Onchocerciasis Control Programme in West Africa
Programme de Lutte contre l'Onchocercose en Afrique de l'Ouest.

JOINT PROGRAMME COMMITTEE
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PROGRESS REPORT OF THE ONCHOCERCIASIS CHEMOTHERAPY PROJECT (OCT) FOR 1989

1. INTRODUCTION

Following review by the Committee of Sponsoring Agencies (CSA) of OCP in 1988, OCT has pursued objectives to:

1. Select and complete preclinical work on candidate macrofilaricides, if possible before 1991; and

2. Complete such development work and associated clinical trials, to allow an effective macrofilaricide to be in use by OCP before 1997.

With this clear delineation of the objectives and time frame of OCT, efforts are now mainly concerned with initiating legal agreements with pharmaceutical companies, and collaborating more closely with the Walter Reed Army Institute of Research (WRAIR) to obtain existing drugs and novel compounds for testing as antifilarial agents. Support for the one remaining multidisciplinary group in the pharmaceutical industry (Wellcome) terminated in June 1989, as its lead series of phenylamidines/ 3'-amidotetramisoles failed to show good macrofilaricidal activity or a satisfactory therapeutic profile in secondary testing in the Brugia/dog model.

The major part of OCT's resources will in future be utilized for the maintenance of drug screening centres and clinical trials centres in endemic areas. Funds previously allocated to drug discovery work within the pharmaceutical industry will now be allocated to preclinical studies (e.g. chemical resynthesis, formulation, toxicology, drug metabolism, etc.) of compounds selected from current chemical leads at the secondary screening level. Any such work which cannot be carried out within the company providing the compounds will need to be financed in a stepwise fashion, and undertaken either by academic groups or by contract laboratories.

It must however be stated that the failure to identify a clinical trials candidate from the Wellcome research effort has inevitably reduced the chances of developing a macrofilaricide suitable for community therapy, within the proposed time frame, i.e. before 1991. Apart from drugs already in human use or new drug combinations, the best chances of success now lie with Ciba-Geigy compound CGP 6140, currently in clinical trials, and the Company's "back-up" compounds, but management problems within the Company have considerably delayed clinical development of CGP 6140 during the past year.

2. COLLABORATION WITH CIBA-GEIGY

2.1 Progress of clinical trials of CGP 6140

A technical seminar was held by OCT immediately prior to the March 1989 Steering Committee meeting, which allowed Ciba-Geigy representatives to make presentations to the OCT Steering Committee members and Secretariat, bringing them up to date with recent developments, and allowing discussions and future planning.

The therapeutic index of CGP 6140 is relatively low, and the general consensus was that macrofilaricidal activity would be difficult to obtain with a single oral dose, if all serious adverse effects were to be avoided. As it had been clearly shown that CGP 6140 is absorbed more reproducibly and about three times more effectively when given after a meal, all dose-finding studies needed to be repeated using postprandial dosing, in conjunction with further pharmacokinetic assays of plasma drug levels.

CGP 6140 is microfilaricidal as well as macrofilaricidal, and a Mazzotti reaction of moderate intensity is usually provoked when a filaricidal dose of drug is administered. However, in patients given high single doses, or if too high a total dose is given by multiple-dosing regimens, the central nervous system (CNS) may be affected and adverse effects present as neurological symptoms. Effects on the CNS seem generally proportional to the dose administered. It has not proved possible to reproduce these neurological symptoms in (fasted) dogs, and thus it is not known whether these observed phenomena are directly due to effects of high drug concentration in the CNS, or are secondarily produced by rapid killing of micro- or macrofilariae. It may therefore be necessary to carry out Phase I clinical studies on uninfected volunteers to see if any direct drug effects are detectable.

From studies carried out to date, usually from patients fasted before treatment, it is known that some doses of CGP 6140 are capable of long-term suppression of mf in the skin, and killing of at least some part of the population of adult worms.

Recent clinical trials in Ghana and Latin America have employed postprandial dosing schedules, and much lower drug levels than used earlier in fasted patients. Thus 2, 3, 5 and 10 mg/kg are being given either as single doses, daily doses for two days, or twice-daily for three days. They have proved clinically acceptable, but do not seem to have given long-term suppression of mf in the skin. Macrofilaricidal activity will only be known following nodulectomy and subsequent analysis.

2.2 Future clinical trials of CGP 6140

Optimization of the postprandial dosing schedule, with avoidance of any adverse effects of the CNS and using the minimum number of doses, is the objective for the immediate future. Histopathological data on the macrofilaricidal effects of earlier dosing regimens and pharmacological data on plasma drug levels are awaited from Ciba-Geigy. It had been proposed to hold a joint WHO/Ciba-Geigy meeting in May 1989, to allow future clinical protocols to be prepared for clinical trials to recommence later in the year, but at this time the pathology reports have still not been made available by Ciba-Geigy.

To establish macrofilaricidal activity in a definitive way, it is planned that multiple, clinically acceptable doses of CGP 6140 be given to patients. The timing of the multiple dosing would be based on the known half-life of the drug and its metabolites, and would be aided by prior computer simulation. Pharmacokinetic studies during the trial would confirm whether actual plasma drug concentrations matched predicted levels. The OCT Steering Committee felt that lack of pharmacokinetic data from previous multiple-dose studies, together with the known variation in bioavailability in fasted patients, made earlier trials difficult to interpret, and future trials should be more guided by pharmacokinetic principles.

2.3 Progress with back-up compounds from Ciba-Geigy

Ciba-Geigy has provided a written summary of macro- and microfilaricidal data in rodents, and preliminary results from recent trials against Onchocerca gibsoni in cattle are available for the four most promising back-up benzthiazoles and benzoxazoles, i.e. CGP 20309, CGP 21833, CGP 24589 and CGP 26702. As no toxicological or pharmacological data are available for these compounds, selection must necessarily be on the basis of activity. The most active compound, including known macrofilaricidal activity against O. gibsoni, seems to be CGP 20309, followed by CGP 24589. It has been requested that Ciba-Geigy should carry out safety toxicology on the two compounds to evaluate their therapeutic index, while awaiting full reports on their efficacy against O. gibsoni and B. malayi in the leaf monkey.

An additional compound, CGI 18041 from Hindustan Ciba-Geigy (India), having a similar chemical structure to the compounds above, has shown full macrofilaricidal activity against B. malayi in the leaf monkey using both single and multiple dosing schedules. Safety pharmacology for CGI 18041 is already available and testing against O. gibsoni in cattle will be initiated.

2.4 Recent discussions with Ciba-Geigy management

Collaboration with OCT and Ciba-Geigy for the development of CGP 6140 has been ongoing for many years. As the time frame for successful development of a macrofilaricide for use by OCP requires more rapid development of all clinical and preclinical candidates, discussions have taken place with Ciba-Geigy higher management to see if any changes could be implemented to speed up development of all candidate compounds under consideration as antifilarial agents.

Dr M. Wilhelm, Director of Research and Development, Pharmaceuticals of Ciba-Geigy, visited WHO on 1 March 1989 and, during his visit, agreement was reached on certain important changes in the collaboration. The discussions and decisions made at that meeting are summarized below.

Ciba-Geigy wished to continue the long-standing collaboration between the Company and WHO, and to develop products for the treatment or prophylaxis of parasitic diseases. The Company maintains a major responsibility to continue development of agents for the chemotherapy of filariasis. In the past, Ciba-Geigy personnel had carried out all preclinical development work on antiparasitic agents without major problems, and the Company is prepared to continue to provide resources for work in this area. It no longer has biological screening facilities in the human parasite area and the Company would be pleased to select compounds from current research areas and provide these to WHO-sponsored laboratories for appropriate testing. Some resources for additional synthetic chemistry would also be available. The Company had however experienced internal management problems in collaborating with WHO in clinical trials of antifilarial agents in recent years and would prefer WHO to carry out all clinical trials, including the Phase I volunteer stage, of any future compounds under development.

From now on the responsibility for the current clinical trials of CGP 6140 in onchocerciasis will be divided between OCT and Ciba-Geigy. OCT will be responsible for the trials in Africa, and Ciba-Geigy for those in Latin America. To allow decisions to be made on future work, reports covering the clinical and pharmacokinetic work and evaluation of the parasitic efficacy of the drug are urgently needed from Ciba-Geigy. In particular, reports on the histopathology of nodules from all clinical studies, the pharmacokinetic studies at the Biopharmaceutical Research Centre (CRB), and an overall report on the cattle study in Australia are required.

With regard to any studies conducted under the responsibility of WHO, Ciba-Geigy agrees to prepare the required trial material and to perform the necessary analytics and other non-clinical work.

Preclinical development of additional benzthiazoles or benzoxazoles

Compounds from these series have already been tested in the B. malayi/leaf monkey and the O. gibsoni/cattle assays, and when data become available on efficacy and pharmacokinetics, discussions between Ciba-Geigy and WHO on their further development will take place.

Development of novel compounds from other research areas

Ciba-Geigy will select and send for testing in WHO-sponsored biological assays, compounds with biological activity in the Agrochemical and Animal Health Research Programmes. WHO will provide guidance on suitable compounds to be tested based on known drug targets identified in parasites, or by selection of analogues of known antifilarial structures. WHO decides on the initiation of development of interesting compounds, and the clinical development would be conducted under the responsibility of WHO. Requirements for preclinical work in the areas of drug metabolism, toxicology, formulation, etc. for compounds showing good activity would be developed jointly by the Company and WHO. Regular meetings between WHO and Ciba-Geigy will be required to ensure minimal delay in compound development.

Preclinical development work for future development projects

Ciba-Geigy is, in principle, prepared to carry out preclinical development work, in particular the preparation of trial material, assays of drug and metabolite levels in man and experimental animals, toxicity and mutagenicity studies, etc. for CG compounds that are or are to be developed by WHO. Ciba-Geigy will pass on pharmacokinetic methodology to WHO-sponsored laboratories if this seems more appropriate.

Legal agreement on collaborative work

Ciba-Geigy has prepared a draft of an amended collaborative agreement and has submitted this to WHO for comment.

3. CLINICAL TRIALS OF OTHER POTENTIAL MACROFILARICIDES

3.1 Multiple doses of ivermectin

Three clinical centres in Liberia, Togo and Mexico have carried out clinical trials involving multiple dosing with ivermectin, which has been followed by examination of adult worms removed from patients by nodulectomy. Although full reports are not yet available, there is no evidence that repeated doses of ivermectin kill adult worms.

In the Mexican study, one observation of interest not previously reported in other clinical trials concerns the appearance of new nodules in patients treated with ivermectin at six-monthly intervals. During the 12-18 months of the study, 48 new nodules have appeared in the 62 ivermectin-treated patients, and 12 nodules in 19 patients in the placebo-treated group. This indicates that repeated treatment with ivermectin, even at six-monthly intervals, does not prevent the development of worms to the adult stage, nor the host reaction in forming a nodule.

Although it had been hoped that multiple dosing with ivermectin, particularly with a short interval between treatments, might have at least a permanently sterilizing effect on Onchocerca females, there is no evidence of this at present. A recent publication (Lyons, E.T. et al. (1988) Am. J. Vet. Res., 49, 983) also indicates that five weekly treatments with 200 µg/kg ivermectin had no effect on the viability of O. cervicalis in horses.

3.2 Combination therapy with ivermectin and other drugs registered for use in man

Dr K. Awadzi, in collaboration with Smith Kline & French and the University of Liverpool, has drawn up draft protocols for combination studies of ivermectin with albendazole or mefloquine. Dr Awadzi has been urged by OCT to proceed as soon as possible with the testing of albendazole alone as the first part of a combination study with ivermectin. Additional protocols will be constructed in the future for similar combination studies, with other compounds showing at least partial macrofilaricidal activity.

4. WELLCOME RESEARCH LABORATORIES, UK - MULTIDISCIPLINARY RESEARCH TO IDENTIFY NOVEL MACROFILARICIDES

In March 1988 a further year of funding was awarded to the Wellcome group, with the understanding that all resources would be applied to the development of the lead series of 3'-amidotetramisoles/phenylamidines. This would allow a decision to be made in mid-1989 on whether any compound was good enough to take forward for Phase I clinical trials.

At the time of the last report to EAC it was noted that, although the chemical series under study showed great promise, there were several outstanding problems to be overcome to allow selection of a candidate for clinical trials. Compounds were rapidly acetylated and excreted by the mammalian host, and the inhibitory effects on worm motility and metabolism were reversible phenomena. Additionally, multiple doses (minimum of three) were required for macrofilaricidal action in animal models. Thus, during the past year, further phenylamidine analogues were synthesized in a search for compounds with an improved therapeutic profile. Although analogues have been made which are less toxic than lead compounds, or are more resistant to acetylation, no compound has shown better activity in animal models than the best leads already identified (A276C and B38C).

To aid in selection of the best clinical trials candidates, the Wellcome group developed several secondary assay systems, which had to be optimized before use. As an *in vivo* model, *B. pahangi* in the dog was used, while adult *O. volvulus* isolated from patients in Liberia was utilized for *in vitro* testing of Wellcome compounds. Because most of the phenylamidines required metabolic activation by the host, an assay was developed in which adult male worms of *O. gibsoni*, *O. gutturosa* and *O. volvulus* were transplanted to mice or gerbils.

Data presented by Wellcome during the technical seminar held in March 1989 indicated that the lead compound A276C had no macrofilaricidal activity against adult *B. pahangi* in dogs when given orally at 4 x 25 mg/kg every six hours, yet this dose was lethal to one of the dogs in the study. In comparison, CGP 20376 showed full macrofilaricidal activity, with some reversible CNS toxicity. A276C also showed no macrofilaricidal activity against male worms of *O. volvulus*, *O. gibsoni* and *O. gutturosa* in the *in vivo* transplant assays. As A276C had therefore failed to show efficacy, while at the same dose showing acute toxicity, it is unlikely that this compound could be proposed for clinical trial. A second analogue, 38C85, also showed toxicity in initial dose-finding studies in the dog, indicating unacceptable inherent toxicity in this chemical series. All evidence available to the Committee indicated that the mode of action of the phenylamidines is very similar to that of levamisole, pyrantel, morantel, etc., and offered few advantages over these fully developed compounds as potential macrofilaricides in onchocerciasis.

In view of the failure of the best available compounds (A276C and 38C85) and the lack of any other compound of improved therapeutic profile in the foreseeable future, the decision was made to terminate funding for this research project in June 1989. A joint Wellcome/WHO meeting took place early in May 1989 which confirmed that Wellcome management had also concluded that there was little chance of development of an effective macrofilaricide in the short term, and amicably agreed to conclude the collaborative programme.

The Wellcome multidisciplinary group has been the major influence on research in the chemotherapy of onchocerciasis during the lifetime of OCT. The group has been extremely innovative in the introduction of novel in vivo and in vitro assays, and has described many biochemical assays to evaluate the viability of adult worms after drug treatments. Pharmacokinetic and drug metabolism studies in laboratory animals have always been used to aid in interpretation of biological results. In vitro studies of O. volvulus in the field have been an integral part of all evaluations of promising compounds. However, as often occurs in pharmaceutical research, all chemical series which have been exhaustively studied have ultimately, for reasons of inadequate efficacy, toxicity or inappropriate metabolism, failed to yield a clinical trials candidate, in spite of good synthetic chemistry and the excellent team work of the group. Having been dispersed it will be extremely difficult to reassemble a similar research group concerned specifically with onchocerciasis chemotherapy.

5. PRECLINICAL DRUG DEVELOPMENT TEAM (PDDT - jointly operated by OCT and TDR/FIL)

The intention to create a small team to manage antifilarial drug development on a day-to-day basis was briefly mentioned in OCT's previous report to EAC. The team has now been operative for about one-and-a-half years and consists of a medicinal chemist (Dr E. Elslager, retired from the Parke-Davis Company - Chairman) and a parasitologist (Dr D. Denham, London School of Hygiene and Tropical Medicine). The OCT Project Manager and Secretary, TDR/FIL attend all formal meetings of the PDDT. A fifth meeting was held in London in May 1989 and OCT-supported scientists in Europe carrying out drug screening participated. While efforts in the USA are now well coordinated by Dr Elslager, it has proved necessary to utilize a second medicinal chemist to monitor European work.

This work of coordination of drug synthesis and testing for compounds requiring independent development has become essential now that all collaborative work on antifilarial drugs, apart from that with Ciba-Geigy, is to be undertaken outside the pharmaceutical industry. It must be appreciated that with earlier collaboration with Upjohn, Wellcome, Merck Sharp & Dohme, etc., much of the administrative work relating to day-to-day progress of drug research and development was carried out by the company concerned. All such work, together with that concerned with procurement and distribution of novel compounds from industrial sources, and with the required legal agreements, must now be carried out by the WHO Secretariat and the PDDT. This is proving extremely difficult with current resources and efforts are being made to employ a part-time consultant in Geneva to deal with the drug handling component of the programmes. It has also been recommended that drug storage, weighing, packaging, recording and shipment be contracted out to an independent laboratory, which could work to current industrial standards with regard to safety and good laboratory practice. Such resources are not available at WHO headquarters.

Additionally, in this more independent environment, funding previously directed to the industrial groups must now be utilized to synthesize and resynthesize test compounds, and for toxicological and drug metabolism studies by contract research laboratories. Any requirements for pharmacokinetic studies in animals or man will be addressed initially to the suppliers of the drug (e.g. Ciba-Geigy, Wellcome) and, if assay methods are unavailable, or the company is unable to carry out the assays, use will be made of collaborating academic laboratories.

6. COLLABORATION WITH WALTER REED ARMY INSTITUTE OF RESEARCH (WRAIR)

WRAIR has over the years collected many samples of novel chemical structure from the pharmaceutical industry and individual chemical laboratories. Antifilarial testing of these compounds has previously been carried out under a collaborative agreement with TDR/FIL. A good working relationship now exists between the PDDT and WRAIR representatives, and a major objective during the past year has been to select specific candidates for preclinical development from the chemical series of WRAIR origin, which have shown good antifilarial activity in the primary rodent screens. Additionally,

selected compounds had novel and patentable chemical structures, no background of predictable toxicity and were available in sufficient quantities for expanded biological evaluation. Of 34 compounds selected, expanded testing in the rodent model has been completed for 20 compounds; 10 of these have been eliminated because, although macrofilaricidal, they were unable to give complete cure at tolerated doses. A further six compounds were dropped as showing mainly microfilaricidal activity rather than good activity as macrofilaricides. Four compounds (WR250466, WR231010, WR129577 and WR179305) are being evaluated in the B. pahangi/dog model. The 14 other compounds will be evaluated in the near future, in some cases when resynthesis has been completed. A contract for such work on chemical resynthesis has been made with the University of Alabama, USA.

7. CHEMICAL SYNTHESIS PROGRAMME AT THE UNIVERSITY OF MICHIGAN, USA

For many years, TDR/FIL has supported a programme of chemical synthesis of compounds originally related to benzimidazoles which were known to have embryostatic activity against filarial worms. A review of biological results available to date has indicated that 13 compounds have been synthesized which show promising antifilarial activity. Again the selection was also based on a novel, patentable structure, with macrofilaricidal activity comparable with existing benzimidazole drugs such as mebendazole and flubendazole. To be selected as clinical candidates, compounds will need to show either improved oral bioavailability, or will be able to be formulated as painless, parenteral preparations.

Five of the selected compounds have been resynthesized and are presently being tested in the secondary in vivo system of B. pahangi in the dog, following confirmation of their macrofilaricidal activity in the primary rodent screen. They will also be evaluated against B. malayi in the leaf monkey. When all required resyntheses are completed for such testing, further novel syntheses based on existing leads (benzylaminopyrimidines, imidazopyridines and analogues of known anthelmintics) will recommence.

8. SUPPLY OF COMPOUNDS FROM THE PHARMACEUTICAL INDUSTRY

Companies already supplying novel compounds for testing include Ciba-Geigy, Merck Sharp & Dohme, Eli Lilly and Beecham, and verbal agreements for testing (awaiting formal agreements) have been negotiated with Smith Kline & French, American Cyanamid (Lederle), Glaxo and Rhône-Poulenc. Discussions are also taking place with further companies regarding the possibility of making compounds available. An important requirement in this context is the preparation of a short, formal document outlining OCT's philosophy in drug development, descriptions of test systems available, quantities of compound required for the various antifilarial assays and the facilities for clinical trials in endemic areas. Such a document is being prepared in collaboration with the Chairman of the PDDT.

9. SUPPORT FOR DRUG SCREENING CENTRES

9.1 In vivo assays

9.1.1 Primary screening in rodents (Dr H. Zahner, Justus-Liebig University, Giessen, FRG)

All new compounds obtained for primary screening by OCT are sent to Dr Zahner for primary assay using B. malayi and Acanthocheilonema viteae in rodents. This laboratory also collaborates with other Ciba-Geigy-funded workers to carry out mode-of-action studies using biochemical and electron microscopic techniques following in vitro or in vivo drug treatment of filarial species.

9.1.2 Secondary and tertiary screening

Secondary screening facilities are maintained at the University of Georgia, USA (B. pahangi in dogs - Dr J. McCall) and at the Institute for Medical Research, Kuala Lumpur, Malaysia (B. malayi in the leaf monkey - Dr J.W. Mak). During the past year extensive use has been made of the cattle screen at James Cook University, Townsville, Australia (O. gibsoni and O. gutturosa - Professor D.B. Copeman). The testing of five compounds from Ciba-Geigy at various doses with appropriate controls (usually using three animals per test group) utilized 100 cattle. Dr H.P. Striebel of Ciba-Geigy, funded by the Company, visited Townsville at the time of drug treatment and again for the slaughter of experimental animals. He also carried out independent histopathological studies of the excised nodules from these experiments.

Financial support will continue for cattle studies as required for Ciba-Geigy back-up compounds, and the PDDT will take decisions on whether any other compounds showing macrofilaricidal activity in secondary screens using other filarial species should also be tested against O. gibsoni.

9.1.3 Primate model using **O. volvulus**

A small study at the Delta Regional Primate Research Center (Tulane University, USA - Dr R.C. Lowrie) is examining the possibility that the Patas monkey and other primate species (African Green Vervet monkey, baboon) could act as hosts for O. volvulus. However, the long period to patency and the difficulty of obtaining infections would make this model of only occasional use in chemotherapeutic studies.

9.1.4 Transplantation of adult **Onchocerca** worms into rodent hosts

OCT-supported workers have, during the past year, made collaborative attempts to transplant adult worms (usually males) of three Onchocerca species into rodents. Although the viability of transplanted worms is limited to periods of a few weeks, it has proved possible to carry out preliminary chemotherapeutic studies in O. gibsoni, O. gutturosa and O. volvulus. These efforts were mainly stimulated by the Wellcome group as a means of testing drugs requiring metabolic activation by the host against Onchocerca adults. However, several drugs (both antifilarial standards and "active" Wellcome compounds) failed to show activity in the Onchocerca transplant system. This may have been due to differing activity against Onchocerca and other filarial species, use of the male worm, or an inherent problem of the transplant assay. Further experience with the system is needed before a definitive decision can be made on its usefulness.

9.2 **In vitro** assays

It is still felt that in vitro activity against an Onchocerca species, particularly the adult female O. volvulus, is an important step in the identification of macrofilaricides for preclinical development. Accordingly, the use of O. gutturosa in an in vitro screening assay will continue to be supported (Dr S. Townson, CAB International Institute of Parasitology, St Albans, UK), as will O. volvulus in vitro assays (Professor D.W. Büttner, Bernhard-Nocht-Institute, Hamburg, FRG). Collaboration between Professor Büttner and Dr J. Comley (Wellcome) in Liberia during the past year has been particularly fruitful in developing biochemical assays of worm viability for use against O. volvulus in chemotherapeutic tests and following clinical trials. These assays should be extremely useful in future work with O. volvulus by the Hamburg group.

10. SUPPORTING RESEARCH

All fundamental work on the identification of novel targets in filariae as the basis for the development of anti-Onchocerca drugs has now been terminated by OCT.

In future, supporting work will consist of support for the drug testing and development pathways. This may involve development of non-histological methods to determine worm viability after chemotherapy, synthesis or resynthesis of test compounds and the various types of work required in preclinical development of promising compounds. Such work will be pursued as required by the progress of individual compounds.

11. PROSPECTS FOR IDENTIFICATION OF A MACROFILARICIDE, AND CLINICAL TRIALS CANDIDATES

CGP 6140 remains the best current prospect for a macrofilaricide in the near future. Bioavailability by the oral route is now better understood and optimization of postprandial dosing regimens is the immediate objective. Dosing to pharmacokinetic principles may allow an effective and safe dosing schedule to be established in spite of the somewhat narrow therapeutic index of this compound. Unfortunately, at present it would seem that some type of multiple dosing schedule will be required for full macrofilaricidal activity.

The request from Ciba-Geigy that OCT should take over greater responsibility for clinical trials is both a challenge and an opportunity. When all available clinical and parasitological data have been received from Ciba-Geigy, OCT can complete its one- and three-year workplan to optimize clinical trials of CGP 6140, and initiate further trials as soon as possible. Once initiated, results from such trials should become available in 18-24 months.

Similarly, the back-up compounds from Ciba-Geigy are also the next most likely candidates for clinical trials. This group of compounds has already been tested in the secondary and tertiary screening systems with good results, and much background is available on their biological properties. Ciba-Geigy has been asked to initiate safety pharmacology and preclinical toxicology on two or three of these compounds to allow selection of the most promising candidate.

The failure of Wellcome to identify a clinical trials candidate from its lead series leaves a gap in the pipeline of drug development. The next compounds to be evaluated for their potential are those from WRAIR and the University of Michigan, currently undergoing secondary screening.

Compounds beginning to enter the primary screening system from other pharmaceutical companies are at present an unknown quantity, and it is unlikely that a candidate for clinical trial will emerge from this source before 1991.

12. OCT BUDGET

The Joint Programme Committee recommended that OCT should operate with a budget of US$7 million for the period 1989-1991, i.e. approximately $2.3 million per annum. With the termination of support for the Wellcome group, more funding is available for the preclinical development of compounds of identified activity emerging from the general screening programme. OCT has been advised that such development work could be carried out by contract research within the currently available budget. Actual funding required will be dependent upon the number of compounds under full development at any time.

13. FUTURE OPTIONS FOR DRUG DEVELOPMENT WITHIN OCP AND OCT

It was acknowledged in the last report to EAC that, by terminating its long-term research base, OCT would be totally dependent on previously identified compounds and drug series, or compounds to be obtained from pharmaceutical companies under future collaborative agreements. It was also stated that this policy contained a high element of risk as the number of good leads identified could not guarantee successful development of an effective macrofilaricide within the defined time frame. The well organized research efforts of the Wellcome group will no longer be available to OCT and thus changes of success are further reduced.

Although it may not be possible to provide a safe and effective macrofilaricide for use by OCP before the termination of the Programme, the need for such a drug, suitable for general distribution in endemic areas, will remain, or will become even more necessary, when OCP has come to an end. Long-term research to develop a macrofilaricide should therefore be pursued via alternative channels. Some work, previously supported by OCT, is continuing within TDR and EEC research programmes.

It is recommended that OCP should continue its short-term funding of OCT in the period 1989-1991 to maximize the chances of successful development of a macrofilaricidal drug. Beyond that period, OCP may wish to continue direct funding only of drugs entering clinical trials. However, in order to take advantage of the available research base in antifilarial chemotherapy, and of compounds or series part way through the development process, OCP should consider making a further guaranteed financial contribution to allow such work to continue within other established programmes.

At present, the best organized and directed programme for antifilarial chemotherapy is TDR. OCT already is fully integrated with TDR/FIL and a thematic review of all drug development within TDR will take place later this year. There is thus an opportunity to optimize the drug discovery and development programmes of WHO, and even without full integration of OCT into such programmes, any decisions made will inevitably have some impact on OCT activities in the years immediately ahead. The PDDT created by OCT and TDR/FIL is perceived as providing an essential need for tropical diseases programmes, and it may be that TDR will choose to create a similar, or perhaps a common, team to direct drug development within the Programme, or to extend the concept to other fields of scientific development, e.g. diagnostics or vaccines.

At its meeting in June 1989, the Expert Advisory Committee (EAC) was strongly in favour of the further integration of OCT into the TDR structure, and requested that OCP, in collaboration with TDR and Project Manager, OCT, prepare a plan for the continuation of research on macrofilaricides, to be presented to the eleventh session of EAC in 1990.

APPENDIX 1

RESEARCH PROJECTS CURRENTLY FUNDED BY OCT (as at 27.7.89)

	Costs (US$)
1. CLINICAL TRIALS CENTRES	
A. Novel macrofilaricides	
AWADZI, Dr K. Onchocerciasis Chemotherapy Research Centre (OCRC) Hohoe Hospital P.O. Box 144 Hohoe, Ghana	
"Clinical trials of drugs for onchocerciasis" (RP: 85006)	196 553
11 months salary for Dr Awadzi as WHO Consultant (to 4 November 1989)	66 810
SOULA, Dr G. Dépt d'Epidémiologie des Affections Parasitaires Ecole Nationale de Médecine et de Pharmacie B.P. 1805 Bamako, Mali	
"Traitement de malades atteints d'onchocercose par le CGP 6140. Ajustement du rythme d'administration et de la dose minimale active. Influence de ce composé sur la transmission" (RP: 87010)	73 000
"CGP 6140 vs ivermectin 2-year follow-up"	5 700
B. Continuing ivermectin work	
RIVAS-ALCALA, Dr A.R. Centro de Investigaciones Ecologicas del Sureste (CIES) Carretera Panamericana y Periférico Sur San Cristobal de Las Casas 29290 Chiapas, Mexico	
"A study of the tolerability, safety and efficacy of successive single oral doses of ivermectin in adults with onchocerciasis" (RP: 86017)	25 252
(TERMINATES 31 MAY 1990)	

Appendix 1

2. DRUG SCREENING CENTRES

Costs (US$)

A. In vitro test systems

TOWNSON, Dr S.
CAB International Institute of Parasitology
395A Hatfield Road
St Albans, Herts AL4 0XU
United Kingdom

"Experimental chemotherapy and screening of drugs against *Onchocerca in vitro* and *in vivo*" (RP: 89001) 132 000

BUTTNER, Professor D.W.
Bernhard-Nocht-Institute
Bernhard-Nocht-Strasse 74
2000 Hamburg 4
Federal Republic of Germany

"*In vitro* and *in vivo* drug tests of adult and larval *O. volvulus* and electron microscopic study of drug effects" (RP: 88006) 110 843

"Examination of nodules from Mali" (RP: 89006) 3 000

B. In vivo test systems

ZAHNER, Dr H.
Institut für Parasitologie
Justus-Liebig-Universität Giessen
Rudolf-Buchheim-Strasse 2
6300 Giessen
Federal Republic of Germany

"Experimental chemotherapy and chemoprophylaxis of filariasis and screening of filaricides" (RP: 85011) 123 480

LOWRIE, Dr R.C.
Tulane University Delta Regional Primate Research Centre
Parasitology Department
Three Rivers Road
Covington, Louisiana 70433
United States of America

"Suitability of the patas monkey (*Erythrocebus patas*) as a host for *Onchocerca volvulus*" (RP: 88003) 39 545

Appendix 1

Costs (US$)

B. In vivo test systems (continued)

MAK, Dr Joon Wah
Head, Filariasis Research Division
Institute for Medical Research
Jalan Pahang
50588 Kuala Lumpur, Malaysia

"Screening potential filaricides against subperiodic *B. malayi* in *Presbytis* spp." (RP: 87013) — 25 000

McCALL, Dr J.W.
Department of Parasitology
College of Veterinary Medicine
University of Georgia

"Drug screening utilizing *Brugia pahangi* in the dog" (RP: 88013) — 9 500

COPEMAN, Professor D.B.
Graduate School of Tropical Veterinary Science
James Cook University of North Queensland
Townsville, QLD 4811
Australia

"Bovine screen for *Onchocerca gibsoni*" (RP: 89003) — maximum of 111 140

3. SUPPORTING WORK

Company to handle compounds for screening (RP: 89008) — 80 000
(Not yet identified)

BAKER, Professor D.C. — 35 260
Department of Chemistry
The University of Alabama
Tuscaloosa, Alabama 35487-0336
United States of America

"Resynthesis and evaluation of antifilarial lead compounds" (RP: 89009)

APPENDIX 2

As at July 1989

LIST OF OCT STEERING COMMITTEE MEMBERS

Mr P. Acred, Chemotherapy Department, Glaxo Group Research Limited, Greenford Road, Greenford, Middlesex UB6 0HE, United Kingdom

Dr E.F. Elslager, Elslager Associates, 4081 Thornoaks Drive, Ann Arbor Michigan 48104, United States of America

Professor P. Gayral, Faculté de Pharmacie, Université Paris-Sud, rue Jean-Baptiste Clément, 92290 Chatenay-Malabry, France

Professor B.M. Greene, Director Division of Geographic Medicine, School of Medicine/ Dept of Medicine, University of Alabama at Birmingham, University Station, Birmingham, Alabama 35294, United States of America

Dr G. Jollès, Directeur Scientifique, Rhône-Poulenc Santé 20, avenue Raymond-Raron, 92165 Antony, France

Dr K. Sachsse, RCC Research and Consulting Company Ltd, Zeigliweg 1, Postfach 4452 Itingen, Switzerland

Coopted member

Dr L.L. Fleckenstein, Research Pharmacologist, GS-14, Dept of Pharmacology, Division of Experimental Therapeutics, Walter Reed Army Institute of Research, Washington, D.C. 20307-5100, United States of America

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