



Malaria Treatment

EDCTP Stakeholder meeting

Place: Vienna, Austria

Date: 14 June 2007

Author(s) :

Michael Makanga

Version Number:

02

Date of approval:

02/08/2007

By:

Charles S Mgone

Table of contents

1. Introduction.....	3
2. Science and products.....	3
Overview of presented products	4
Summary discussion on products and science	4
Meeting deliberations:	4
3. Sites in Africa	6
Overview of presented sites:	6
Summary discussion on Sites in Africa	6
4. EDCTP procedures	8
Overview EDCTP procedures	8
5. Recommendations to EDCTP	9
Annexes	10
Annex 1: Hosting country contribution to the stakeholder meeting	10
Annex 2: EDCTP Guidelines for Stakeholder meetings	11
Annex 3: Instructions for presentations	15
Annex 4: Agenda.....	16
Annex 5: List of participants	17
Annex 6: Discussion paper	17

1. Introduction

The EDCTP stakeholders' meeting on malaria treatment hosted by Austria was the eighth among the ten thematic stakeholders' and consultative meetings organised by EDCTP in the planning and implementation of the new strategy for funding projects. The aims of the meeting were to identify malaria treatment products for clinical trials; identify capacity gaps and requirements for conducting clinical trials; and to agree upon the mode of formulating grant proposals, either through open calls or brokering.

The meeting was chaired by Dr Pascal Ringwald of the Global Malaria Programme, World Health Organisation.

2. Science and products

Overview of participating organisations

Public organisations:

- World Health Organisation: (<http://www.who.int>)
- Vienna School of Clinical Research (VSCR), Austria: (<http://www.vscr.at>)
- Institute of Tropical Medicine Antwerp, Belgium: (<http://www.itg.be/itg>)
- Medical Research Council, UK: (<http://www.mrc.ac.uk/index.htm>)
- Statens Serum Institut, Denmark: (<http://www.ssi.dk>)
- Bundesministerium für Bildung und Forschung, Germany: (<http://www.bmbf.de>)
- Subdirección General de Evaluación y Fomento de la Investigación (SGEFI), Spain
- Institut de Recherche pour le Développement (IRD), Faculté de Pharmacie, Paris, France: (<http://www.ird.fr/>)
- European Commission: (http://ec.europa.eu/index_en.htm)
- EDCTP: (<http://www.edctp.org>)

Public Private Partnerships:

- The Medicines for Malaria Venture (MMV): (<http://www.mmv.org>)
- Drugs for Neglected Diseases initiative (DNDi): (<http://www.dndi.org>)
- Malaria Clinical Trials Alliance (MCTA): (<http://www.indepth-network.org/mcta>)

Private Sector: None

Other:

- East African Network for Monitoring Antimalarial Treatment:
(<http://www.eanmat.org>)

Overview of presented products

Two organisations, MMV and DNDi had presentations on antimalarial products in development that are currently in their portfolios.

MMV has 24 projects in its product development portfolio. Of these five, all of which are artemisinin based, are in phase III testing. These include chlorproguanil-dapsone (Lapdap[®]) artesunate (CDA), coartem[®] dispersable, artesunate - pyronaridine (Pyramax[®]) and dihydroartemisinin - piperaquine for uncomplicated malaria and intravenous artesunate for severe malaria. All these products will be made available for phase IIIb and phase IV studies after registration with prior authorisation from MMV.

Other products that are in the pipeline include tafenoquine for the treatment of *Plasmodium vivax*, currently in phase II and not funded, isoquine (an improved aminoquinoline) on hold, MK-4815 awaiting toxicology results and funding, and 4(1H)-pyridone GSK-932121 a backup product for previous pyridines. The last three are in preclinical phase and the remaining 15 projects are still in discovery and exploratory phases.

DNDi has two antimalarial products in its product development portfolio namely artesunate-amodiaquine coformulated product (registered) and artesunate mefloquine coformulated product (in phase III) testing. DNDi is willing to make these products available for future studies where these products could be used to generate quality data and also as reference products.

Summary discussion on products and science

The chair gave a scientific overview on the field of malaria treatment covering both uncomplicated and severe malaria as reflected in annex 6. He discussed areas on WHO changes in threshold levels for changing malaria treatment policy comparing the WHO criteria of 1998, 2003 and 2005; rational for combination therapy vis-à-vis ACTs; WHO treatment guidelines; and WHO standardised protocol for assessment of therapeutic efficacy.

Meeting deliberations:

It was observed that currently there are very few antimalarial products in the development pipeline for phase I and II clinical trials, but noted that MMV has five products that are about to complete phase III trials. Priority was therefore on phase IIIb studies involving special categories of patients. These include safety and efficacy assessments in infants, patients with tuberculosis and HIV (including antimalarial drug interactions with antiretroviral drugs), as well as in pregnancy. However, it was agreed that pregnancy associated malaria would be discussed in a separate stakeholders' meeting.

It was also discussed that there is need to support development of new combination antimalarials (both artemisinin and non-artemisinin based combinations). New partner antimalarials with novel mechanisms of action also need to be investigated. The choice of these, however, should be made in a rational way and emphasis made on use of GMP products for all combinations.

It was observed that there is need for systematic pharmacokinetic (PK) studies especially with artemisinin based combinations with long acting partner drugs, especially in settings of high transmission. However, these studies need to be done in sites with good PK facilities. This was identified as an important deficiency.

MMV expressed interest of collaboration on studies involving intravenous (IV) artesunate and phases IIIb and IV studies involving products which are in their pipeline. It was, however, emphasised that applicants should obtain prior authorisation from MMV or other product developers for use of unregistered products.

DNDi expressed interest of collaboration on studies involving artesunate - amodiaquine and artesunate - mefloquine combinations, PK studies and non-product specific pharmacovigilance.

It was acknowledged that phase IV clinical trials are not in the mandate of EDCTP except in exceptional circumstances where there is strong justification for national relevance in informing policy and pharmacovigilance. However, the participants advised that EDCTP could consider supporting more phase IV studies in future. These could include home-based malaria treatment in the deployment of ACTs and intermittent preventive treatment in children and infants (IPTi and IPTc) which are currently not included in the malaria treatment guidelines since there is need for more work to be done in this area. It was also agreed that the effect of drug pressure as a result of IPTi and IPTc vis-à-vis protection of ACTs needs to be investigated.

The table below summarises the products in the MMV and DNDi product development pipelines that were discussed in this meeting.

Name of Product	Presented by	Where in pipeline
Chlorproguanil-dapsone (Lapdap [®]) - artesunate (CDA)	MMV	Phase III
Coartem [®] Dispersable Tablet	MMV	Phase III
Dihydroartemisinin - piperaquine	MMV	Phase III
Artesunate – pyronaridine (PYRAMAX [®])	MMV	Phase III
Intravenous Artesunate	MMV	Phase III
Artesunate - Mefloquine (co-formulated)	DNDi	Phase III
Tafenoquine	MMV	Phase II
Isoquine (an improved aminoquinoline)	MMV	Preclinical testing
4 (1H)-pyridones Back ups	MMV	Preclinical testing
MK-4815	MMV	Preclinical testing

3. Sites in Africa

Overview of presented sites:

Representatives of MCTA and EANMAT gave presentations on some of the sites in Africa and an update of activities of their organisations. The Developing Countries Coordinating Committee (DCCC) representative from Congo Brazzaville and a researcher from the Gambia gave input from the Central and West African point of view since one of speakers from Cameroon was unable to make it for this meeting.

Summary discussion on Sites in Africa

The definition of clinical trial sites was discussed and it was agreed that the ICH GCP definition should be adopted. According to ICH GCP a trial site is defined as 'the location (s) where trial-related activities are actually conducted.'

It was generally recognised by all participants present that there was a shortage of sites to conduct clinical trials in Africa. The development of sites should, however, be done in the context of clinical trials and not in isolation. Thus the capacity developed should be optimally utilised and sustained. The need to support African sites to set up good facilities for pharmacokinetics sample handling and analysis was pointed out as a potential gap.

The idea of EDCTP encouraging less developed institutions to link up with more established one in the future EDCTP integrated calls was applauded. It was recommended that a balanced approach of linking less developed institutions with more established ones should be encouraged and that the more established institutions also should be strengthened in the areas that they are good at in order to foster a more effective mentoring process. This would link up well with the concept of networks of excellence that EDCTP plans to support.

The table below summarises the southern partner institutions that were either represented or featured in discussion of sites in Africa through their association with MCTA and EANMAT.

Name of site	Country	Trial experience	Represented in person
MRC laboratories, Fajara	Gambia	Yes (drugs and vaccines)	Yes
College of Medicine, University of Ibadan	Nigeria	Yes (drugs)	No (MCTA)
State Specialist Hospital, Maiduguri	Nigeria	Yes (drugs)	No (MCTA)
Queen Elizabeth Central Hospital, Blantyre	Malawi	Yes (drugs)	No (MCTA)
Ndirande Health Centre	Malawi	Yes (drugs)	No (MCTA)

EDCTP Stakeholder meeting: Malaria treatment

Vienna 14 June 2007

KEMRI-Wellcome Trust Collaborative Centre, Kilifi	Kenya	Yes (drugs and vaccines)	No (MCTA)
Ifakara Health Research and Development Centre, Bagamoyo	Tanzania	Yes (drugs and vaccines)	No (MCTA)
Albert Schweitzer Hospital (HAS)	Gabon	Yes (drugs and vaccines)	Yes
Centre for Clinical Research- KEMRI, Kisumu	Kenya	Yes (drugs and vaccines)	Yes
Manhica Health Research Centre	Mozambique	Yes (drugs and vaccines)	Yes
Kumasi Centre for Collaborative Research	Ghana	Yes (drugs and vaccines)	No (MCTA)
Amani Centre of NIMR	Tanzania	Yes (drugs and vaccines)	No (MCTA)
Nanoro Health Centre, Ouagadougou	Burkina Faso	Yes (drugs)	No (Antwerp Institute of Tropical Medicine)
EANMAT Sentinel Sites	Kenya – 8 Uganda - 8 Tanzania mainland – 8 Rwanda – 6 Burundi – 6 Zanzibar – 2	Majority of these have potential for upgrading and are health centres involved in routine drug efficacy testing not clinical trials. (Tororo & Jinja in Uganda and Rukara in Rwanda currently involved in EDCTP supported drug clinical trial)	Yes (EANMAT Treasurer)
Centre d'Etudes sur les Ressources Végétales (CERVE)	Congo - Brazzaville	Yes (drugs)	Yes

4. EDCTP procedures

Overview EDCTP procedures

EDCTP can fund proposals through an open call or a brokering procedure. Both were explained to the audience. More information is available in the Guidelines for Stakeholders' meetings (see Annex 2)

Summary discussion EDCTP funding procedure and timelines for initiating funding procedure

It was generally agreed that an open call would be the appropriate funding procedure for malaria treatment.

Recommended procedure:

Open call for proposals with all funds in one envelope but addressing the two high priority areas stated in the meeting recommendations. These clinical trials were recommended cost approximately 4 million Euros on average.

Recommended time to initiate funding procedure (s):

Call for proposals to be published as soon as possible in 2007.

Possible funding partners:

Pledged and potential contributions to topic			
Organisation	Country	Amount	Certainty
MMV	Switzerland	To be determined (tbd)	
DNDi	Switzerland	Tbd	
	UK	Cash contribution of 800,000 Euros	Yes: for African and UK investigators
	Spain	Cash contribution tbd	Spanish participation required
	Germany	Cash contribution tbd	Germany participation required
	Austria	Cash contribution tbd	Towards capacity development: training aspects
	France	No firm commitment	No
	Denmark	No firm commitment	No
	Belgium	No firm commitment	No

5. Recommendations to EDCTP

1. Open call for proposals was recommended
2. To fund phase IIIb clinical trials with focus on efficacy and safety assessment in special categories of patients such as infants, HIV/AIDS and tuberculosis co-infected individuals including studies on interactions of antimalarials with antiretroviral therapies. This applies to both drugs for uncomplicated and complicated or severe *Plasmodium falciparum* malaria
3. To support development of new antimalarial products (phase II and III studies) for both artemisinin-based combinations and non-artemisinin-based combinations including antibiotic antimalarial products, while ensuring that there sufficient phase I data available and GMP products are used
4. To support systematic pharmacokinetics studies on the different available combination antimalarials especially artemisinin-based combination therapies (ACTs) both in development and those already registered. This should be coupled with the need to set up sites with good pharmacokinetics handling and analysis facilities
5. Not to exclude longitudinal studies in view of the long half lives of many of the partner drugs in the available artemisinin-based combinations
6. To put all the available funds in one basket and support calls for proposals on the following:
 - Phase III b studies in special categories of patients mentioned under recommendation 2 including systematic pharmacokinetic studies in 4
 - Studies investigating new products in recommendation 3.

Annexes

Annex 1: Hosting country contribution to the stakeholder meeting

Estimate of all costs covered by hosting country	
Item	Amount
Travel	
Hotel	
Catering	2,064.03 Euros
Administration support	
Venue	
Other	
Sum	2,064.03 Euros

Signed by organising Member State:

Name

Date

Annex 2: EDCTP Guidelines for Stakeholder meetings

Introduction

This document aims to describe all aspects related to the aim, organisation and outcome of the EDCTP stakeholder meetings.

EDCTP aims to organise to 2 types of stakeholder meetings: 7 meetings will focus on disease specific topics and one meeting will concentrate on Nodes of Excellence. The disease-specific topics will have a focus on products in the pipeline. These topics are listed below:

- Malaria treatment and malaria in pregnancy (combined meeting)
- Malaria vaccines
- TB treatment
- TB vaccines
- HIV treatment
- HIV vaccines
- HIV microbicides

The Nodes of excellence meeting will focus on the integrated approach of EDCTP towards the establishment of regional nodes of excellence in sub-Saharan Africa with particular focus on reference laboratories and centres specialised in data management encompassing clinical trials design, conduct, and analysis skills, building on sites with existing capacities and competences in these areas.

These guidelines aim to describe the generic approach towards organising both types of meetings. All stakeholder meetings on disease related topics will be hosted by one of the participating European Member States whereas the stakeholder meeting about Nodes of Excellence will be hosted by one of the African partners participating in EDCTP. The expected outcome, communication aspects, timelines and financial issues concerning stakeholder meetings will be clarified. In addition the role of the hosting member state, the organising committee including the independent chair as well as the expected list of participants are described.

To ensure transparency these guidelines are made public and the EDCTP Secretariat will ensure that the implementation will be carried out and documented correctly.

Aim and objectives of a stakeholder meeting

A stakeholder meeting is a one day meeting. It is the start of a process that leads towards EDCTP funding one or more projects through a call or brokering procedure.

The expected outcome of these meetings is:

1. To make recommendations to EDCTP for:
 - The development of cooperative projects and coordination of efforts
 - Priorities for EDCTP:
 - for disease specific topics EDCTP requires priorities in terms of product and sites whereas
 - for nodes of excellence EDCTP needs priorities in terms of sites, location as well as required skills and capacity
2. Expression of a willingness of the various stakeholders to contribute to the topic both in financial as well as practical terms. These will be followed up by the EDCTP secretariat.
3. Establishment of trust in the EDCTP approach with our stakeholders.

The meetings with a disease-specific topic will have the following objectives:

- Identify products in the pipeline
- Identify potential suitable sites to do the trial
- Recommend priority in terms of product and sites
- Recommend if the funding procedure is a call or brokering or no-go
- Recommend EDCTP timelines concerning the initiation of funding for each topic area

EDCTP Stakeholder meeting: Malaria treatment

Vienna 14 June 2007

The stakeholder meeting on Nodes of Excellence has similar priorities:

- Identify potential sites
- Identify needs in terms of skills and capacity
- Recommend priorities in terms of needs and sites
- Recommend if the funding procedure is a call or brokering or no- go
- Recommend EDCTP timelines concerning the initiation of funding

Organisational aspects

All stakeholder meetings on disease-related topics will be hosted by one of the participating European Member States whereas the stakeholder meeting about Nodes of Excellence will be hosted by one of the African partners participating in EDCTP.

All meetings will be organised by an Organising Committee that consists of:

- An independent expert to chair
- A representative of the hosting country. For the European Member States this is the European Networking Officer (ENO) representing the country while for the Nodes of Excellence meeting this role should be fulfilled by the relevant member of the Developing Country Coordinating Committee (DCCC),
- The Partnership Board (PB) and DCCC disease experts
- The Executive Director and Operations Manager from the EDCTP Secretariat

The independent chair will be identified by EDCTP Secretariat, PB and DCCC representatives of the organising committee before the date of the stakeholder meeting is set. The candidate will be approved by the GA in a written procedure. If the hosting country is identified before a chair is selected the representative of the hosting country will also be involved in selecting the chair. The Terms of reference for the Independent chair are the following:

To work with the EDCTP stakeholders' meeting planning group to ensure that the meeting is planned and implemented transparently avoiding or declaring any conflict of interest to give an optimal, independent and objective advice to the EDCTP. This, via the EDCTP Secretariat should take into account the following:

1. The presence of appropriate representation of all significant bodies including industry, private-public partnerships and other stakeholders that are relevant to the topic; ensuring that the representation at the meeting is sufficiently senior to contribute with authority
2. There are appropriate and effective arrangements for conducting the meeting including drafting and approving of the agenda; noting of the attendance; ensuring of adequate participation and deliberation of all the relevant issues
3. Provision in an agreed timescale of a good quality report of the meeting.

Travel and hotels are arranged in close collaboration between the hosting country and the EDCTP Secretariat and the hosting country is expected to play an active role in this. The hosting country should organise location, catering and administrative support as well as assist delegates with their visa requirements. In addition the hosting country is responsible for sending out the invitations to participants. The final list of participants to be invited will be provided by the EDCTP Secretariat in collaboration with the Organising Committee.

Participants

It is a requirement that the following parties are represented at the stakeholder meeting:

- Funders both from the European Member States and if applicable third parties. Each European Member State will be asked to send one representative. It is up to the individual country to accept this invitation or not
- Product developers, Public Private Partnerships and/or industry (disease specific topics only)
- Representatives of African sites that have the capacity to carry out phase II or III trials

EDCTP Stakeholder meeting: Malaria treatment

Vienna 14 June 2007

- Experts in the field. Each European Member State may bring one expert of their own choosing
- Independent experts if applicable.

Most participants will be identified by the Organising Committee with the exception of the representatives of the European Member States. Each European Member State is free to send one expert in the field and one representative of their funding body of their own choosing.

It is normally expected that a stakeholder meeting will have no more than around 40 participants.

Invitations to the participants need to go out at least 6 weeks in advance.

Agenda

The agenda for the stakeholder meeting is set by the Organising Committee using the format developed by the EDCTP Secretariat. The generic format for the meetings on disease specific topics is shown below.

EDCTP Stakeholder Meeting

Topic
location, date 2007
Address
Contact

Agenda items	By	Timelines
<i>Coffee/Tea</i>	<i>All</i>	
1.0 Welcome by host	host	
2.0 Approval of the Agenda	All	
3.0 Science and products 3.1 Scientific overview of the field 3.2 Products in the pipeline: relevant stakeholder (more added if required) More added if required		
Coffee break	All	
4.0 Discussion on products and science	All	
5.0 Sites in Africa 5.1 Relevant stakeholder (more added if required) 5.3 DCCC		
Lunch	All	
6.0 Discussion on sites	all	
7.0 EDCTP procedures	SEC	
8.0 Recommendations on how to proceed in terms of products, sites and funding procedure	all	
9.0 Summary of recommendation	Chair	

Communication

Because EDCTP stakeholder meetings should demonstrate transparency and independence it is important that the meetings are widely advertised and that the hosting country does not have a perceived conflict of interest with the topic. EDCTP will however, not publish a call for participants. The advertisements for the stakeholder meetings will focus on announcement of topics, locations, aims and dates. They should list a contact address and encourage those that would like more information to make contact. If someone contacts EDCTP with a wish to participate, this request will be passed on to the Organising Committee who will make a decision.

Advertising of the stakeholder meetings will be through the following means:

- Internet:
 - EDCTP website
 - Requesting constituency members to publish at their websites
 - Other relevant websites
- Paper advertisement:
 - Publishing of adverts in Lancet as soon as all the dates are set
- Ask EDCTP constituencies to communicate to appropriate parties

EDCTP Stakeholder meeting: Malaria treatment

Vienna 14 June 2007

- If the opportunity arises mention of EDCTP stakeholder meetings in presentations or meetings

Timelines

The dates for the various stakeholder meetings will be set as soon as the independent chair and hosting country have been identified and once the chair agrees to the Terms of Reference. It is expected that the stakeholder meetings for TB vaccines, malaria vaccines, HIV vaccines and HIV treatment will take place during the first quarter of 2007. The stakeholder meetings for Nodes of Excellence, malaria treatment/pregnancy, TB treatment and HIV microbicides are scheduled for the second quarter of 2007.

Financial issues

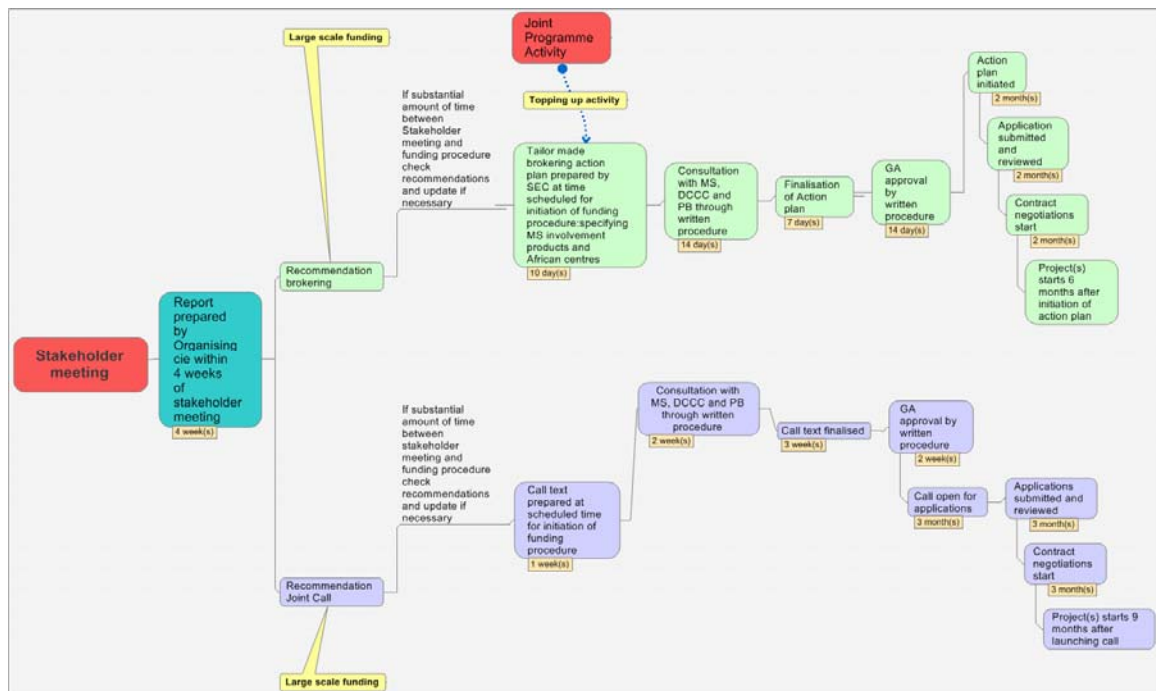
If the stakeholder meeting is hosted by a European country, it is expected that this country will at least as a minimum cover the costs for use of the location, catering during the meeting, administrative support and any other local expenses. If the hosting country is African these costs need to be discussed with the EDCTP Finance Manager. EDCTP will normally pay for travel and hotel for external participants as well as for PB and DCCC members. EDCTP expects that the European Member states will at least pay for travel and hotel of the participants they delegate. EDCTP will pay for travel and hotel of European MS participants and experts only if the European Member State is unable to do so.

Outcome/follow up

The organising committee will produce a report of the meeting within 4 weeks. The report will be presented to EDCTP. EDCTP will initiate its funding procedures at the appropriate time after considering the report. The timing for launching calls or brokering initiatives can range from 2007-2009 depending on the on the availability of products and sites. A final list of expected dates for initiation of funding procedures will be prepared after all stakeholder meetings have taken place. The diagram below summarises both funding procedures. More information on the EDCTP funding procedures can be found at the website.

A summary of both procedures is described below:

- *Call for proposals*
A call text is drafted based on the recommendations that came out of the stakeholder meeting. After consultation of the various EDCTP constituencies and approval of the General Assembly the call will be published. An EDCTP call is normally open for applications for a period of 3 months. The applications are then checked against the eligibility criteria as defined in the call text and eligible applications will be reviewed by at least 2 external experts as well as the EDCTP Scientific Review Committee (SRC). The SRC ranks the applications and makes a recommendation for funding. This recommendation is examined by the PB which ensures the quality of the review procedure and also assess if the proposal is in line with the EDCTP strategy. The PB makes the final recommendation for funding to the General Assembly who approve the application.
- *Brokering*
A brokering action plan is prepared by the EDCTP Secretariat and requires to be approved by the General Assembly after consultation with the EDCTP constituencies. The action plan will be initiated resulting in an application for funding. This application is checked for eligibility as described in the brokering action plan and reviewed by at least two external experts as well as the relevant EDCTP SRC. The SRC make a recommendation for funding or rejection which is examined by the PB which examines both the procedure as well as the alignment of the project with the EDCTP strategy. Upon recommendation of the PB the GA make the decision to fund the project or not.



Annex 3: Instructions for presentations

Expected outcome of the meeting

The expected outcome of the EDCTP stakeholder meetings is to make recommendations to EDCTP for:

- The development of cooperative projects and coordination of efforts
- Priorities for EDCTP in terms of product and sites
- Expression of a willingness of the various stakeholders to contribute to the topic both in financial as well as practical terms.
- Establishment of trust in the EDCTP approach with our stakeholders

The stakeholder meeting is considered the start of a process that leads towards EDCTP funding of one or more projects through an open call or brokering.

Audience

The audience will be a mixture of experts in the field and people who represent funding agencies and may not have a scientific/medical background. Therefore we would like to suggest that your presentation should be aimed at a general audience.

Expected contents of your presentation

Given the expected outcome of the meeting and the composition of the audience EDCTP would like to provide you some points regarding the expected contents of your presentation.

If you talk about science and products

- A short introduction on the organisation you are representing
- Without going into too much scientific details basic information about the products in the pipeline:
 - Basic principles of the product
 - Status with respect to clinical testing: what has been done/what is ongoing and what is planned/needed
 - Availability of the product
 - Restrictions with respect to the use of the product: is it only available for persons associated with your organisation/is it for sale?

In addition to the presentation could you provide a short summary document on each product that should enable the participants to the meeting to assess its scientific validity and potential.

EDCTP Stakeholder meeting: Malaria treatment

Vienna 14 June 2007

If you talk about sites in Africa

- A short introduction on the organisation you are representing
- Basic information about the sites you are representing:
 - Capacity and trial experience
 - Commitment to other trials/availability to do the trial
 - Local malaria situation

Duration of your presentation

The time available per presentation is limited to 15 minutes. The presentations will be followed by an initial discussion of 1 hour.

Annex 4: Agenda

EDCTP Stakeholder Meeting

Malaria treatment

Vienna June 14 2007

Palais Porcia, Herrengasse 23

1000-1630

Aim of the meeting:

- Identify and prioritise potential products in the pipeline
- Identify potential suitable sites to do the trial
- Recommend if the funding procedure of EDCTP will be an open call, brokering or whether EDCTP should fund this topic at all
- Recommend EDCTP 's timeline concerning the initiation of funding for this topic

Agenda items	By	Timelines
<i>Coffee/Tea</i>	<i>All</i>	<i>9:00 – 9:15</i>
1.0 Welcome	Charles Mgone, Christiane Druml and Chair Dr Pascal Ringwald	9:15 – 9:30
2.0 Approval of the Agenda	All	9:30-9:40
3.0 EDCTP procedures	Charles Mgone	9:40-9:50
4.0 Science and products		
4.1 Scientific overview of the field	Pascal Ringwald	9:50-10:05
4.2 Products in the pipeline: MMV	Carl Craft	10:05-10:20
4.3 Products in the pipeline: DNDi	Jean-René Kiechel	10:20-10:35

EDCTP Stakeholder meeting: Malaria treatment

Vienna 14 June 2007

<i>Coffee break</i>	<i>All</i>	<i>10:35-10:50</i>
5.0 Discussion on products and science	All	10:50-11:30
6.0 Sites in Africa		
6.1 EANMAT	TBD	11:30-11:45
6.2 MCTA	Osman Sankoh	11:45-12:00
6.3 ADRN	Wilfred Mbacham	12:00-12:15
<i>Lunch</i>	<i>All</i>	<i>12:15-13:15</i>
7.0 Discussion on sites	all	13:15-14:00
8.0 Concluding remarks on sites	Chair	14:00-14:30
9.0 Member States commitment	Member State representatives	14:30-15:15
10.0 Recommendations on how to proceed in terms of products, sites and funding procedure	all	15:15-15:45
11.0 Summary of recommendation	Chair	15:45-16:00
<i>Tea</i>	<i>all</i>	<i>16:00-16:15</i>

Annex 5: List of participants

Jean-René Kiechel, DNDi France
DNDi12 Allée des Merisiers,
91640 Janvry,
France.
Tel: +33 6 07 89 86 74
jean-rene.kiechel@wanadoo.fr

Umberto D'Alessandro, ATM Belgium
ITG
Nationale straat 155
2000 Antwerp
Belgium.
Tel: +32 3 247 6354
Fax: +32 3 247 63 59
udalessandro@itg.be

Carl J Craft, MMV Switzerland
Medicines for Malaria Venture
(MMV)
International Center Cointrin
Entrance G, 3rd floor
Route de Pré-Bois 20
P.O. Box 1826
CH-1215 Geneva 15
Switzerland.
Tel: +41 22 799 4067
Fax: +41 22 799 4061
craftjc@mmv.org

Harald Noedl, Austria
Head of the Exp. Tropical Med. and
Field Research unit,
Inst. of Specific Prophylaxis and
Tropical Medicine
Medical University of Vienna
Kinderspitalgasse 15
Vienna, Austria.
Phone: +43-1-4277-64882
Fax: +43-1-4277-64899
Email:
harald.noedl@meduniwien.ac.at

EDCTP Stakeholder meeting: Malaria treatment

Vienna 14 June 2007

Philippe Deleron, France
IRD UR010, Laboratoire de
parasitologie, Faculte de
pharmacies, 4 avenue e
l'observatoire
75006
PARIS Cedex 10
France.
Tel: (+33) 014 281 94 01
Fax: (+33)015 373 96 17
phillipe.deleron@ird.fr

Michael Ramharter, Austria
Department of Internal Medicine I,
Division of Infectious Diseases,
Medical University of Vienna,
1090 Vienna
Austria.
Tel: (01) 40400 4440
michael.ramharter@meduniwien.ac.at

Diana Dunstan, UK
Medical Research Council,
20 Park Crescent
London W1N 1AL
United Kingdom.
Tel: +44 (207) 637 6021
Fax: +44 (20) 76366289
diana.dunstan@headoffice.mrc.ac.uk

Claudia Herok, Germany
BMBF
Hannoversche Str. 28-30
10115 Berlin
Germany.
Tel: +49 1888-57 5296
Fax: + 49 1888-57 8 5296
Claudia.Herok@BMBF.BUND.DE

Rafael de Andrés Medina, Spain
Subdirección General de
Investigación Sanitaria-Fondo de
Investigación
Instituto de Salud Carlos III,
Sinesio Delgado 628029
Madrid
Spain.
Tel: +34 (91) 822 2508
Fax: +34 (91) 387 7766
rdam@isciii.es

Bernhards Ogutu Ragama, Kenya
Walter Reed Project
P.O. Box 54
00200 Kisumu
Kenya.
Tel: +254 20 722541
Fax: +254 20 720030
bogutu@wrp-ksm.org

Marcus Gmeiner, Austria
Vienna School of Clinical Research
Koelblgasse 10,
1030 Vienna,
Austria.
Tel: +43 1 7134051-16;
Fax: +43 1 7134051-99
markus.gmeiner@vschr.at

John Ouma, Kenya
EANMAT
Box 57864,
00200
Nairobi, Kenya.
ouma@wananchi.com

Sam Dunyo, the Gambia
Medical Research Laboratories
PO Box 273
Banjul
The Gambia

Michael Makanga, South Africa
EDCTP,
PO Box 19070,
Tygerberg 7505,
Cape Town,

EDCTP Stakeholder meeting: Malaria treatment

Vienna 14 June 2007

Tel: +220.5735421
Fax: +220 4496513
sdunyo@mrc.gm

South Africa

Tel: +27 21 938 0819
Fax: +27 21 938 0569
makanga@edctp.org

Christiane Druml, Austria
Ethics Committee of the Medical
University of Vienna
Borschkegasse 8b,
Vienna 1090
Austria.
Tel: +43 (140400) 2147
Fax: +43 (140400) 1690
christiane.druml@meduniwien.ac.at

Brigitte Bloechl-Daum, Austria
Department of Clinical Pharmacology
Medical University Vienna
Waehringer Guertel 18-20
A-1090 Vienna
Austria.
Tel: +43 (1) 40400 2981
Fax: +43 (1) 40400 2998
[brigitte.bloechl-
daum@meduniwien.ac.at](mailto:brigitte.bloechl-daum@meduniwien.ac.at)

Dario Zanon, Belgium
European Commission
rue de Cheup de Mors 21 03/53
BE1044 Brussels,
Belgium.
Tel: +32 (2) 2080250
Fax: +32 (2) 2084561
dario.zanon@cec.eu.int

Peter Kremsner, Germany
University of Tuebingen
Wilhelmstrasse 27
72074 Tuebingen
Germany.
Tel: +49 (7071) 29 87179
Fax: +49 (7071) 295 189
peter.kremsner@uni-tuebingen.de

Clara Menendez, Spain
Center for International Health,
Hospital Clinic
Gran Via de les Corts Catalanes,
585
08007 Barcelona
Spain.
Tel: +258 21 810002
Fax: +258 21 810002
MENENDEZ@clinic.ub.es

Pascal Ringwald, Switzerland
World Health Organization,
Roll Back Malaria Department,
1211 Geneva 27, Switzerland.
Tel: +41 22 791 3469
Fax: +41 22 791 4824
E-mail: ringwaldp@who.int

Christa Janko, Austria
Vienna School for Clinical Research
Barichgasse 40-42
A-1031 Vienna
Austria.
Tel: +43 (1) 713 40 5111
JANKO_CHRISTA@LILLY.COM

Francine Ntoumi, Netherlands
EDCTP Secretariat
P.O. Box 93015
2509 AA, The Hague
The Netherlands.
Tel: +31 70 344 0891
Fax: +31 70 344 0899
ntoumi@edctp.org

Charles S. Mgone, Netherlands
EDCTP Secretariat
P.O. Box 93015

David Coles, Netherlands
EDCTP Secretariat
P.O. Box 93015

2509 AA, The Hague
The Netherlands.
Tel: +31 70 3440890
Fax: +31 70 3440899
mgone@edctp.org

2509 AA The Hague
The Netherlands.
Tel: +31 70 3440885
Fax: +31 70 3440899
coles@edctp.org

Annex 6: Discussion paper

Treatment of malaria

Document prepared by Dr P Ringwald
Global Malaria Programme
WHO

This document is based on the WHO document Guidelines for treatment of malaria (WHO/HTM/MAL/2006.1108)

I. Objectives of the treatment

- The objective of treating uncomplicated falciparum malaria is to cure the infection. A secondary but equally important objective of treatment is to prevent the emergence and spread of resistance to antimalarials. Tolerability, the adverse effect profile and the speed of therapeutic response are also important considerations.
- The primary objective of antimalarial treatment in severe malaria is to prevent death. Prevention of recrudescence and avoidance of minor adverse effects are secondary.
- The objective of treating malaria caused by *P. vivax* and *P. ovale* is to cure both the blood stage and the liver stage infections, and thereby prevent both relapse and recrudescence. This is called radical cure.

II. Antimalarial combination therapy

By analogy with the treatment of tuberculosis and human immunodeficiency virus infection, the novel antimalarial treatment strategy to overcome multidrug resistance is the use of drug combinations. Antimalarial combination therapy is the simultaneous use of two or more blood schizontocidal drugs. The concept is based on the potential of two or more simultaneously administered schizontocidal drugs with independent modes of action to improve therapeutic efficacy and also to delay the development of resistance to the individual components of the combination. Drug combinations such as sulfadoxine–pyrimethamine, sulfalene–pyrimethamine, proguanil–dapsons, chlorproguanil–dapsons and atovaquone–proguanil are operationally considered as single products and not considered to be antimalarial combination therapy.

Artemisinin derivatives are particularly interesting constituents to be used in combination since 7-day course of monotherapy is needed to achieve effective cure

but when given in combination with slowly eliminated antimalarials, shorter courses of treatment (3 days) are effective. In 3-day artemisinin based combination therapy (ACT) regimens, the artemisinin component is present in the body during only two asexual parasite life-cycles but reduces massively the parasite biomass. However, complete clearance of parasites is dependent on the partner medicine being effective and persisting at parasitocidal concentrations until all the infecting parasites have been killed. Thus the partner compounds need to be relatively slowly eliminated. Courses of ACTs of 1–2 days are not recommended so far.

To achieve the desired therapeutic effectiveness, a drug must be intrinsically efficacious and must be taken in the correct doses at the proper intervals. Patient adherence is a major determinant of the response to antimalarials, as most treatments are taken at home without medical supervision. Three-day regimens of medicines such as ACTs are adhered to reasonably well. Co-formulation is probably a very important contributor to adherence. User-friendly packaging, such as blister packs, also encourages completion of the treatment course and correct dosing.

Although there are some minor differences in oral absorption and bioavailability between the different artemisinin derivatives, there is no evidence that these differences are clinically significant in current formulations. Nevertheless, stability of dihydroartemisinin must be monitored more carefully. It is the properties of the partner medicine that determine the effectiveness and choice of combination. ACTs with amodiaquine, atovaquone-proguanil, chloroquine, chlorproguanil-dapsone, clindamycin, doxycycline, lumefantrine, mefloquine, piperazine, pyronaridine, proguanil-dapsone, sulfadoxine–pyrimethamine, sulfalene–pyrimethamine and tetracycline have all been evaluated in trials carried out across the malaria-affected regions of the world. Some of these are studies for product development.

The following ACTs are currently recommended (alphabetical order):

- artemether-lumefantrine

This is currently available as co-formulated tablets containing 20 mg of artemether and 120 mg of lumefantrine. The total recommended treatment is a 6-dose regimen of artemether-lumefantrine twice a day for 3 days.

- artesunate-amodiaquine

This is currently available as co-packaged and co-formulated tablets. The total recommended treatment is 4 mg/kg body-weight (bw) of artesunate and 10 mg base/kg bw of amodiaquine given once a day for 3 days.

- artesunate + mefloquine

This is currently available as separate scored tablets containing 50 mg of artesunate and 250 mg base of mefloquine, respectively. Co-formulated tablets are under development but are not available at present. The total recommended treatment is 4 mg/kg bw of artesunate given once a day for 3 days and 25 mg base/kg bw of mefloquine usually split over 2 or 3 days.

- artesunate + sulfadoxine(sulfalene)–pyrimethamine.

This is currently available as separate scored tablets containing 50 mg of artesunate, and tablets containing 500 mg of sulfadoxine and 25 mg of pyrimethamine. The total recommended treatment is 4 mg/kg bw of artesunate given once a day for 3 days and a single administration of sulfadoxine-pyrimethamine (25/1.25 mg base/kg bw) on day 1.

Several other new antimalarial combinations are at the late stage of development, but they need to be reviewed for safety and efficacy data before they are included in WHO treatment guideline:

- Artemisinin-naphthoquine
- Artemisinin-piperaquine
- Artesunate-chlorproguanil-dapsone
- Artesunate-pyronaridine
- Dihydroartemisinin-piperaquine

III. Treatment of severe malaria

Two classes of drugs are currently available for the parenteral treatment of severe malaria: the cinchona alkaloids (quinine and quinidine) and the artemisinin derivatives (artesunate, artemether and artemotil). Although there are a few areas where chloroquine is still effective, parenteral chloroquine is no longer recommended for the treatment of severe malaria because of widespread resistance. Intramuscular sulfadoxine– pyrimethamine is also not recommended. Following initial parenteral treatment, once the patient can tolerate oral therapy, it is essential to continue and complete treatment with an effective oral antimalarial.

The risk of death from severe malaria is greatest in the first 24 h. It is recommended during the transit time between referral and arrival at appropriate health facilities that patients are treated with the first dose of one of the recommended treatments by the parenteral route if possible or by the intra-rectal route before referral. This could be intramuscular artemether, artesunate or quinine, or a rectal formulation

of artemisinin or artesunate.

IV. Treatment of *P. vivax*, *P. ovale*, *P. malariae*

P. vivax is still generally very sensitive to chloroquine, although resistance is prevalent and increasing in some areas, notably Oceania, Indonesia and South America. Resistance to pyrimethamine has increased rapidly in some areas, and sulfadoxine-pyrimethamine is consequently ineffective. There are relatively few data on treatment responses in chloroquine-resistant vivax malaria. Studies from Indonesia indicate that amodiaquine is efficacious, and there is some evidence that mefloquine and quinine can also be used. The artemisinin derivatives would also be expected to be highly effective. To achieve radical cure, relapses must be prevented by giving primaquine, but glucose-6-phosphate dehydrogenase deficiency must be monitored before.

Resistance of *P. ovale* and *P. malariae* to antimalarials is not well characterized and infections caused by these two species are considered to be generally sensitive to chloroquine.

V. Monitoring drug efficacy

V.1. WHO standard protocol for monitoring antimalarial drug efficacy

In order to interpret and compare results within and between regions and to follow trends over time, monitoring antimalarial drug efficacy must be conducted with similar procedures and standards. The WHO protocol for monitoring antimalarial drug efficacy is not designed for either the evaluation of new or experimental drugs or the direct comparison of the efficacy of one drug to another. Such studies usually require design, ethical, and statistical considerations that are beyond the scope of this protocol. But, modifications to the WHO protocol that do not change its fundamental design or intended purpose (such as when measuring blood levels of the drugs, combining with assessments of in vitro sensitivity and/or molecular markers for drug resistance, or extending the period of follow-up) can be made and, when technically and logistically feasible, are even encouraged. Using this protocol will allow countries to compile baseline data on new antimalarial drugs and compare in future these results with their routine surveillance data.

Protocol must follow International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) in particular with respect to ethics and the antimalarial medicine used in trials must be of unquestionable quality and meet all the standards required by ICH guidelines.

V.2. Clinical studies in special groups (people with HIV infection, pregnant women, patients with severe malaria)

Chronic infections are an exclusion criterion for routine monitoring of therapeutic efficacy; however, because of the high prevalence of HIV positive individuals in areas in which malaria is endemic, clinical research is needed for this particular group. Therapeutic efficacy tests should be performed in this patient population, alone or in comparison with an HIV-negative control group. The risk that resistance to antimalarial drugs will extend with the AIDS epidemic must be considered seriously.

During a first or second pregnancy, protective immunity against malaria tends to diminish, without disappearing completely. Together with changes in pharmacokinetics (apparent increase in the volume of distribution, with a resulting reduction in plasma drug concentration), this fall in immunity is responsible for a higher treatment failure rate than in other women of the same age. Like *Plasmodium*-HIV co-infection, pregnancy is an exclusion criterion, but clinical research on this group is important, as studies on therapeutic efficacy are necessary for selecting and implementing intermittent preventive treatment within a national policy. Such studies are also important for determining tolerance and adverse effects in pregnant women.

Severe, complicated malaria is a major exclusion criterion in routine efficacy monitoring, and the appearance of signs of gravity after day 0 is considered to be

treatment failure. Such patients cannot take drugs orally, but the efficacy of drugs administered by other routes has been evaluated in several studies. The results of these studies are difficult to interpret, as a considerable proportion of the patients may die at a time when their parasitaemia has completely disappeared.