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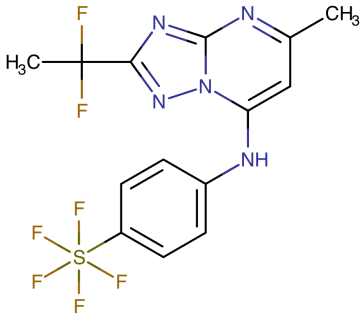


DSM265

Developer(s)

Medicines for Malaria Venture

Originator

https://www.mmv.org/

Switzerland

MMV is a Swiss-based not-for-profit organization working through a product development partnership model to deliver a portfolio of accessible medicines with the power to treat, prevent and eliminate malaria. We close critical gaps in research, development and access – working “end-to-end” to expand the use of existing antimalarials and innovate new compounds to protect public health.

Takeda Pharmaceuticals

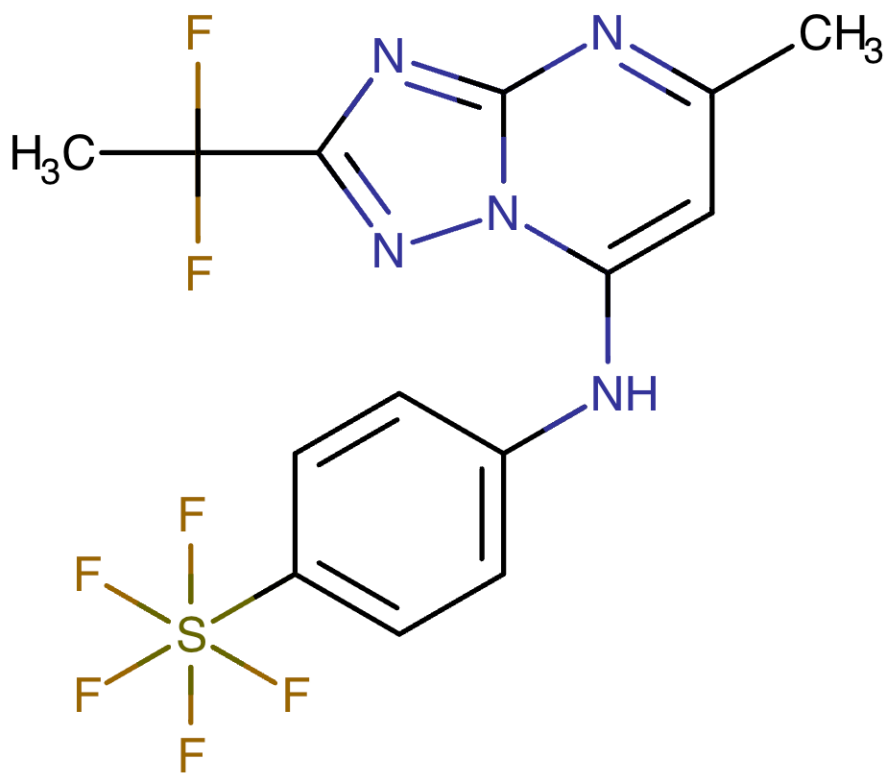
Originator

https://www.takeda.com/

Japan

Takeda aims to discover and deliver life-transforming treatments in our core therapeutic and business areas, including gastrointestinal and inflammation, rare diseases, plasma-derived therapies, oncology, neuroscience and vaccines.

Drug structure



DSM265 Chemical Structure

Sourced from Drugbank

Drug information

Associated long-acting platforms

Oral solid form

Administration route

Oral

Therapeutic area(s)

Malaria

Use case(s)

Pre-Exposure Prophylaxis (PrEP)
Treatment

Use of drug

Ease of administration

Self-administered

User acceptance

Not provided

Dosage

Available dose and strength

investigational

Frequency of administration

Not provided

Maximum dose

Not provided

Recommended dosing regimen

Not provided

Additional comments

Not provided

Dosage link(s)

Not provided

Drug information

Drug's link(s)

https://go.drugbank.com/drugs/DB12397

Generic name

DSM265

Brand name

Not provided

Compound type

Small molecule

Summary

DSM265 is an orally-active investigational compound currently in clinical development for the treatment and prevention of malaria. DSM265 functions through selectively inhibiting the dihydroorotate dehydrogenase (DHOPH) enzyme essential for Plasmodium falciparum pyrimidine biosynthesis. Preclinical studies indicated that DSM265 was effective against pre-erythrocytic Plasmodium falciparum and displayed potential as an antimalarial chemoprophylactic due to a favourable pharmacokinetic profile that enables once-weekly dosing. Subsequent in-human clinical trials have shown that while orally administered DSM265 displays high-levels of tolerability and safety, it only induces limited pre-erythrocytic protection, indicating that alternate dosing or combination therapy approaches may be required.

Approval status

It appears that the development of DSM265 is suspended.

Regulatory authorities

The product did not progress to approval

Delivery device(s)

No delivery device

Scale-up and manufacturing prospects

Scale-up prospects

Spray-dried dispersion (SDD) formulations were developed to improve both the solubility and bioavailability of DSM265, in which the drug is present in a stable amorphous state. The spray-drying technology is scalable and suitable for continuous processing, which could potentially facilitate the commercial-scale manufacture of DSM265. Progressive improvements to the chemical synthesis pathway and sourcing of lower-cost starting materials have substantially reduced the overall manufacturing cost of the DSM265 drug substance.

Tentative equipment list for manufacturing

Not provided

Manufacturing

The current spray-dried formulation of DSM265 may generate packaging issues due to poor flow properties. Additionally, the oral suspension is administered and dispersed using an aqueous solution containing sweetener and solubilising agents. The requirement for an accompanying dosing medium increases the costs of drug administration and poses commercial as well as logistical challenges. Development of a granulation process to improve the flow properties of the formulation whilst also incorporating the necessary solubilising excipients to enable water-based reconstitution would be beneficial.

Specific analytical instrument required for characterization of formulation

Not provided

Clinical trials

MMV_DSM265_14_01

Identifier

NCT02450578

Link

https://clinicaltrials.gov/ct2/show/NCT02450578

Phase

Phase I

Status

Completed

Sponsor

Medicines for Malaria Venture

More details

Not provided

Purpose

Evaluate the Prophylactic Antimalarial Activity of a Single Dose of DSM265 in Non-immune Healthy Adults by Controlled Human Malaria Infection With PfSPZ Challenge

Interventions

Intervention 1

Drug: DSM265 400mg

Intervention 2

Drug: Placebo to DSM265 400 mg

Intervention 3

Biological: Plasmodium falciparum sporozoite challenge

Intervention 4

Drug: Malarone

Countries

Germany

Sites / Institutions

Not provided

Trials dates

Anticipated Start Date

Not provided

Actual Start Date

2015-10-01

Anticipated Date of Last Follow-up

Not provided

Estimated Primary Completion Date

Not provided

Estimated Completion Date

Not provided

Actual Primary Completion Date

2016-04-01

Actual Completion Date

2016-04-01

Studied populations

Age Cohort

- Adults

Genders

- All

Accepts pregnant individuals

No

Accepts lactating individuals

No

Accepts healthy individuals

Yes

Comments about the studied populations

Good health based on medical history and physical examination- Body mass index >18 and <30 kg/m2

Health status

Negative to : HIV, HBV, HCV

Study type

Interventional (clinical trial)

Enrollment

22

Allocation

Randomized

Intervention model

Parallel Assignment

Intervention model description

Not provided

Masking

Quadruple-blind masking

Masking description

Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)

Frequency of administration

Other : "Single dose "

Studied LA-formulation(s)

Other(s) : "Oral Suspension "

Studied route(s) of administration

Oral

Use case

PrEP

Key resources

Type	Title	Content	Link

Link	DSM265 for Plasmodium falciparum chemoprophylaxis: a randomised, double blinded, phase 1 trial with controlled human malaria infection	https://doi.org/10.1016/s1473099(17)30139-1

MMV_DSM265_13_02

Identifier

NCT02123290

Link

https://clinicaltrials.gov/ct2/show/NCT02123290

Phase

Phase II

Status

Completed

Sponsor

Medicines for Malaria Venture

More details

Not provided

Purpose

Examine the efficacy of DSM265 in uncomplicated Plasmodium falciparum and Plasmodium vivax blood-stage malaria in adult patients.

Interventions

Intervention 1

Drug: DSM265

Countries

Peru

Sites / Institutions

Not provided

Trials dates

Anticipated Start Date

Not provided

Actual Start Date

2015-01-12

Anticipated Date of Last Follow-up

Not provided

Estimated Primary Completion Date

Not provided

Estimated Completion Date

Not provided

Actual Primary Completion Date

2015-12-02

Actual Completion Date

2016-01-01

Studied populations

Age Cohort

- Adults

Genders

- All

Accepts pregnant individuals

No

Accepts lactating individuals

No

Accepts healthy individuals

No

Comments about the studied populations

Participants have a body weight between 45-90kg and a confirmed mono-infection of P. falciparum or P. vivax.

Health status

Positive to : Malaria
Negative to : HBV, HCV, TB

Study type

Interventional (clinical trial)

Enrollment

45

Allocation

Non-randomized

Intervention model

Parallel Assignment

Intervention model description

Not provided

Masking

Open label

Masking description

None (Open Label)

Frequency of administration

Other : "Single dose or escalated/de-escalated doses "

Studied LA-formulation(s)

Other(s) : "Oral suspension "

Studied route(s) of administration

Oral

Use case

Treatment

Key resources

Type	Title	Content	Link
Link	Antimalarial activity of single-dose DSM265, a novel plasmodium dihydroorotate dehydrogenase inhibitor, in patients with uncomplicated Plasmodium falciparum or Plasmodium vivax malaria infection		https://doi.org/10.1016/s1473099(18)30309-8

MMV_DSM265_14_03

Identifier

NCT02562872

Link

https://clinicaltrials.gov/ct2/show/NCT02562872

Phase

Phase I

Status

Completed

Sponsor

Medicines for Malaria Venture

More details

Not provided

Purpose

Evaluate the Pharmacokinetics, Prophylactic Activity, Tolerability and Safety of Single Dose DSM265 in a Controlled Human Malarial Infection Challenge

Interventions

Intervention 1

Drug: DSM265

Intervention 2

Drug: DSM265 Placebo

Intervention 3

Biological: Sporozoites

Intervention 4

Biological: Infective mosquito bite

Countries

United States of America

Sites / Institutions

Not provided

Trials dates

Anticipated Start Date

Not provided

Actual Start Date

2016-03-01

Anticipated Date of Last Follow-up

Not provided

Estimated Primary Completion Date

Not provided

Estimated Completion Date

Not provided

Actual Primary Completion Date

2017-05-01

Actual Completion Date

2017-05-01

Studied populations

Age Cohort

- Adults

Genders

- All

Accepts pregnant individuals

No

Accepts lactating individuals

No

Accepts healthy individuals

Yes

Comments about the studied populations

Participants are in good health with a body mass index of >18 and <30kg/m2.

Health status

Negative to : Malaria, HIV, HBV, HCV

Study type

Interventional (clinical trial)

Enrollment

24

Allocation

Randomized

Intervention model

Parallel Assignment

Intervention model description

Not provided

Masking

Quadruple-blind masking

Masking description

Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)

Frequency of administration

Other : "Single dose "

Studied LA-formulation(s)

Other(s) : "Oral Suspension "

Studied route(s) of administration

Oral

Use case

PrEP

Key resources

Not provided

DSMOZ-2

Identifier

NCT02573857

Link

https://clinicaltrials.gov/ct2/show/NCT02573857

Phase

Phase I/II

Status

Terminated

Sponsor

Medicines for Malaria Venture

More details

Not provided

Purpose

Characterise the Transmission Blocking and Antimalarial Activity of OZ439 and DSM265 in Blood Stage Plasmodium Vivax or Plasmodium Falciparum Infection Respectively.

Interventions

Intervention 1

Drug: DSM265

Intervention 2

Drug: OZ439

Countries

Australia

Sites / Institutions

Not provided

Trials dates

Anticipated Start Date

Not provided

Actual Start Date

2015-10-01

Anticipated Date of Last Follow-up

Not provided

Estimated Primary Completion Date

Not provided

Estimated Completion Date

Not provided

Actual Primary Completion Date

2016-05-01

Actual Completion Date

2016-05-01

Studied populations

Age Cohort

- Adults

Genders

- All

Accepts pregnant individuals

No

Accepts lactating individuals

No

Accepts healthy individuals

Yes

Comments about the studied populations

Not provided

Health status

Negative to : Malaria, HIV, HBV, HCV

Study type

Interventional (clinical trial)

Enrollment

16

Allocation

Non-randomized

Intervention model

Single group assignment

Intervention model description

Not provided

Masking

Open label

Masking description

None (Open Label)

Frequency of administration

Other : "Single dose "

Studied LA-formulation(s)

Other(s) : "Oral Suspension "

Studied route(s) of administration

Oral

Use case

Treatment

Key resources

Type	Title	Content	Link
Link	DSM265 at 400 Milligrams Clears Asexual Stage Parasites but Not Mature Gametocytes from the Blood of Healthy Subjects Experimentally Infected with Plasmodium falciparum		https://doi.org/10.1128/aac.18

MMV_DSM265_18_01

Identifier

NCT03637517

Link

https://clinicaltrials.gov/study/NCT03637517

Phase

Phase I

Status

Completed

Sponsor

Medicines for Malaria Venture

More details

Phase 1 study designed to evaluate the relative bioavailability of a single dose of a test formulation, DSM265-TPGS 34% SDD powder in comparison with a reference DSM265 25% SDD powder formulation used in early clinical trials.

Purpose

Malaria: Relative Bioavailability and Food Effect of DSM265

Interventions

Not provided

Countries

Not provided

Sites / Institutions

Not provided

Trials dates

Anticipated Start Date

Not provided

Actual Start Date

2018-10-03

Anticipated Date of Last Follow-up

2020-02-25

Estimated Primary Completion Date

Not provided

Estimated Completion Date

Not provided

Actual Primary Completion Date

2018-11-19

Actual Completion Date

2018-11-19

Studied populations

Age Cohort

- Adults

Genders

- All

Accepts pregnant individuals

Unspecified

Accepts lactating individuals

Unspecified

Accepts healthy individuals

Yes

Comments about the studied populations

1. Subjects or their legally authorized representative must voluntarily sign and date each informed consent, approved by an Independent Ethics Committee(IEC) / Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures. 2. Male or female between 18 and 55 years of age inclusive at the time of screening. 3. Body Mass Index (BMI) is ≥ 18.0 to ≤ 29.9 kg/m2 after rounding to the tenths decimal. BMI is calculated as weight in kg divided by the square of height measured in meters. 4. Females must be of Non-Childbearing Potential as defined below Females do not need to use birth control during or following study drug treatment if considered of non-childbearing potential due to meeting any of the following criteria: * Postmenopausal, age ≤ 55 yea

Health status

Not provided

Study type

Interventional (clinical trial)

Enrollment

42

Allocation

Randomized

Intervention model

Parallel Assignment

Intervention model description

Not provided

Masking

Open label

Masking description

Not provided

Frequency of administration

Not provided

Studied LA-formulation(s)

Not provided

Studied route(s) of administration

Not provided

Use case

Not provided

Key resources

Not provided

B16-963

Identifier

NCT02750384

Link

https://clinicaltrials.gov/study/NCT02750384

Phase

Phase I

Status

Terminated

Sponsor

Medicines for Malaria Venture

More details

This is a single-dose, fasting and non-fasting, open-label, randomized, three-regimen, parallel group study in 42 subjects

Purpose

Bioavailability and Effect of Food on DSM265 Granules in Healthy Adult Subjects

Interventions

Not provided

Countries

Not provided

Sites / Institutions

Not provided

Trials dates

Anticipated Start Date

Not provided

Actual Start Date

2016-05-01

Anticipated Date of Last Follow-up

2016-09-13

Estimated Primary Completion Date

Not provided

Estimated Completion Date

Not provided

Actual Primary Completion Date

2016-07-01

Actual Completion Date

2016-07-01

Studied populations

Age Cohort

- Adults

Genders

- All

Accepts pregnant individuals

Unspecified

Accepts lactating individuals

Unspecified

Accepts healthy individuals

Yes

Comments about the studied populations

Inclusion Criteria: * Female subjects of non-child bearing potential: * surgically sterile (by hysterectomy and/or bilateral oophorectomy and/or bilateral salpingectomy or bilateral tubal ligation) OR * postmenopausal (without use of hormonal contraceptive and spontaneous amenorrhea for 12 months and follicle stimulating hormone \> 40 IU/mL age appropriate for menopause and no other medical explanation for amenorrhea) * Males: * If he (including those who have had a vasectomy) is sexually active with female partner(s) of childbearing potential, he must agree, from Day 1 through 120 days after the dose of study drug to practice the continuous acceptable methods of contraception with his partner(s). * If he has a female partner who is postmenopausal or permanently sterile, the mal

Health status

Not provided

Study type

Interventional (clinical trial)

Enrollment

11

Allocation

Randomized

Intervention model

Parallel Assignment

Intervention model description

Not provided

Masking

Open label

Masking description

Not provided

Frequency of administration

Not provided

Studied LA-formulation(s)

Not provided

Studied route(s) of administration

Not provided

Use case

Not provided

Key resources

Not provided

Excipients

Proprietary excipients used

Not provided

Novel excipients or existing excipients at a concentration above Inactive Ingredients Database (IID) for the specified route of administration

Not provided

Residual solvents used

Not provided

Patent info

Description

DSM-265 compound

Brief description

Inhibitors of parasitic dihydroorotate dehydrogenase enzyme (DHOD) are candidate therapeutics for treating malaria. Illustrative of such therapeutic agents include the compound: and a triazolopyrimidine class of compounds that conform to Formula (IX): and their solvates, stereoisomers, tautomers and pharmaceutically acceptable salts. (DSM-265 given as Example 44) Method of treating Malaria.

Representative patent

WO2011041304

Category

Compound

Patent holder

Board of Regents, University of Texas System; Monash University; Medicines For Malaria Venture; University of Washington; Glaxosmithkline Investigacion Y Desarrollo, S.L

Exclusivity

Not provided

Expiration date

September 14, 2031

Status

Granted: EP, US, CN, CA, BR, JP, IN, HK

Supporting material

Publications

Alka Marwaha, John White, Farah El_Mazouni, Sharon A Creason, Sreekanth Kokkonda, Frederick S. Buckner, Susan A. Charman, Margaret A. Phillips, and Pradipsinh K. Rathod. Bioisosteric Transformations and Permutations in the Triazolopyrimidine Scaffold To Identify the Minimum Pharmacophore Required for Inhibitory Activity against *Plasmodium falciparum* Dihydroorotate Dehydrogenase. Journal of Medicinal Chemistry 2012 *55* (17), 7425-7436 DOI: www.doi.org/10.1021/jm300351w

Plasmodium falciparum causes approximately 1 million deaths annually. However, increasing resistance imposes a continuous threat to existing drug therapies. We previously reported a number of potent and selective triazolopyrimidine-based inhibitors of *P. falciparum* dihydroorotate dehydrogenase that inhibit parasite in vitro growth with similar activity. Lead optimization of this series led to the recent identification of a preclinical candidate, showing good activity against *P. falciparum* in mice. As part of a backup program around this scaffold, we explored heteroatom rearrangement and substitution in the triazolopyrimidine ring and have identified several other ring configurations that are active as *Pf*DHODH inhibitors. The imidazo[1,2-*a*]pyrimidines were shown to bind somewhat more potently than the triazolopyrimidines depending on the nature of the amino aniline substitution. DSM151, the best candidate in this series, binds with 4-fold better affinity (*Pf*DHODH IC50 = 0.077 μM) than the equivalent triazolopyrimidine and suppresses parasites in vivo in the *Plasmodium berghei* model.

Jose M. Coteron, María Marco, Jorge Esquivias, Xiaoyi Deng, Karen L. White, John White, Maria Koltun, Farah El Mazouni, Sreekanth

Kokkonda, Kasiram Katneni, Ravi Bhamidipati, David M. Shackleford, Iñigo Angulo-Barturen, Santiago B. Ferrer, María Belén Jiménez-Díaz, Francisco-Javier Gamo, Elizabeth J. Goldsmith, William N. Charman, Ian Bathurst, David Floyd, David Matthews, Jeremy N. Burrows, Pradipsinh K. Rathod, Susan A. Charman, and Margaret A. Phillips. Structure-Guided Lead Optimization of Triazolopyrimidine-Ring Substituents Identifies Potent *Plasmodium falciparum* Dihydroorotate Dehydrogenase Inhibitors with Clinical Candidate Potential. Journal of Medicinal Chemistry 2011 *54* (15), 5540-5561. DOI: www.doi.org/10.1021/jm200592f

Drug therapy is the mainstay of antimalarial therapy, yet current drugs are threatened by the development of resistance. In an effort to identify new potential antimalarials, we have undertaken a lead optimization program around our previously identified triazolopyrimidine-based series of *Plasmodium falciparum* dihydroorotate dehydrogenase (*Pf*DHODH) inhibitors. The X-ray structure of *Pf*DHODH was used to inform the medicinal chemistry program allowing the identification of a potent and selective inhibitor (DSM265) that acts through DHODH inhibition to kill both sensitive and drug resistant strains of the parasite. This compound has similar potency to chloroquine in the humanized SCID mouse *P. falciparum* model, can be synthesized by a simple route, and rodent pharmacokinetic studies demonstrated it has excellent oral bioavailability, a long half-life and low clearance. These studies have identified the first candidate in the triazolopyrimidine series to meet previously established progression criteria for efficacy and ADME properties, justifying further development of this compound toward clinical candidate status.

Sulyok M et al. “DSM265 for Plasmodium falciparum chemoprophylaxis: a randomised, double blinded, phase 1 trial with controlled human malaria infection.” Lancet Infect Dis. 17(6):636-644 (2017).

Background:

A drug for causal (ie, pre-erythrocytic) prophylaxis of Plasmodium falciparum malaria with prolonged activity would substantially advance malaria control. DSM265 is an experimental antimalarial that selectively inhibits the parasite dihydroorotate dehydrogenase. DSM265 shows in vitro activity against liver and blood stages of P falciparum. We assessed the prophylactic activity of DSM265 against controlled human malaria infection (CHMI).

Methods:

At the Institute of Tropical Medicine, Eberhard Karls University (Tübingen, Germany), healthy, malaria-naive adults were allocated to receive 400 mg DSM265 or placebo either 1 day (cohort 1A) or 7 days (cohort 2) before CHMI by direct venous inoculation (DVI) of 3200 aseptic, purified, cryopreserved P falciparum sporozoites (PfSPZ Challenge; Sanaria Inc, Rockville, MD, USA). An additional group received daily atovaquone-proguanil (250-100 mg) for 9 days, starting 1 day before CHMI (cohort 1B). Allocation to DSM265, atovaquone-proguanil, or placebo was randomised by an interactive web response system. Allocation to cohort 1A and 1B was open-label, within cohorts 1A and 2, allocation to DSM265 and placebo was double-blinded. All treatments were given orally. Volunteers were treated with an antimalarial on day 28, or when parasitaemic, as detected by thick blood smear (TBS) microscopy. The primary efficacy endpoint was time-to-parasitaemia, assessed by TBS. All participants receiving at least one dose of chemoprophylaxis or placebo were considered for safety, those receiving PfSPZ Challenge for efficacy analyses. Log-rank test was used to compare time-to-parasitemia between interventions. The trial was registered with ClinicalTrials.gov, number NCT02450578.

Findings:

22 participants were enrolled between Oct 23, 2015, and Jan 18, 2016. Five

participants received 400 mg DSM265 and two participants received placebo 1 day before CHMI (cohort 1A), six participants received daily atovaquone-proguanil 1 day before CHMI (cohort 1B), and six participants received 400 mg DSM265 and two participants received placebo 7 days before CHMI (cohort 2). Five of five participants receiving DSM265 1 day before CHMI and six of six in the atovaquone-proguanil cohort were protected, whereas placebo recipients (two of two) developed malaria on days 11 and 14. When given 7 days before CHMI, three of six volunteers receiving DSM265 became TBS positive on days 11, 13, and 24. The remaining three DSM265-treated, TBS-negative participants of cohort 2 developed transient submicroscopic parasitaemia. Both participants receiving placebo 7 days before CHMI became TBS positive on day 11. The only possible DSM265-related adverse event was a moderate transient elevation in serum bilirubin in one participant.

Interpretation:

A single dose of 400 mg DSM265 was well tolerated and had causal prophylactic activity when given 1 day before CHMI. Future trials are needed to investigate further the use of DSM265 for the prophylaxis of malaria.

Additional documents

No documents were uploaded

Useful links

- Commercial formulation development of DSM265
- Formulation Optimization Work on DSM265
- DSM265 for Plasmodium falciparum chemoprophylaxis: a randomised, double blinded, phase 1 trial with controlled human malaria infection
- Antimalarial activity of single-dose DSM265, a novel plasmodium dihydroorotate dehydrogenase inhibitor, in patients with uncomplicated Plasmodium falciparum or Plasmodium vivax malaria infection
- DSM265 at 400 Milligrams Clears Asexual Stage Parasites but Not Mature Gametocytes from the Blood of Healthy Subjects Experimentally Infected with Plasmodium falciparum

Access principles

Collaborate for development

Consider on a case by case basis, collaborating on developing long acting products with potential significant public health impact, especially for low- and middle-income countries (LMICs), utilising the referred to long-acting technology

Not provided

Share technical information for match-making assessment

Provide necessary technical information to a potential partner, under confidentiality agreement, to enable preliminary assessment of whether specific medicines of public health importance in LMICs might be compatible with the referred to long-acting technology to achieve a public health benefit

Not provided

Work with MPP to expand access in LMICs

In the event that a product using the referred to long-acting technology is successfully developed, the technology IP holder(s) will work with the Medicines Patent Pool towards putting in place the most appropriate strategy for timely and affordable access in low and middle-income countries, including through licensing

Not provided

Comment & Information

It appears that the development of DSM265 may be stopped.