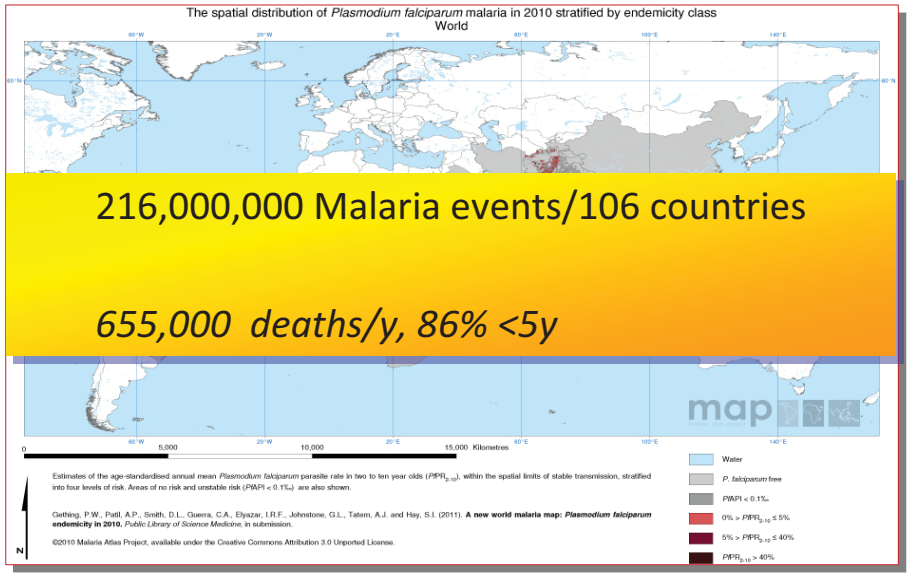
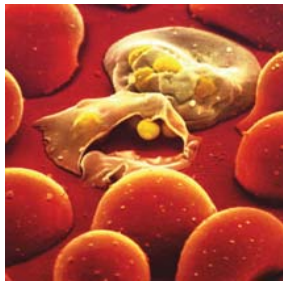


THE CULPRIT



THE RESULT

THE VECTOR

The Scientists that understood the disease

Alphonse Laveran

Ettore Marchiafava

Angelo Celli

Camillo Golgi

Amico Bignami

Giovan Battista Grassi

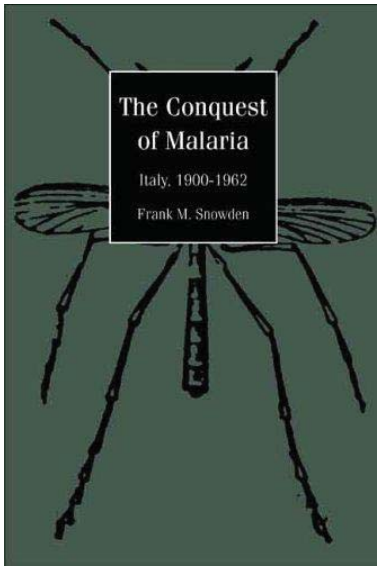
Giuseppe Bastianelli

Sir Patrick Manson

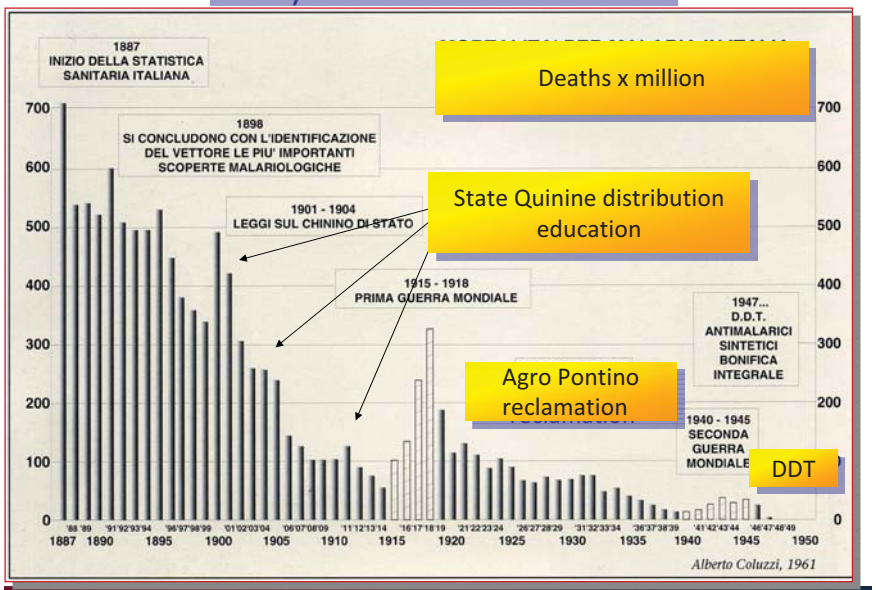
Sir Ronald Ross

Italy & Malaria

Frank M. Snowden 2006, Yale University Press, New Haven



Italy: Eradication of Malaria



Sigma-tau contribution

Severe malaria	Uncomplicated malaria
IV ARTESUNATE	Eurartesim®
FDA	EMA
Validation batches comlpeted	REGISTERED

Medicine for Malaria Venture target

Medicines for Malaria Venture

Our mission & vision

MMV, a not-for-profit public-private partnership, was established as a foundation in Switzerland in 1999.

Our mission is to reduce the burden of malaria in disease-endemic countries by discovering, developing and facilitating delivery of new, effective and affordable antimalarial drugs.

Our vision is a world in which these innovative medicines will cure and protect the vulnerable and under-served populations at risk of malaria, and help to ultimately eradicate this terrible disease.

Repositioning

Pfizer Azithromycin based combination.

New Chemical Entities

GSK Tafenoquine Phase II/III

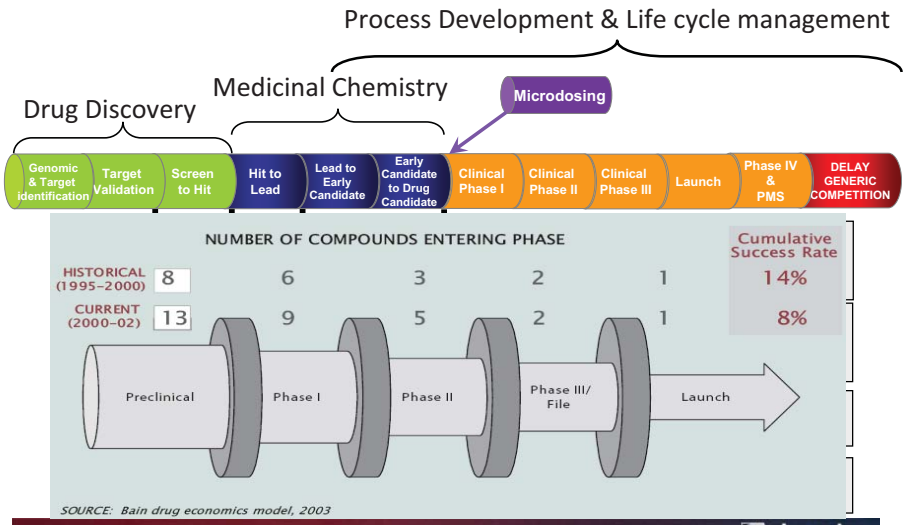
Rambaxy Arterolane registered only in India…

Shin Poong Pharm. Pyramax , EMA decision based on article 58 on 17/2/201

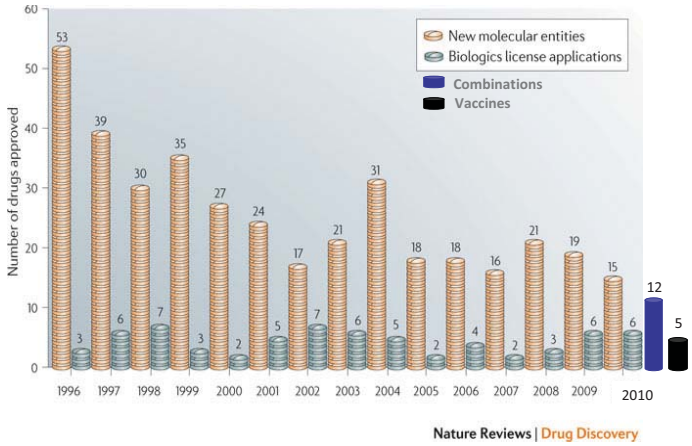
Vaccine

GSK Succesfull phase III trials. Protection efficiency?

Drug Discovery & Development



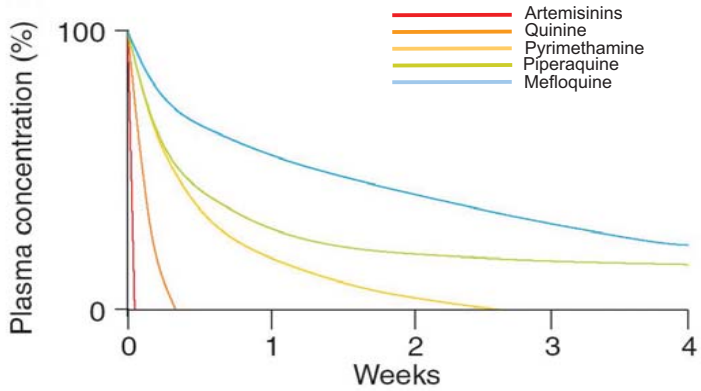
2010 FDA APPROVAL



Nature Review in Drug Discovery **2011,** *10*, 82.

Combinations!!! Better use of the available weapons

Artemisinin-based Combination Therapies



Combinations!!! Better use of the available weapons

Artemisinin-based Combination Therapies

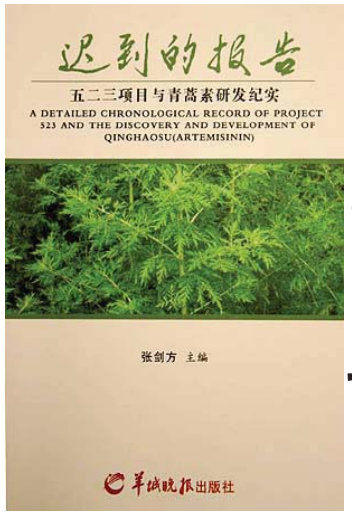
Antimalarial	$t_{1/2}$ of artemisinin derivative	$t_{1/2}$ of partner drug	Regions currently in use*
Artemether–lumefantrine	~3 hr	4–5 days	Africa, EM, SE Asia, WP and SA
Artesunate–mefloquine	<1 hr	14–21 days	Africa, SE Asia, WP and SA
Artesunate–amodiaquine	<1 hr	9–18 days‡	Africa and EM
Dihydroartemisinin–piperaquine	45 min	~5 weeks	SE Asia
Artesunate–pyronaridine§	<1 hr	16 days	NA
Chloroquine‖	NA	1–2 months	Africa, EM, SE Asia, WP and SA
Sulphadoxine–pyrimethamine‖	NA	~4 days (S) or ~8 days (P)	Africa, EM (IPT in Africa, EM and WP)

*Data from REFS 106,140. ‡This refers to the $t_{1/2}$ of the active metabolite monodesethylamodiaquine; the $t_{1/2}$ of amodiaquine is ~3hr. §Recently completed Phase III trials. ‖These former first-line antimalarials are included as a reference. EM, eastern Mediterranean; IPT, intermittent preventive treatment; NA, not applicable; P, pyrimethamine; S, sulphadoxine; SA, South America; SE Asia, Southeast Asia; $t_{1/2}$, half-life; WP, Western Pacific.

Fixed Dose Combinations!!!!

PRODUCT	COMPANY	FIRST APPROVAL
Coartem® Artemether & Lumefantrine 1980 / 1970	Novartis	Switzerland
Coarsucam® Artesunate & Amodiaquine 1980 / 1946	Sanofi	Morocco
Eurartesim® DHA & Piperaquine 1980 / 1960	Sigma-tau	EMA

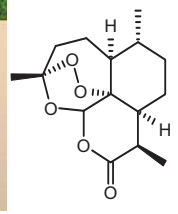
Traditional Chinese Medicine



Qīng Hāo
Artemisia Annua 青蒿

1971-1974

QUINGHAOSU
Artemisinin 黄花蒿

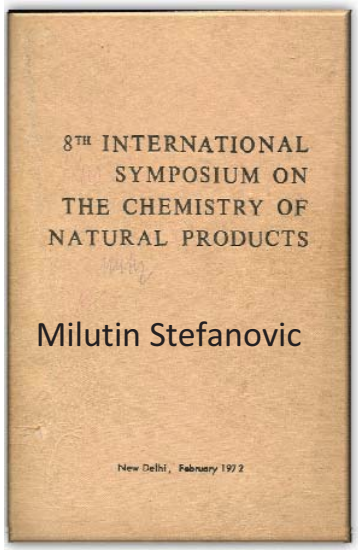


1977

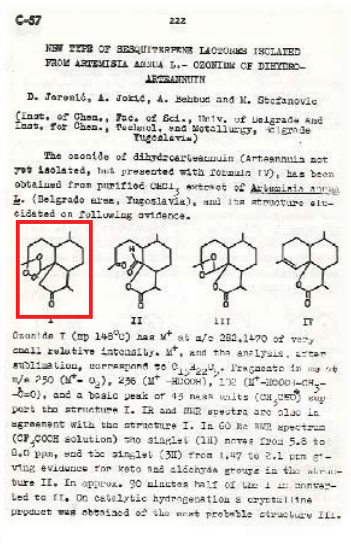
Only 541 Scientists Were Exempt From the Re-education Process

Beijing:	Project 523 Head Office
	Biophysics CAS Inst.
	Traditional Chinese Materia Medica Inst.
Jinan:	Materia Medica Inst.
	Parasitic Diseases Inst.
Shanghai:	Materia Medica CAS Inst.
	Organic Chemistry Inst.
Chongqing:	Sichuan Materia Medica Inst.
Jiansu Province:	Gaoyou Country Health Dept.
Guangzhou:	Univ. of Chinese Traditional Medicine
Kunming:	Yunnan Materia Medica Inst.
Guilin:	Guiling Pharmaceutical Factory

THE FIRST TO DISCOVER AND SHARE



Milutin Stefanovic



C-57 222

NEW TYPE OF SESQUITERPENE LACTONES ISOLATED FROM ARTEMISIA ANNUA L.- OZONIDE OF DIHYDRO-ARTEANNUIN

D. Jeremić, A. Jokić, A. Sehbut and M. Stefanovic

(Inst. of Chem., Fac. of Sci., Univ. of Belgrade and Inst. for Chem., Technol. and Metallurgy, Belgrade Yugoslavia)

The ozonide of dihydroarteannuin (Arteannuin not yet isolated, but presented with formula IV), has been obtained from purified $CHCl_3$ extract of Artemisia annua L. (Belgrade area, Yugoslavia), and the structure elucidated on following evidence.

I II III IV

Ozonide I (mp 148°C) has M^+ at m/e 282.1470 of very small relative intensity. M^+, and the analysis, after sublimation, corresponds to $C_{15}H_{22}O_5$. Fragments in mass m/e 250 ($M^+ - O_2$), 236 ($M^+ - HCOOH$), 138 ($M^+ - HCOOH - CH_3-\overset{O}{\overset{\|}{C}}-CH=O$), and a basic peak of 43 mass units ($CH_3\overset{O}{\overset{\|}{C}}$) support the structure I. IR and NMR spectra are also in agreement with the structure I. In 60 Mc NMR spectrum (CF_3COOH solution) two singlet (1H) moves from 5.8 to 6.0 ppm, and the singlet (3H) from 1.47 to 2.1 ppm giving evidence for keto and aldehyde groups in the structure II. In approx. 90 minutes half of the I is converted to II. On catalytic hydrogenation a crystalline product was obtained of the most probable structure III.

An approach to steroidal analogues of artemisinin

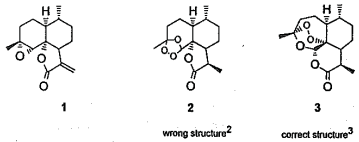
MILUTIN STEFANOVIĆ,[a] NINA TODOROVIĆ,[b] and BOGDAN SOLAJA[a]

[a]*Faculty of Chemistry, University of Belgrade, P. O. Box 550, YU-11001, Belgrade and* [b]*Institute of Chemistry, Technology and Metallurgy, Belgrade, Yugoslavia*

(Received 2 February 1993)

This article reports the synthesis of seco-cholestane and Δ^2- and Δ^3-19-nor-5α, 10α-cholestene derivatives of types D and E/F, respectively. The key reaction in the synthesis of E/F is the PtO_2-catalysed hydrogenation of 5(10)-double bond accompanied with hydrogenolysis at normal pressure.

On a piece of silk unearthed from a Han dynasty tomb (168 B.C.) it was discovered that: Chinese traditional medicine used the plant *Artemisia annua* L. (in Chinese *qing hao*, sweet wormwood) in the treatment of haemorrhoids. Later, the same plant was mentioned in the *Handbook of Prescriptions for Emergency Treatments* (340 A.D.) and in the *Compendium of Materia Medica* written in 1596 by the famous Chinese herbalist Li Shizhen. He prescribed extracts of *qing hao* in the treatment of chills and the fever of malaria. However, efforts to prove the antipyretic and antimalarial activity of warm water extracts of *Artemisia annua* were disappointing.[1] This plant was for the first time examined by our group, and from the specimen found growing in the Belgrade surroundings, several sesquiterpene lactones of cadinane structure were isolated, among them:

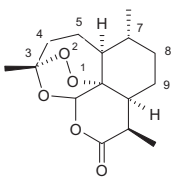


1 arteannuin B[4,5]

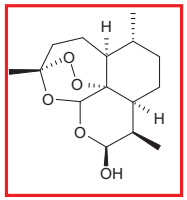
2 wrong structure[2]

3 correct structure[3] artemisinin (arteannuin, arteannuin A, qinghaosu, QHS)

Artemisinin derivatives



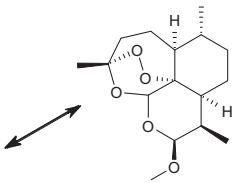
artemisinin



DHA

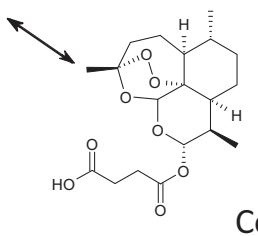
the drug

Eurartesim



artemether

Coartem

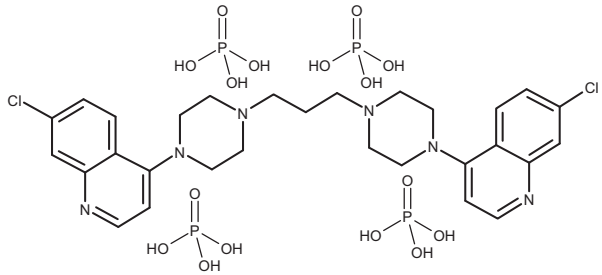


artesunate

Coarsucam

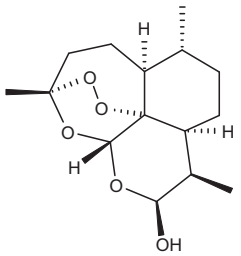
EURARTESIM®

PIPERAQUINE POSPHATE (PQP)

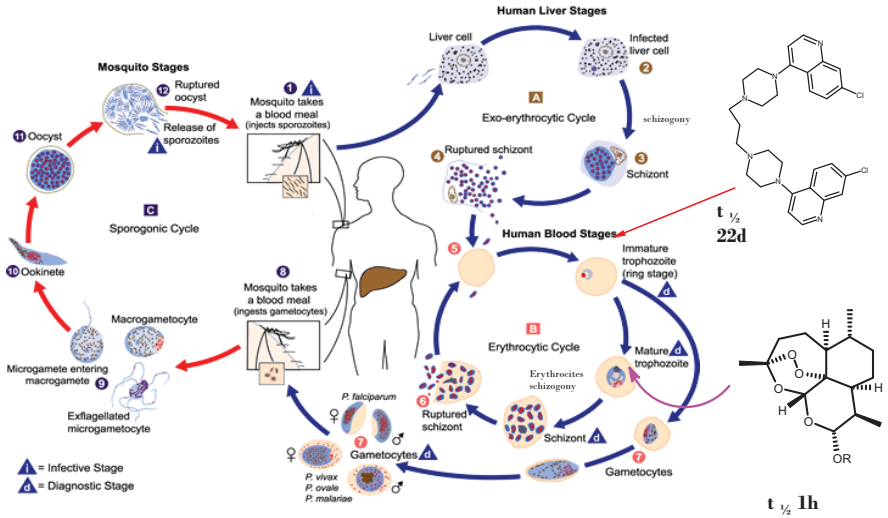


cGMP

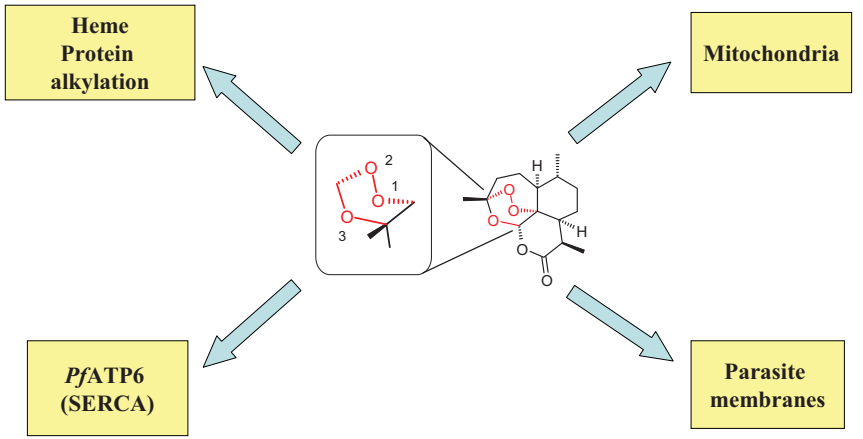
DIHYDROARTEMISININ (DHA)



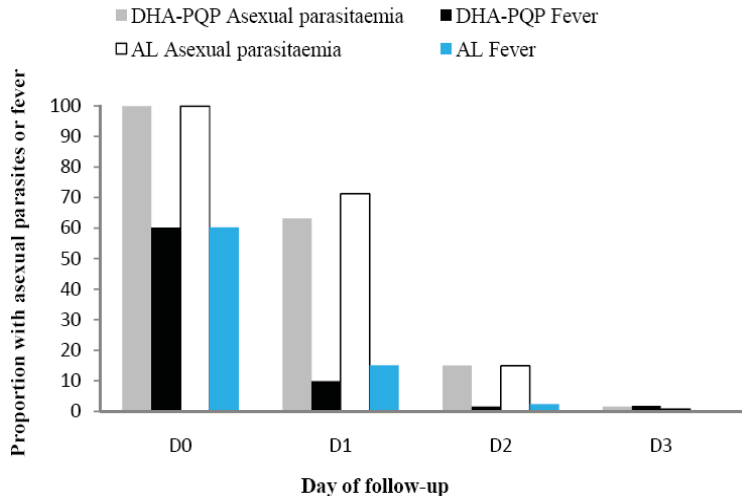
The Malaria Cycle



Potential Targets Artemisinin Derivatives



Parasitaemia and fever clearance



Total Quality

- ✓ Preclinical Development — GLP
- ✓ Clinical Development — GCP
- ✓ DS/DP — GMP — EH&S — GREEN CHEMISTRY

EURARTESIM LOGISTICS

China
Vietnam
Kenya
Artemisinin

Collaboration with the International Pharmacopoeia

GMP

Collaboration with the International Pharmacopoeia and the USP

Supplier 1
DHA

Suppliers 2
PQP

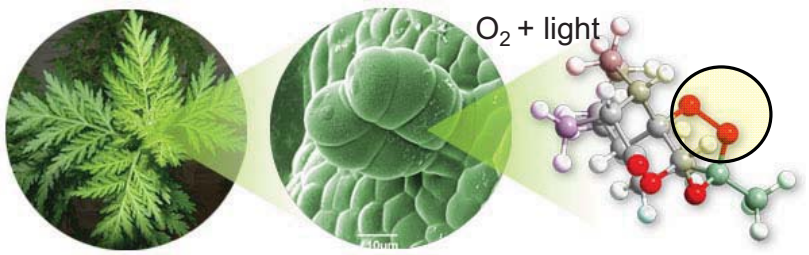
Sigma Tau
Drug Product

Artemisia annua FIELDS

THE KEY PHARMACOPHORIC

Pharmacophoric mojety

O_2 + light



Artemisia annua glandular trichomes

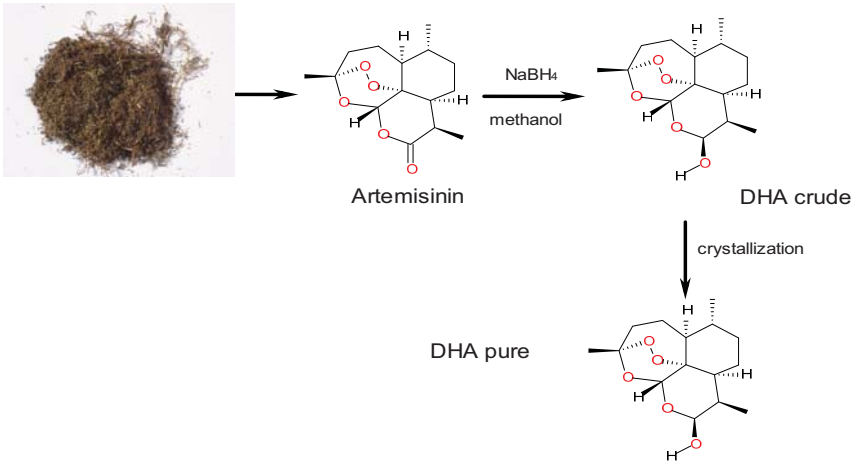
Artemisinin

Artemisinin WW

Table 1
Summary of analysis results for variety of artemisinin samples produced in various regions, in different years and purified using different methods. Actual suppliers and lots are not disclosed. N.D.= not detected.

Manufact. country	Supplier	Manufact. year-lot	Artemisitene (%)	(+)-9-Epi-artemisinin (%)	Total impurities (%)	Assay (vs. WHO ref standard) (%)
Vietnam	V-1	2008-1	0.06	0.36	0.42	99.0
	V-1	2008-2	0.06	0.36	0.42	99.5
	V-1	2008-3	0.06	0.35	0.41	99.3
	V-1	2009-1	0.04	0.35	0.39	99.8
	V-1	2009-2	0.05	0.32	0.37	99.6
	V-1	2010-1	0.04	0.33	0.37	98.9
China	C-1	2007-1	0.03	0.30	0.33	99.3
	C-1	2007-2	0.05	N.D.	0.05	99.0
	C-1	2007-3	0.04	0.17	0.21	99.5
	C-21	2008-1	0.05	0.30	0.35	98.9
	C-21	2008-2	0.03	0.26	0.29	99.2
	C-21	2008-3	0.04	N.D.	0.04	100.1
	C-32	2008-1	0.07	0.20	0.27	100.0
	C-32	2008-2	0.06	0.20	0.26	99.6
	C-42	2008-1	0.04	N.D.	0.04	101.0
	C-52	2009-1	0.08	N.D.	0.08	99.6
	C-52B	2009-2	0.08	N.D.	0.08	99.8
	C-52B	2009-3	0.10	N.D.	0.10	100.2
Kenya	K-1	2008-1	0.05	0.52	0.57	99.2
	K-1	2008-2	0.03	0.73	0.76	99.8
	K-1	2008-3	0.04	0.20	0.24	99.0
	K-1	2010-1	0.05	0.07	0.12	99.8
	K-1	2010-2	0.06	0.09	0.15	99.2
	K-1	2010-3	0.05	0.12	0.17	100.3
India	I-1	2008-1	0.01	0.44	0.45	99.1
	I-1	2008-2	0.01	0.50	0.51	99.2
Brasil	B-1	2006	<0.05	0.09	0.09	99.6
Madagascar	M-1	2008	0.02	0.50	0.52	99.1
	M-1	2010	0.05	0.50	0.55	99.8
	M-1	2010	0.04	0.49	0.53	99.6

DHA The Process



Molecules **2010,** *15,* 1309-1323

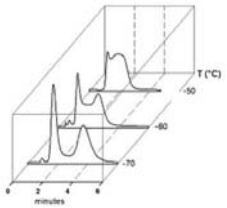
Review

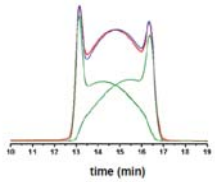
Stereodynamic Investigation of Labile Stereogenic Centres in Dihydroartemisinin

Ilaria D'Acquarica 1,*, Francesco Gasparrini 1,*, Dorina Kotoni 1, Marco Pierini 1, Claudio Villani 1, Walter Cabri 2, Michela Di Mattia 2 and Fabrizio Giorgi 2

1 Dipartimento di Chimica e Tecnologie del Farmaco, Sapienza Università di Roma, P. le Aldo Moro 5 00185 Roma, Italy

2 Analytical Development, R&D Department, sigma-tau S.p.A., Via Pontina km 30,400, 00040 Pomezia, Italy





JOC The Journal of Organic Chemistry *JOC* **2011,** *76,* 1751–1758 ARTICLE

pubs.acs.org/joc

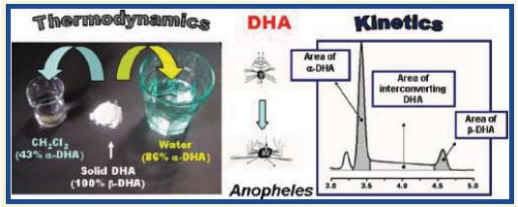
Stereolability of Dihydroartemisinin, an Antimalarial Drug: A Comprehensive Thermodynamic Investigation. Part 1†

Walter Cabri,† Ilaria D'Acquarica,§ Patrizia Simone,§ Marta Di Iorio,§ Michela Di Mattia,† Francesco Gasparrini,*,§ Fabrizio Giorgi,‡ Andrea Mazzanti,† Marco Pierini,*,§ Marco Quaglia,‡ and Claudio Villani‡§

†Analytical Development, R&D Department, sigma-tau S.p.A., Via Pontina km 30.400, 00040 Pomezia, Italy

§Dipartimento di Chimica e Tecnologie del Farmaco, Sapienza Università di Roma, P. le Aldo Moro 5, 00185 Roma, Italy

‡Dipartimento di Chimica Organica "A. Mangini", Università di Bologna, Italy



JOC The Journal of Organic Chemistry *JOC* **2011,** *76,* 4831–4840 ARTICLE

pubs.acs.org/joc

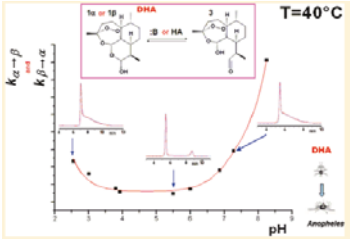
Stereolability of Dihydroartemisinin, an Antimalarial Drug: A Comprehensive Kinetic Investigation. Part 2

Walter Cabri,† Ilaria D'Acquarica,‡ Patrizia Simone,‡ Marta Di Iorio,‡ Michela Di Mattia,† Francesco Gasparrini,*,‡ Fabrizio Giorgi,† Andrea Mazzanti,§ Marco Pierini,*,‡ Marco Quaglia,† and Claudio Villani‡

†Analytical Development, R&D Department, Sigma-Tau S.p.A., Via Pontina km 30.400, 00040 Pomezia, Italy

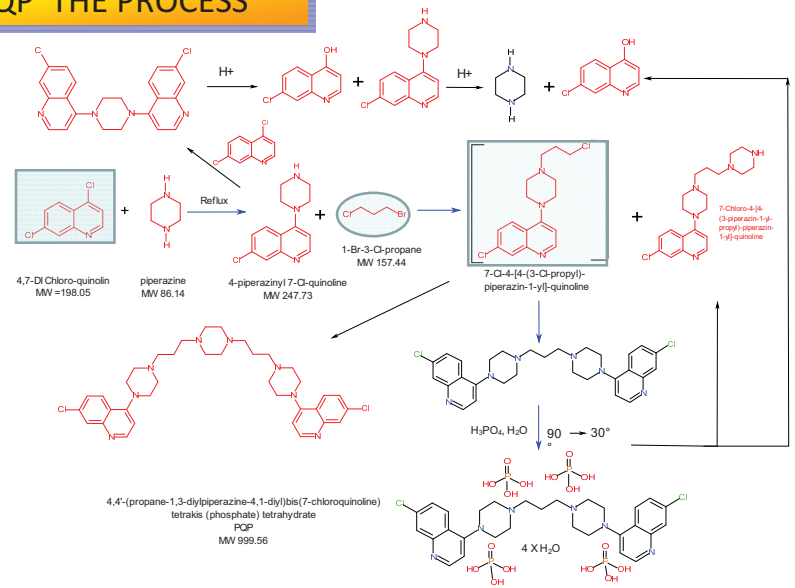
‡Dipartimento di Chimica e Tecnologie del Farmaco, Sapienza Università di Roma, P. le Aldo Moro 5, 00185 Roma, Italy

§Dipartimento di Chimica Organica "A. Mangini", Università di Bologna, Viale Risorgimento 4, 40136 Bologna, Italy

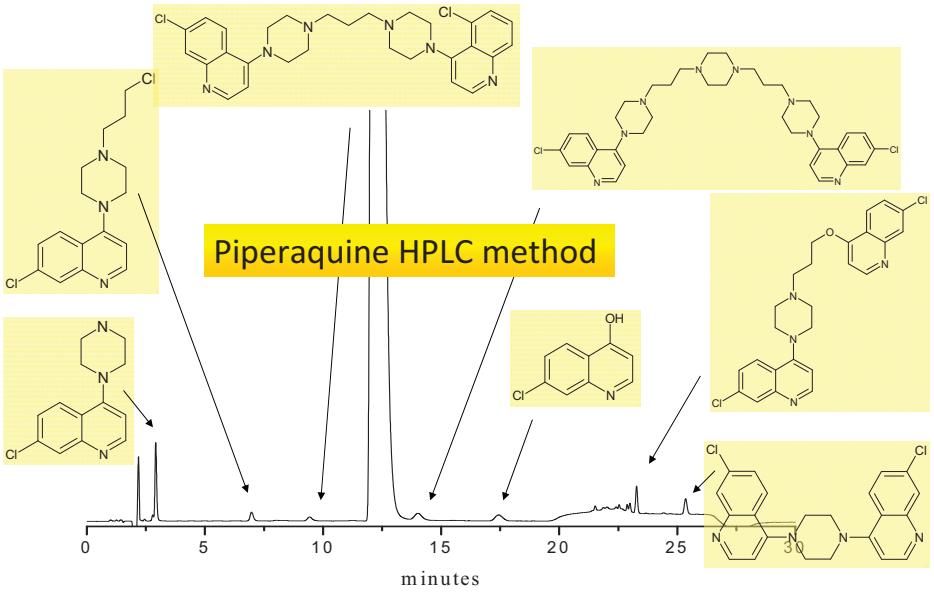


Piperaquine tetraphosphate tetrahydrate

PQP THE PROCESS



Piperaquine HPLC method

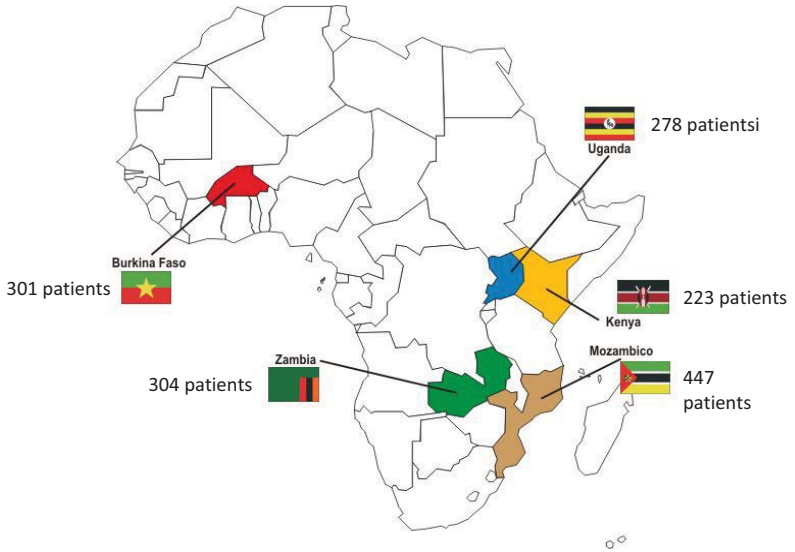


We Achieved :

Complete control of the processes, the logistic.
Identification and control of all decomposition pathways. All impurities have been qualified from a toxicological point of view. Genotoxic evaluation was generated according to the more recent ICH, EMA and FDA guidelines.
Our suppliers have established a complete Environmental, Health and Safety control.
Satisfactory 2y stability data at 30°

Eurartesim® is free from genotoxic impurities

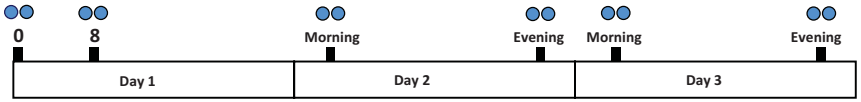
Phase III trial in Africa: 5 countries



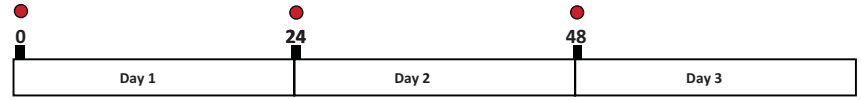
Manhiça, Mozambico

Dose Regimens for children

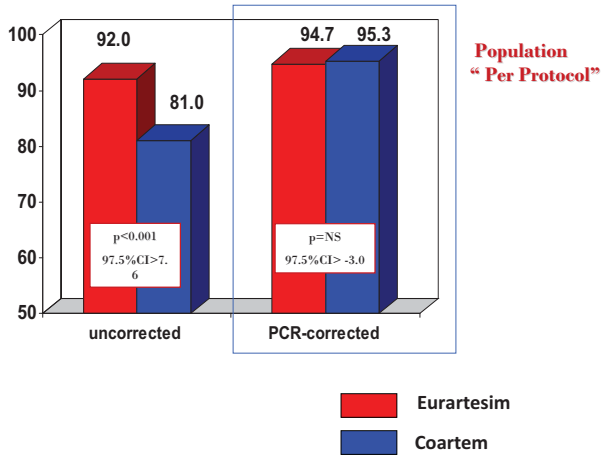
Coartem (6-dose regimen for children >15 <25 Kg: 12 tablets over 56 hours)



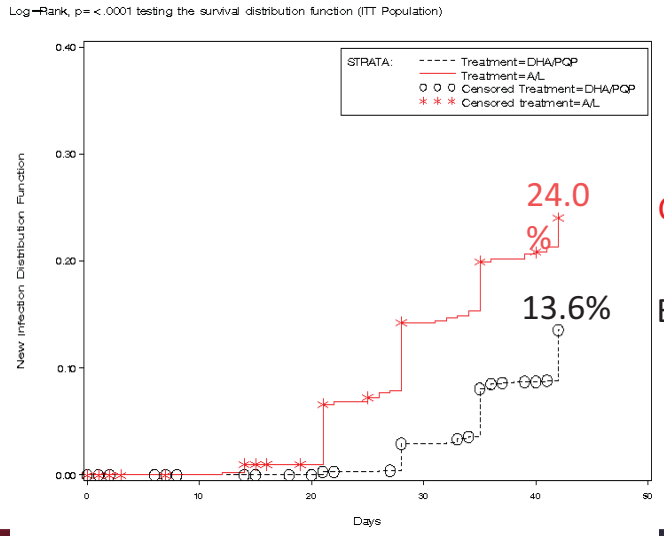
Eurartesim (3-dose regimen for children >13 <23 Kg: 3 tablets over 48 hours)



Eurartesim is equivalent to Coartem 28 d



Eurartesim protect the patient better then Coartem from new infections



24.0 %

Coartem

13.6%

Eurartesim

1882 Italy & Malaria

Malaria map (1882) by sen. Luigi Torelli

The map was developed to verify the health and hygienic conditions along the railway lines.

About 8331 kilometers of railways, 3762 were well in malarial areas.

Analytical Development
Fabrizio Giorgi
Michela Di Mattia
Cristina Di Giovanni
Silvana Lalli
Giuseppe Marazzi
Elena Badaloni
Michela Forte
Fabrizio Piccirilli
Roberto Deias
Lucilla Mastrofrancesco
Gianfranco D'amore
Lucia Critelli
Marco Quaglia
Massimiliano Ricci

Toxicology
Rita Lucreziotti
Giancarlo Gramiccioli
Domenico Intorre
Daniela Pesce
Rosangela Ferretti

Chemical & Pharmaceutical Development
Silvia Armaroli
Giulio Carzana
Marco Torri
Stefano Banfi
Roberto Castagnani
Andrea Quattrociocchi

Technical Support
Emanuela Tassoni (MedChem)
Lia Dell'uomo (Scientific staff)
Mosè Santaniello (Developability)
Maria Grazia Cima (Developability)

Metabolism
Silvia Pace
Carlo Tallarico
Francesco Manera

General Pharmacology
Franco Borsini
Giovanni Mattera
Maria Antonietta Stasi

Professor Francesco Gasparrini & Professor Guy Mazue