.7% (combination), and 6.9% (control). No severe adverse events were reported by the women after the administration of ivermectin, albendazole, or the combination during the second trimester of pregnancy (Ndyomugyenyi et al., 2008).

Patients with hepatic impairment or liver diseases

Since albendazole is rapidly degraded in the liver to its primary pharmacologically active metabolite albendazole sulfoxide, it can be assumed that hepatic impairment may have a significant effect on the pharmacokinetics of albendazole sulfoxide.

Albendazole - The PK of albendazole in patients with impaired hepatic function has not been studied. However, since albendazole is rapidly degraded in the liver to its primary pharmacologically active metabolite

(albendazole sulfoxide), it can be assumed that hepatic impairment may have a significant effect on the PK of albendazole sulfoxide. During treatment with albendazole, mild to moderately elevated hepatic enzymes can occur which usually return to normal after discontinuation of treatment. Cases of hepatitis have also been reported. Patients presenting abnormal levels of hepatic function tests (transaminases) before starting albendazole treatment, should be closely monitored and therapy discontinued if the enzyme values are significantly increased, or the blood cell counts are declining to a clinically significant extent. Patients with liver disease, including hepatic echinococcosis, appear to be more susceptible to myelosuppression leading to pancytopenia, aplastic anaemia, agranulocytosis, and leukopenia and should therefore, be monitored more closely.

Ivermectin - Transient hyper-eosinophilia, liver dysfunction including acute hepatitis, increased liver enzymes, hyper-bilirubinaemia and haematuria have been reported after treatment.

Immunocompromised patients

Efficacy and dosing regimen of ivermectin in immunocompromised patients being treated for intestinal strongyloidiasis have not been established by adequate clinical studies. There have been reported cases which show the persistence of infestation following a single dose of ivermectin, particularly in this type of patients.

Patients with a history of allergic reactions

Persons with hypersensitivity to the active substances or to any of the excipients of the FDC should not receive the FDC orodispersible tablet.

Ivermectin - After treatment with microfilaricidal active substances, patients with hyperreactive onchodermatitis or “Sowda” (observed in Yemen) may be more likely than others to experience severe cutaneous adverse reactions (oedema and aggravation of onchodermatitis). In addition, severe cutaneous adverse reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis, which can be life-threatening or fatal, have been reported in association with ivermectin treatment. If signs and symptoms suggestive of these reactions appear, ivermectin should be withdrawn immediately and an alternative treatment considered.

2.6.7.6. Safety related to drug-drug interactions and other interactions

While the concomitant use of albendazole with cimetidine, praziquantel and dexamethasone increases the plasma concentration of its active metabolite (albendazole sulfoxide), ritonavir, phenytoin, carbamazepine, and phenobarbital may possibly reduce the plasma concentrations of albendazole sulfoxide. The clinical relevance of this is unknown, but may result in reduced efficacy, especially in the treatment of systemic helminth infections. Patients should be monitored for efficacy and may require alternative dose regimens or therapies. Due to unclear interactions with hormonal ovulation inhibitors, taking the "pill" alone as contraceptive method is not recommended during treatment with albendazole.

No interaction studies have been performed for ivermectin. However, concomitant treatment with diethylcarbamazine citrate (DEC) and ivermectin in mass chemotherapy campaigns for filariasis caused by

Wuchereria bancrofti in Africa is not recommended. Systematic exposure to DEC in such patients may result in the occurrence of serious side effects related to the rapid and effective microfilaricidal effects of its active substance.

2.6.7.7. Discontinuation due to adverse events

- Clinical Studies conducted by the applicant

- Study BLCL-IVA-EU-01

Four subjects were discontinued due to TEAEs (hyperthermia, nausea and myalgia, hypersensitivity, and urinary tract infection), which were all considered not drug related. There were no treatment-related SAEs or TEAEs leading to study drug discontinuation.

- Study ALIVE

There were no TEAEs leading to discontinuation in the study.

- Key studies publications presented by the applicant

There were no events leading to discontinuation in any of the key published studies.

2.6.8. Discussion on clinical safety

Two of the most recommended drugs against soil-transmitted helminths (STHs) are albendazole and ivermectin, both being part of the World Health Organization's list of essential medicines (World Health Organization, 2019). The safety profiles of albendazole and ivermectin are supported by a long history of mass drug administration (MDA) among STH endemic communities (McPherson et al., 2023b). Albendazole was registered for human use in 1982 and is widely used as an anthelmintic and antiprotozoal agent in endemic countries; ivermectin was approved as an antiparasitic agent for human use in 1987 and is one of the most prescribed medications worldwide (Molyneux and Ward, 2015). Oral ivermectin is currently approved for paediatric population with a weight equal or above 15 kg. The standard dose is 200 µg/kg body weight.

The applicant developed two fixed dose combination (FDC) strengths, 400 mg albendazole/9 mg ivermectin and 400 mg albendazole/18 mg ivermectin, which would allow the delivery of doses of ivermectin between 200 and 600 µg/kg depending on weight. Although the currently approved ivermectin dose is 200 µg/kg in subjects with more than 15 kg body weight, higher doses up to 600 µg/kg appear to be well tolerated by adults and children as evaluated in one published scientific literature provided by the applicant (e.g., Matamoros, 2021). Furthermore, in a systematic literature review and meta-analysis on the safety of high doses of ivermectin conducted by Navarro et al. (Navarro et al., 2020), the safety of high-dose ivermectin appeared to be comparable to standard doses. In this meta-analysis, 5 studies for a variety of indications were included using 400 µg/kg as the cut-off and no differences in the severity of the AEs between standard ivermectin dose and doses higher than 400 µg/kg were observed. This meta-analysis also added evidence to the safety of ivermectin at doses up to 800 µg/kg, although this conclusion was based on a small number of

studies and lacked blinding. Of note, organ system involvement only showed an increase in ocular events in the higher-dose group in one trial for the treatment of onchocerciasis, all of them transient and mild to moderate in intensity. Additionally, the CHMP considered that the rationale for using the proposed FDC was also supported by the results of the randomised controlled trial in Honduras in school-aged children (Matamoros et al., 2021), where the safety and efficacy of the concomitant administration of albendazole 400 mg + ivermectin 600 µg/kg either as a single dose or as a daily dose for 3 consecutive days in comparison to albendazole 400 mg (single dose or daily dose for 3 consecutive days, respectively) for the treatment of *T. trichiura* infections was studied. This study population included children 2-14 years. No safety concerns emerged. However, information regarding safety in certain age- or weight- groups in the paediatric population is missing and the number of study participants was limited (157 children enrolled in 4 groups). Thus, the safety results from Matamoros et al., 2021 should be regarded with caution when drawing any conclusion on the safe use of the ivermectin/ albendazole FDC single-dose and daily dose for 3 consecutive days in children.

To support the overall safety evaluation for fixed dose combination of albendazole and ivermectin, the applicant conducted two randomised clinical studies (BLCL-IVA-EU-01: 78 adult healthy volunteers and ALIVE: 128 subjects Phase II and 866 subjects Phase III). Additionally, the applicant presented 8 key published clinical studies in STH (Ndyomugyenyi et al., 2008; Knopp et al., 2010; Speich et al., 2015; Matamoros et al., 2021; Hürlimann et al., 2022; Sprecher et al., 2023; Welsche et al., 2023; McPherson et al., 2023a) and 2 studies in lymphatic filariasis (Dembele et al., 2010 and Fimbo et al., 2022). The CHMP considered that according to published data, approximately 15,000 persons infected with STH (including children <6 years old and pregnant women) and 9,700 persons infected with lymphatic filariasis were exposed to an ivermectin/ albendazole combination. Overall, based on the extensive clinical experience with administration of these agents individually and the data on combination administration, the CHMP considered that the extent exposure presented by the applicant was acceptable.

In both Study BLCL-IVA-EU-01 in healthy subjects as well as in the Phase II/III Study ALIVE in children and young adults with STH infection, the most reported AEs were mild or moderate in intensity and resolved without medical intervention. No treatment-emergent SAEs or deaths were reported. Only one participant experienced a severe AE (cellulitis). No drug-related events leading to discontinuation, no serious adverse drug reactions or deaths causally related to the medicinal product were reported either in the clinical studies conducted by the applicant or supportive key publications.

In Study BLCL-IVA-EU-01, the safety analysis population included 78 healthy volunteers that received at least one dose of test- (FDC of albendazole 400 mg and ivermectin18 mg) or reference products (Stromectol and Eskazole). Of these, 37 participants reported a total of 62 TEAEs. 13/75 subjects that received Test medication reported 18 TEAEs, of which 9 were considered drug related. 26/73 participants that received Stromectol reported 26 TEAEs, of which 17 were considered drug related, and 13/72 participants that received Eskazole reported 18 TEAEs, of which 11 were considered drug related. The most common TEAE was headache (Test=5.3%; Stromectol=12%; and Eskazole=8.3%). All the TEAEs were mild (51) or moderate (11) in intensity. Four subjects were discontinued due to TEAEs, all of which were considered not treatment related.

Overall, no new or unexpected TEAEs were observed within study BLCL-IVA-EU-01 and the frequency of reported TEAEs was in line with the reference products safety information. Notably, a new warning on neurotoxicity was added to the reference product Stromectol: “Cases of neurotoxicity, such as loss of consciousness and coma, have been reported with the use of ivermectin in patients without Loa loa infection. These reactions have generally resolved with supportive care and discontinuation of ivermectin. Limited data indicate that the risk of neurotoxic effects may be increased in patients with reduced P-glycoprotein activity, e. g. loss-of-function mutation in the ABCB1 gene (MDR1).” Since no genotyping was performed in study BLCL-IVA-EU-01, no further information on the risk of neurotoxicity in patients with reduced P-glycoprotein activity is available. Nevertheless, sections 4.8 and 4.9 were updated in order to highlight that impaired consciousness and coma are related to ivermectin neurotoxicity (in line with Stromectol).

In Study ALIVE, the administration of FDC as a single dose (FDC-SD) and FDC one dose/day for 3 days (FDCx3) demonstrated a manageable safety profile. In Phase II of Study ALIVE, the most frequently reported TEAEs (>10%) by SOC were gastrointestinal disorders (total of 22 participants (17.2%): 18 participants (17.8%) in the FDC Pooled group and 4 participants (14.8%) in the Albendazole arm. The most frequently reported TEAEs (>5%) were abdominal pain (12 participants [9.4%]) and diarrhoea (7 participants [5.5%]). Safety data per weight group (15 -23 kg, 23-30 kg and 30-45 kg) were presented for phase II of ALIVE study in order to justify the highest dose of 600 µg/kg in group II (30-45 kg; 18 mg ivermectin/400 mg albendazole) and group III (15-23 kg; 9 mg ivermectin/400 mg albendazole). Overall, the number of study participants and TEAEs was limited and thus interpretation of data should be conducted with caution. The number of TEAEs was the highest in group I (23-30 kg) and comparable between group II (30-45 kg) and III (15-23 kg) for the FCD SD. For the FDCx3 regimen, the number of TEAEs was highest and comparable between group I and II. The highest number of study drug-related TEAEs was observed with group II (n = 6 [40.0%]. All TEAEs were mild and mostly related to gastrointestinal disorders, as assessed by the applicant. Based on the stratified safety data provided for the phase II part of the ALIVE study, the highest dose of 600 µg/kg in group II (30-45 kg; 18 mg ivermectin/400 mg albendazole) and group III (15-23 kg; 9 mg ivermectin/400 mg albendazole) is justified. In accordance with the SmPC of Eskazole, albendazole may not be given to children <6 years of age. However, within the phase II study, albendazole was given as a single dose or over three days to children with a body weight of 15-23 kg, i.e. children 5 years of age. The applicant sufficiently discussed the safety implications of repeatedly dosing children <6 years with 400 mg albendazole based on WHO-PQ (2021a). The applicant provided additional safety data for mono-/co-infection and worm burden for the phase II part of the study ALIVE as requested. Overall, the number of co-infected subjects and the number of TEAEs was low. Based on the safety data provided, there was no evidence for an increased risk of adverse events in subjects with co-infection, neither for the FDC SD nor FDCx3 regimen. Regarding the severity of worm burden, the number of subjects and TEAEs was very limited in some subcategories. Nevertheless, the number of study drug-related TEAEs was comparable in all subcategories. In summary, there was no evidence that a higher worm burden is correlated with a higher occurrence of TEAEs (especially gastrointestinal disorders) following FDC SD or FDCx3. Moreover, the occurrence of TEAEs was equally distributed between the investigated nematode species.

In the Phase III of Study ALIVE, a total of 229 participants (26.4% overall) experienced 325 TEAEs (267 TEAEs from 184 participants in the pooled FDC group and 58 TEAEs from 45 participants in the Albendazole

group). Of the 229 participants, 214 experienced mild and 14 moderate TEAEs (11 in the pooled FDC and 3 in the Albendazole group). Study drug-related TEAEs were reported in a total of 176 participants (145 (22.2%) in the pooled FDC and 31 (14.6%) in the Albendazole arm). The most frequently reported TEAEs (>10% overall) by SOC were gastrointestinal disorders reported by 172 participants (19.9%), including 138 participants (21.1%) in the FDC Pooled group and 34 participants (16.0%) in the Albendazole arm. The most frequently reported moderate TEAEs (≥2 participants) in the FDC Pooled group were headache (3 participants), pyrexia (2 participants) and vomiting (2 participants).

In Study ALIVE Phase III, study drug-related TEAEs were reported in a total of 176 participants (20.3%), including 145 participants (22.2%) in the FDC Pooled group and 31 participants (14.6%) in the ALB arm. The most frequently reported study-drug related TEAEs in the pooled FDC included abdominal pain, headache, diarrhoea, nausea and vomiting. In the Albendazole arm, the most reported study-drug related TEAEs were abdominal pain, headache, vomiting, parasitic gastroenteritis and diarrhoea. Safety data per weight strata, i.e. < 45 kg (9 mg IVM/400 mg ALB) and ≥ 45 kg (18 mg IVM/400 mg ALB) as well as for mono- and coinfection and for worm burden was presented for phase III of ALIVE study. Slightly more subjects in the FDCx3 group had study drug-related AEs (26.6%) compared to FDC SD (20.9%). However, TEAEs (especially for gastrointestinal and nervous system disorders) were equally distributed between both weight groups and dosing regimens. Based on the safety data provided for phase III part of the ALIVE study, the dosing of patients based on body weight, i.e. BW ≥ 45 kg: albendazole 400 mg/ ivermectin 18 mg and BW < 45 kg: albendazole 400 mg/ ivermectin 9 mg, can be considered safe. Regarding worm burden, the number of patients in some subcategories was low, limiting reliable conclusions. A slight trend for an increased occurrence of study drug-related TEAEs within the FDCx3 compared to FDC SD was observed. Nevertheless, no safety concern in TEAEs by PT for worm burden and for different species could be identified. The summary of TEAEs by infection subgroup revealed that the number of study drug-related TEAEs was higher in the co-infected than mono-infected group for FDC SD. No differences in study drug-related TEAEs were observed for FDCx3. Based on the safety data provided, there was no evidence for an increased risk of adverse events in subjects with co-infection, neither for the FDC SD nor the FDCx3 regimen. Overall, the number of pre-treatment AEs was low and equally distributed throughout the study arms. The most common pre-treatment AE related to the initial parasitic infestation was abdominal pain. It is reasonable to conclude that this pre-treatment AE may favour the overall safety profile of FDC 400 mg ALB - 18/9 mg IVM regarding gastrointestinal disorders.

In the key published studies concerning the treatment of STHs provided by the applicant, the most common reported reactions across all studies were abdominal pain/abdominal cramp (13%-50%), headache (11.0%-50%), body rash/itching (1.4%-25%), and dizziness (5%-6%). In populations treated with an ivermectin/ albendazole combination against lymphatic filariasis, the most common AEs with relatively higher incidence rates were headache (1.23%), drowsiness (1.15%), fever (1.12%), dizziness (1.06%), and abdominal pain (0.88%).

Dembele et al., 2010, determined the effect of 2 doses of annual, standard-dose albendazole-ivermectin therapy versus 4 doses of twice-yearly, increased-dose albendazole-ivermectin therapy in the treatment of *Wuchereria bancrofti* microfilaremia. A single high dose of ivermectin/ albendazole was well tolerated, and no

new, unexpected or severe AEs were observed. Given the limited number of patients included and diverging dosing regimens, no conclusion on the safety of ivermectin/ albendazole FDC SD and x3 can be drawn.

The applicant presented some safety considerations for special populations (intrinsic factors) for children, elderly, immunocompromised patients, patients with a history of allergic reactions, patients with hepatic impairment or liver diseases, which were addressed in the SmPC. Further to a request from the CHMP, the applicant conducted a literature review, with a pre-specified search strategy criterion, to identify further details on the use of ivermectin and albendazole in the elderly, patients with renal/ hepatic impairment and in pregnant women. Safety data on the elderly population was found to be very limited (the mean age of patients included in studies was below 65 and from the publications retrieved, it was not possible to identify whether elderly patients were included). Cases of renally impaired patients receiving albendazole and/or ivermectin treatment described in literature were limited.

Patients with initial hepatic impairment treated with ivermectin and/ or albendazole have not been identified in any publications. Nevertheless, several case reports of albendazole induced liver toxicity were identified and summarised by the applicant.

Regarding pregnant women, no additional information beyond the data provided in the initial submission package dossier was found. Only very sparse data is available on the use of albendazole or ivermectin during pregnancy. The applicant presented one study (Ndyomugyenyi et al., 2008) where no severe adverse events were reported by the women after the administration of ivermectin, albendazole, or the combination during the second trimester of pregnancy. In a meta-analysis by Nicolas et al., 2020 it remained unclear whether exposure to ivermectin during pregnancy increases the risk of spontaneous abortions and stillbirths.

For both benzimidazole derivatives like albendazole and ivermectin, animal studies have shown reproductive toxicity. However, the potential risk for humans is unknown. Considering whether the use of this fixed-dose combination should be contraindicated in pregnant women, the CHMP acknowledged that this product is intended to be used in two different settings - MDA campaigns and individual setting - where the use in pregnant women may be considered, if clinically justified.

Because of the teratogenic properties of albendazole, the use of ivermectin/albendazole orodispersible tablets is contraindicated in the framework of an MDA in pregnant women and in women who intend to become pregnant. For the individual therapy (i.e. outside the scope of a mass drug administration), the use of ivermectin/albendazole orodispersible tablets is not recommended, especially during the first trimester of pregnancy. It should only be used during pregnancy if the clinical condition of the woman requires treatment with albendazole and ivermectin. The CHMP was of the view that the distinction between the use in pregnancy in these two settings is adequately reflected in sections 4.3 and 4.6 of the SmPC.

With regards to clinical laboratory evaluations, in Study BLCL-IVA-EU-01, two subjects presented with high abnormal values of CPK at the end-of-study. Both cases were considered clinically relevant by the Investigator and reported as drug-related TEAE. No further abnormality with respect to the clinical laboratory evaluation was regarded of clinical relevance by the Investigator and no discontinuations were observed due to TEAEs related to a laboratory abnormality. No laboratory safety assessments in the ALIVE study were conducted.

In Study BLCL-IVA-EU-01, one subject presented with low abnormal values of diastolic blood pressure during Period 3 and one subject presented with high abnormal values of body temperature at admission of Period 3. These events were considered clinically relevant by the Investigator and reported as TEAE. No further out-of-range vital signs were judged to be clinically relevant by the Investigator, and no abnormality in the 12-lead ECG recordings was considered of clinical relevance by the Investigator. In both Phases II and III of the ALIVE study, there were no clinically meaningful median changes from baseline in any vital signs.

The CHMP considered that the phase I and phase II/III studies were conducted in regions without epidemiological risk of *Loa loa* infections. However, this may not be the case for future MDA campaigns in Africa. The SmPC of Stromectol (ivermectin) states that side effects are related to the parasite density and are mild and transient in the majority of cases, but their severity may be increased in patients infected with more than one parasite, particularly in the case of infestation with *Loa loa*. Therefore, contraindications for individual patients with high *Loa Loa* microfilaria and for MDA settings in *Loa Loa* endemic areas were included in section 4.3 and a warning was updated in section 4.4.

The CHMP considered the applicant´s commitment to change the colour of Ivermectin/Albendazole 18/400 mg orodispersible tablet to yellow, in order to distinguish between both strengths. This measure was taken to prevent inadvertent mix-up of tablet strengths, which could result in decreased efficacy or increased safety risks. The CHMP highlighted that two doses with identical presentation would pose a risk of medication errors, particularly during mass drug administration, where the medicines will possibly be handled by non-healthcare professionals.

2.6.9. Conclusions on the clinical safety

Safety of ivermectin and albendazole has been widely demonstrated as both have been extensively used in MDA programs including a high number of subjects. Two clinical studies conducted by the applicant confirmed this favourable safety profile of albendazole + ivermectin co-administration. In both the PK study BLCL-IVA-EU-01 in healthy subjects as well as in the Phase 2/3 Study ALIVE in children and young adults with STH infection, most reported AEs were mild or moderate in intensity and resolved without medical intervention. The informative values of key published studies are considered low.

The CHMP considers the following measures necessary to address issues related to safety:

In order to further mitigate the risk of medication errors, the applicant will change the colour/ formulation of the highest strength in order to differentiate the two strengths. The product information will be updated accordingly.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 36

Summary of safety concerns	
Important identified risks	• Encephalopathy following treatment in patients with heavy Loa loa co-infection (ivermectin)
Important potential risks	• None
Missing information	• None

2.7.2. Pharmacovigilance plan

No additional pharmacovigilance activities

2.7.3. Risk minimisation measures

Table 37

Safety concern	Routine risk minimisation activities	Pharmacovigilance activities
Encephalopathy following treatment in patients with heavy Loa loa co-infection	Routine risk communication: *SmPC section 4.8.* *PL section 4.* Routine risk minimisation activities recommending specific clinical measures to address the risk: *According to section 4.3 of the SmPC, treatment with Ivermectin/Albendazole orodispersible tablets is contraindicated in patients with high Loa loa microfilaria and for MDA settings in Loa loa endemic regions, unless a feasible and validated risk mitigation strategy can be put in place which should follow WHO recommendations or*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Drug exposure during pregnancy follow-up questionnaire. Additional pharmacovigilance activities: None.

Safety concern	Routine risk minimisation activities	Pharmacovigilance activities
	relevant national guidelines for safe use in these settings. *According to section 4.4 of the SmPC, for individual treatment (outside the scope of a mass drug administration) in Loa loa endemic areas, special measures (e.g. pre-treatment diagnostic tests such as Giemsa-stained thin or thick blood smears, any validated quantifiable Loa loa diagnostic test available in the country,, knowledge of regional Loa loa prevalence, monitoring of patients for serious CNS adverse events) should be taken before any treatment with ivermectin. Generally, patients with a high Loa loa microfilaria must not be given ivermectin unless feasible and validated risk mitigation strategies are put in place. Given the limited access to diagnostic tests in MDA settings, MDA treatment with ivermectin in Loa loa endemic areas is contraindicated. In these cases, alternative treatment strategies are necessary. Overall, monitoring patients for serious CNS symptoms is essential to prevent adverse effects and affected patients should be referred and managed appropriately.* Other routine risk minimisation measures beyond the Product Information: Legal status: restricted medical prescription.	

2.7.4. Conclusion

The CHMP considers the risk management plan version 0.5 acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant is in line with the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The first periodic safety update report should cover the six-month period following the initial scientific opinion for this product on 30 January 2025.

Subsequently, the scientific opinion holder shall submit periodic safety update reports for this product every 6 months until otherwise agreed.

2.9. Product information

2.9.1. User consultation

A user testing of the package leaflet was not submitted by the applicant. This is not a mandatory requirement for a scientific opinion on a medicinal product under Article 58 of Regulation (EC) No 726/2004.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The soil-transmitted helminth infections (STH) primarily comprise hookworm (*Ancylostoma duodenale* and *Necator americanus*), roundworm (*Ascaris lumbricoides*) and whipworm (*Trichuris trichiura*). *Strongyloides stercoralis* is also a soil-transmitted helminth infection, but currently not covered by WHO activities. Soil-transmitted helminths live in the intestine of infected individuals where they produce thousands of eggs each

day that are passed in the faeces, and when the environmental conditions are favourable, the eggs develop into infective stages. Humans become infected by contaminated water, food, hands or utensils or through penetration of the skin. There is no direct person-to-person transmission or infection from fresh faeces. Infections are widely distributed in all WHO regions, with the greatest numbers occurring in sub-Saharan Africa, the Americas and Asia. According to the WHO data, soil-transmitted helminth infections accounts for over 5.18 million disability-adjusted life years worldwide and are associated with anaemia, malnutrition, and impaired physical and cognitive development.

Lymphatic filariasis (LF) is a parasitic helminth disease caused by the filarial parasites *Wuchereria bancrofti, Brugia malayi* or *B. timori*. The filarial nematodes that cause this disease are transmitted by blood-feeding insects (Mosquitos in the genera *Culex*, *Anopheles*, *Mansonia* and *Aedes*). They produce a chronic and long-term infection in tropical regions that manifests by lymphoedema, hydrocele and elephantiasis. In Africa, the causative agent of lymphatic filariasis is *Wuchereria bancrofti.*

The aim of the ivermectin/ albendazole fixed dose combination is to combine an integrated approach not only against the burden caused by soil-transmitted helminth infections, but also filariasis, thus providing much needed help in fighting neglected tropical diseases.

3.1.2. Available therapies and unmet medical need

Increasing concerns about the success of monotherapy strategies and/or single dose administration for deworming campaigns opened the opportunities for evaluation of different treatment strategies.

Therefore, the use of drug combinations with dissimilar modes of action, like albendazole and ivermectin, might represent a more effective strategy against soil-transmitted helminth infections, as the recommended single dose monotherapies show limited efficacy, particularly against *T. trichiura*.

Albendazole is widely used in preventive chemotherapy programmes targeting soil-transmitted helminth infections worldwide. However, the efficacy of albendazole alone against *T. trichiura* is unsatisfactory and low cure rates of single-dose administration have also been reported for hookworm infection.

Ivermectin has recently been recognised as a key anti-parasitic medicine approved for the treatment and control of strongyloidiasis and scabies and has been safely used for decades in mass drug administration campaigns for onchocerciasis and lymphatic filariasis (LF). Ivermectin is also capable of killing arthropods – including some mosquito species.

3.1.3. Main clinical studies

Clinical Development Programme

The clinical development programme comprises two clinical trials (see

Table 38):

– Comparative bioavailability trial (BLCL-IVA-EU-01) – the 18/400 mg fixed-dose combination (FDC) was compared with administration of ivermectin (Stromectol 6x3 mg) and albendazole (Eskazole 1x400 mg) in adults under light meal conditions to demonstrate similar exposure based on geometric least-square mean ratios (GMRs) but not on 90% confidence interval (CI) that fall within 80-125%.

– Efficacy and safety trial (ALIVE) – to demonstrate superior efficacy of a single dose of the FDC vs. a single dose of 400 mg albendazole given alone and superior efficacy of a 3-day FDC regimen vs. a single dose of 400 mg albendazole given alone for treatment of each of whipworm, hookworm and strongyloidiasis. The efficacy of single dose-single day vs single dose 3-day FDC regimen was also be compared.

Table 38: Overview of clinical trials with ivermectin, albendazole

Table 1 Overview of Clinical Trials with Ivermectin, Albendazole					
Trial	**Phase**	**Status**	**Population**	**Site/s**	**Objective**
BLCL-IVA-EU-01	BA	completed	Adult healthy volunteers N=78	Porto, Portugal	To characterize the PK and to assess the BE after a single dose of FDC ivermectin-albendazole under light meal conditions of Test product versus the Reference products Stromectol® and Eskazole®. To assess the safety and tolerability of a single oral dose of investigational medicinal products.
ALIVE	2/3	completed	Paediatric population from 5 to 18 years old infected by hookworms, *T. trichiura*, and/or larvae of *S. stercoralis* N=1223	Mozambique, Kenya, Ethiopia	To evaluate the efficacy of the FDC ivermectin-albendazole as a single dose or 3-dose regimen compared to the standard single dose regimen of albendazole To evaluate the safety of the three drug regimens.

ALB=albendazole; BA=bioavailability; BE=bioequivalence; IVM=ivermectin; PK=pharmacokinetics

3.2. Favourable effects

The primary efficacy objective (Phase II and III Intent-to-Treat population) was the cure rate (CR)R at 21 days after treatment (by microscopy) for the FDC Single Dose arm (CR 82.9% [95% CI: 78.2, 87.5]) and for the FDC x3 arm (CR 97.2% [95% CI: 95.2, 99.3) compared with the ALB arm (CR 35.9% [95% CI: 27.7, 44.1]) (CR differences 47.2% and 61.3%, respectively [p < 0.0001 for both comparisons]). These data support the indication for treatment of Trichuriasis caused by *Trichuris trichiura* (whipworm).

The secondary objective for cure rate in hookworm infection was also met.

The efficacy of the fixed-dose combination for curing *S. stercoralis* infections in the ALIVE study was considered inconclusive due to the small sample size. Therefore, this study alone would not support this indication. However, since ivermectin (monocomponent) has been shown to be very efficacious against *S.*

stercoralis, the CHMP considered that the fixed-dose combination could be used to replace ivermectin for treatment of *S. stercoralis* (particularly in the mass drug administration setting).

Results of the subgroup analyses of cure rate for *T. trichiura* were consistent with results of the primary analysis using the Intent-to-Treat population, showing higher cure rates for the fixed-dose combination single dose and fixed-dose combination administered on 3 consecutive days compared with the albendazole arm for the subgroups defined by ivermectin drug exposure (> 400 µg/kg; ≤ 400 µg/kg), age category 5-14 years, co-infection status as mono-infected and worm burden “light” or “moderate”. For the subgroup of participants who were co-infected, the subgroup analysis was also consistent with the main analysis using the Intent-to-Treat population, showing a significantly higher cure rate for *T. trichiura* in the fixed-dose combination administered on 3 consecutive days arm compared with the albendazole arm, but no difference in cure rates between the fixed-dose combination single dose arm and albendazole arm.

The efficacy of the treatment in filariasis is inferred based on the results of a study conducted in Mali and published in 2010 (Dembele et al. 2010).

Safety of ivermectin and albendazole has been widely demonstrated, as both active substances have been extensively used in mass drug administration programmes including a high number of subjects. Two clinical studies conducted by the applicant confirmed the favourable safety profile of albendazole + ivermectin co-administration.

3.3. Uncertainties and limitations about favourable effects

Not enough adults >65 years were included in the ALIVE trial and the publications submitted did not include enough patients of that age group. Nevertheless, the CHMP considered that the reported clinical experience has not identified differences in responses between the elderly and younger patients.

Although it is clear that albendazole and ivermectin are widely used, its massive administration can lead to resistance development. Pending new data from exposed individuals, the definite establishment of a resistance profile for the ivermectin and albendazole combination is prevented by the absence of results of the resistance analysis of isolates from soil-transmitted helminth species collected in the ALIVE trial. Therefore, the CHMP considered that resistance data should be submitted as soon as they become available.

Efficacy has only been demonstrated for treatment of *T. trichiura* and *A. lumbricoides* in the pivotal study. For the other indications, efficacy is inferred based on data of the single agents, which is considered acceptable.

3.4. Unfavourable effects

In both the PK study BLCL-IVA-EU-01 in healthy subjects as well as in the Phase 2/3 Study ALIVE in children and young adults with STH infection, most reported AEs were mild or moderate in intensity and resolved without medical intervention.

In the context of the benefit-risk discussion, the CHMP considered the following unfavourable effects, as further detailed in the Effects Table:

- Hypersensitivity reactions
- Encephalopathy following treatment in patients with heavy Loa loa co-infection
- Hepatic enzymes increased
- Myelosuppression
- Lack of efficacy in immunocompromised patients

3.5. Uncertainties and limitations about unfavourable effects

No systematic evaluation of hepatic enzymes is anticipated in mass drug administration. In this context, the CHMP considered that if access to liver function tests is limited, the patient's history of liver disease, heavy alcohol consumption, or use of hepatotoxic drugs should at least be assessed and the patient monitored for any clinical signs of hepatic adverse reactions, including jaundice, dark urine, right upper quadrant abdominal pain, ascites or unexplained fatigue, particularly in patients with risk factors such as pre-existing liver disease or co-administration of other medicinal products. This has been reflected in section 4.4 of the SmPC.

Considering that only a limited number of patients in the ALIVE trial were exposed to a dose 600 µg/ kg (i.e. an equivalent of the 9 mg of ivermectin administered in a 15 kg child), doses above 600 µg/ kg can be seen as an uncertainty about unfavourable effects in children around the lower weight/ height bracket. This patient population might be potentially at an increased risk or exacerbation of adverse drug reactions, in particular during the mass drug administration. In this context, the CHMP also considered that there are published study data indicating good tolerance of ivermectin doses up to 600 µg/ kg (e.g., Matamoros, 2021), while acknowledging several study limitations precluding definite conclusions.

Not enough patients with immunosuppression were included in the ALIVE trial or in the publications provided. However, the CHMP was of the view that this issue is rather an efficacy concern than a safety concern, noting cases which showed the persistence of infestation following a single dose of ivermectin in immunocompromised patients.

3.6. Effects Table

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
CR at 21 days after treatment	Treatment of Trichuriasis caused by *Trichuris trichiura*	CR at 21 days after treatment (by microscopy)	FDC Single Dose arm FDC x3 arm	ABD	for the FDC Single Dose arm (CR 82.9% [95% CI: 78.2, 87.5]) and for the FDC x3 arm (CR 97.2% [95% CI: 95.2, 99.3) compared with the ALB arm (CR 35.9% [95% CI: 27.7, 44.1]) (CR differences 47.2% and 61.3%, respectively [p < 0.0001 for both comparisons])/small number of patients>65 years age/ potential of resistance/no treatment of 1 vs 3 days of FDC indication is given	ALIVE trial

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Decrease of microfilaremia	To determine the effect of increased dose and frequency of albendazole-ivermectin treatment on microfilarial clearance,	Decrease of microfilaremia	2 doses of annual, standard-dose albendazole-ivermectin therapy (400 mg and 150 µg/kg; np26)	4 doses of twice-yearly, increased-dose albendazole-ivermectin therapy (800 mg and 400 µg /kg; np 25)	Small number of patients Only publication used on filariasis	Dembele et al
Unfavourable Effects						
Hypersensitivity reactions (ivermectin)			IVE/ABD		It is an important identified risk included in the NAP IVE RMP and PSUR. Labelled for IVE and ABD	NAP RMP

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Encephalopathy following treatment in patients with heavy Loa loa co-infection (ivermectin)	The use of ivermectin in patients co-infected with *Loa loa* may cause SAEs like encephalopathies, neurotoxicity (e.g., depressed level of consciousness and coma).		IVE		Data is retrieved from literature. No cases were identified in clinical development programme. It is an important identified risk included in the NAP RMP and PSUR.	NAP RMP; labelled SmPC IVE
Hepatic enzymes increased (albendazole)	Albendazole therapy has been associated with transient and asymptomatic elevations in serum aminotransferase levels in up to 50% of patients treated for more than a few weeks. These abnormalities rapidly improve with stopping therapy which is rarely required (~4%).		ABD		This event was not assessed in ALIVE study (no laboratory analysis was performed).	

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Myelosuppression (albendazole).	Reversible leukopenia has been reported during albendazole therapy. Rarely, granulocytopenia or pancytopenia have resulted in death.		ABD		Data is retrieved from literature. No cases were identified in clinical development programme.	
Lack of efficacy in immunocompromised patients (ivermectin	Efficacy and dosing regimen of ivermectin in immunocompromised patients being treated for intestinal strongyloidiasis have not been established by adequate clinical studies. There have been reported cases which show the persistence of infestation following a single dose of ivermectin, particularly in this type of patients		IVE		It is an important potential risk in the NAP RMP (there is no centralised RMP).	NAP RMP;
Ivermectin dose >600 µg/kg	Potential overdose in children around the lower weight/ height bracket	N.A.	Filariasis and STH in the FDC	N/A	Uncertainty in mass campaigns use (increased risk/ exacerbation of adverse reactions)	Matamoros

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The ivermectin/ albendazole fixed-dose combination represents a promising tool to alleviate the burden of soil-transmitted helminth infections and filariasis morbidity. A probable reduction of transmission could be expected and ultimately contribute to the achievement of UN Sustainable Development Goals.

The primary efficacy objective in the ALIVE study (cure rate at 21 days) was met for *T. trichiura* and it can be expected that the same is also true for the other soil-transmitted helminths, based on the publications provided. The inference of efficacy for the treatment of filariasis based on published data was endorsed by the CHMP.

The CHMP considered that no patients above 65 years old were included but was of the view that these patients are not the ones who are expected to benefit the most from this intervention.

The safety of ivermectin and albendazole has been widely documented, as both have been extensively used in mass drug administration programmes including a high number of subjects.

In both the PK study BLCL-IVA-EU-01 in healthy subjects, as well as in the Phase II/III study ALIVE in children and young adults with STH infection, most reported adverse events were mild or moderate in intensity and resolved without medical intervention.

The population of children around the lower weight/ height bracket might be potentially at an increased risk or exacerbation of adverse drug reactions, which is particularly relevant during the mass drug administration.

Encephalopathy following treatment in patients with heavy *Loa loa* co-infection has been included in the Risk Management Plan as an important identified risk. The mitigation strategies proposed by the applicant were endorsed. In particular, the treatment is contraindicated in patients with high *Loa loa* microfilaria and for mass drug administration settings in *Loa loa* endemic regions, unless a feasible and validated risk mitigation strategy can be put in place which should follow WHO recommendations or relevant national guidelines for safe use in these settings.

As the studies submitted by the applicant did not justify the “prevention” of lymphatic filariasis and soil-transmitted helminth infections, the indication initially applied for was eventually restricted to “treatment” only. Furthermore, given that the age-defined target population in the main study was considered consistent with the weight range supporting dose recommendations (≥ 15 kg body weight should cover 90 percent of children ≥ 5 years of age) and the dose recommendations can be covered with the proposed formulation(s)/strength(s), the CHMP considered that the target population specified in section 4.1 should be defined by age only. Moreover, the indication “treatment of lymphatic filariasis” has been aligned with ivermectin products authorised in the EU to “Treatment of proven or suspected microfilaremia in patients with lymphatic filariasis caused by *Wuchereria bancrofti*”.

From a public health perspective, having ivermectin/ albendazole available as a treatment option in pregnant women was regarded highly relevant for the individual patient care. In view of the applicant´s response regarding the contraindication in pregnancy, the CHMP considered that this fixed-dose combination is

intended to be used in two different settings: Mass Drug Administration campaigns and Individual setting, where the use in pregnant women may be considered if clinically justified. Because of the teratogenic properties of albendazole, the use of Ivermectin/Albendazole orordispersible tablets has been contraindicated in the framework of a mass drug administration campaign in pregnant women and in women who intend to become pregnant. For the individual therapy (i.e. outside the scope of a mass drug administration) ivermectin/albendazole orodispersible tablets are not recommended especially during the first trimester of pregnancy. It should only be used during pregnancy if the clinical condition of the woman requires treatment with albendazole and ivermectin.

The CHMP agreed that the distinction between the use in pregnancy in these two settings is adequately reflected in sections 4.3 and 4.6 of the SmPC.

3.7.2. Balance of benefits and risks

The balance of benefits and risks is considered to be favourable for Ivermectin/Albendazole.

3.7.3. Additional considerations on the benefit-risk balance

Aside from the convenience of having a fixed-dose combination formulation of ivermectin and albendazole instead of separate containers with separate tablets, one of the major aspects of this new product is that it is an ‘orodispersible’ formulation. This should presumably have an impact on the number of episodes of choking that occur in young children during the mass drug campaigns, although no data were presented to support this. The population of patients within a mass drug programme most likely to suffer a choking episode are young children under four years of age.

Overall, the CHMP was of the opinion that the importance of this fixed-dose formulation for use in mass-drug administration programmes is represented by safety-related improvements (i.e. diminished choking hazard), as well as benefits in terms of logistics.

3.8. Conclusions

The overall benefit/risk balance of Ivermectin/Albendazole is positive, subject to the conditions stated in section ‘Recommendations’.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP adopted by consensus a scientific opinion as the benefit-risk balance of Ivermectin/Albendazole in the treatment of soil-transmitted

helminth infections and microfilaraemia in patients with lymphatic filariasis is favourable. The scientific opinion is subject to the attached product information and the following condition(s).

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the scientific opinion

- Periodic Safety Update Reports

The first periodic safety update report should cover the six-month period following the initial scientific opinion for this product on 30 January 2025.

Subsequently, the scientific opinion holder shall submit periodic safety update reports for this product every 6 months until otherwise agreed.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- Risk Management Plan (RMP)

The Scientific opinion Holder (SOH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the scientific opinion application and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.