Accord-UK Ltd

INVESTIGATIONAL MEDICINAL PRODUCT DOSSIER PLACEBO

Study Title: Chloroquine/ hydroxychloroquine prevention of coronavirus disease (COVID-19) in the healthcare setting; a randomised, placebo-controlled prophylaxis study (COPCOV)

Internal Reference Number / Short title: COPCOV
OxTREC Ref: 25-20
Protocol number: VIR20001
Date and Version No: Version 4.0 dated 9 April 2020
EudraCT Number: 2020-001441-39
The study is a double-blind, randomised, placebo-controlled trial that will be conducted in healthcare settings. Participants will be healthcare workers, or other individuals at significant risk, who can be followed reliably for 5 months. 40,000 participants will be recruited with a predicted average of 400-800 participants per site in 50-100 sites.

MAY 2020

	Name	Position	Signature	Date
Prepared by	David Tighe	Principal Scientist	D. Tighe	01 MAY 2020
Approved by	Mark King	Director, Quality Operations (QP)		01/May/2020

Version	Reason for change
01	Original
02	Shelf life amended to 12 months in 2.1.P.8

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1. INTRODUCTION

A UK Marketing Authorisation for Hydroxychloroquine Sulfate 200mg Film-coated Tablets was originally granted to Lambda Therapeutic Limited, Sage House, 319 Pinner Road, North Harrow, Middlesex, HA1 4HF, United Kingdom, PL 29959/0015. The MA grant date was 25.03.2020. A change of ownership from Lambda Therapeutic Limited to Accord-UK Ltd was granted on 31.03.2020 (PL 0142/1254). During the manufacturing transfer into the Accord-UK site changes were made to some sections of the Module 3. At the time of writing these changes are in the process of submission of a grouped Type II MA variation.

In order to capture these changes, an IMP dossier for the test product was compiled in accordance with EMA/CHMP/QWP/545525/2017 Guideline on the requirements for the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials, section 5.

The study is a randomised double blind placebo-controlled clinical trial.

This dossier has been compiled for product designed to act as placebo tablets for Accord-UK Ltd Hydroxychloroquine Sulfate 200mg Film-coated Tablets.

1. SYNOPSIS

Study Title	Chloroquine/ hydroxychloroquine prevention of coronavirus disease (COVID-19) in the healthcare setting; a randomised, placebo-controlled prophylaxis study (COPCOV)	
Protocol number	VIR20001	
Study Design	Randomised double-blind, placebo-controlled trial	
Study Participants	Healthcare workers in a healthcare facility delivering direct care to patients with either proven or suspected COVID-19. Adults (exact age is dependent on local country requirements).	
Planned Sample Size	40,000 total participants	
Planned Study Period	12 months; individual trial duration maximum 5 months	
	Objectives	**Outcome Measures**
Primary	To determine if chloroquine or hydroxychloroquine prophylaxis prevents symptomatic COVID-19 infection in healthcare workers.	The number of symptomatic COVID-19 infections will be compared between participants randomised to chloroquine or hydroxychloroquine, and placebo groups.
Secondary	To determine if chloroquine or hydroxychloroquine prophylaxis attenuates COVID-19 infections.	The symptoms severity and duration of COVID-19 illness, in those who become infected during the study will be compared between the two groups using a respiratory severity score.
	To determine if chloroquine or hydroxychloroquine prophylaxis prevents asymptomatic COVID-19 infection.	The number of asymptomatic cases of COVID-19 will be determined by comparing serology in all participants at time of enrolment and at the end of follow up.
	To determine if chloroquine or hydroxychloroquine prophylaxis prevents all-cause symptomatic acute respiratory illnesses.	The number and severity of symptomatic acute respiratory illnesses will be compared in participants randomised to chloroquine or hydroxychloroquine, and placebo groups.
Tertiary	To characterise genetic and baseline biochemical markers associated with symptomatic COVID-19, respiratory illness and disease severity.	Genetic loci and levels of biochemical components will be correlated with occurrence of and disease severity of COVID-19 or other Acute Respiratory Infections (ARIs).
	To assess the impact of chloroquine or hydroxychloroquine prophylaxis on	The days lost to work, and the relationship between the subjective assessment of well-

	work and behaviour during the pandemic.	being and the decision to self-isolate when unwell (i.e. not go to work) will be examined in relation to the infection and treatment arm.
	To perform health economic analyses to assess the impact of chloroquine or hydroxychloroquine prophylaxis on costs and quality of life measures	The trial will collect data on use of health care resources and health related quality of life (EQ-5D-3L) to determine the effects between treatment groups.

2. INFORMATION ON THE CHEMICAL AND PHARMACEUTICAL QUALITY CONCERNING PLACEBO PRODUCT

2.1 CHEMICAL PHARMACEUTICAL AND BIOLOGICAL DATA

2.1.P PLACEBO PRODUCT

2.1.P.1 DESCRIPTION AND COMPOSITION

Description:

White to off-white, plain, 9mm, round, biconvex, film-coated tablets

Unit composition:

Computer Reference Number	Unit dose Formulae mg/tab	Ingredient Name	Ingredient weight (kg)
6036004	216.14	Lactose DC Type 2	237.75
6005137	47.00	Microcrystalline Cellulose 102	51.70
6034115	47.00	Starch 1500	51.70
6001030	0.30	Colloidal Silicon Dioxide	0.330
6023090	1.56	Magnesium Stearate	1.716
Total	312.00	Total	343.196
Tablet Coat			
50949409	9.36	Opdadry II 85F18422	12.87

* Weight includes 25% overage for process losses during coating

2.1.P.2 PHARMACEUTICAL DEVELOPMENT

The tablet is identical in appearance to the test product. The film coating is the same as the test product therefore smell and taste will be masked in the same way.

2.1.P.3 MANUFACTURE

2.1.P.3.1 Manufacturer(s)

Product Name	Dosage Form	Manufacturing Site, QC testing and Primary Packing	Secondary Packing Site	Final Certification of IMP batches
Hydroxychloroquine Sulfate Placebo Tablets	Tablets	Accord-UK Ltd	Piramal Healthcare	Accord-UK Ltd

RESPONSIBILITY	PIRAMAL	ACCORD	SPONSOR
CTA and Ethics committee approval			X
PSF / IMPD		X	

RESPONSIBILITY	PIRAMAL	ACCORD
Secondary Packaging Materials: Inserts / Labels / Cartons		
Supply any information necessary for packing of the product		X
Specifications		X
Approved label copies		X
Preparation of secondary packaging materials	X	
Audit report provided on request by	X	
Purchasing	X	
Quality Control and Release	X	
Reference samples	X	

RESPONSIBILITY	PIRAMAL	ACCORD

Product		
Specifications		X
Approved label copies		X provided by the sponsor
Providing randomisation codes		X provided by the sponsor
Secondary packing operations	X	
Packing instructions	X	
Application of randomisation code to each pack	X	
In-process control testing for secondary packing	X	
Packing Batch Record and associated documentation	X	
Reference samples	X	X
Batch Certification by QP - Bulk product and primary packing		X
Batch Certification by QP - Secondary packing	X	
Final Batch Certification by QP		X
Data loggers provided by		X
Distribution to study centres and maintenance of distribution records	X	
Resolution of distribution temperature excursions	X	

Accord-UK Ltd (MIA (IMP) 142)
Whiddon Valley, Barnstaple, Devon EX32 8NS, United Kingdom

Piramal Healthcare UK Ltd (MIA (IMP) 29595)
Whalton Road, Morpeth, Northumberland NE61 3YA, UK

3.2.P.3.2 Batch Formula

Details of the IMP batch sizes are described as follows:

Name of product	Exhibit batch size\ Proposed commercial batch size
Hydroxychloroquine sulfate placebo film coated tablets	1,100,000 tablets

Batch formula of Hydroxychloroquine sulfate placebo film-coated tablets

Granulation Material				
Unit Dose Formula (mg)	Computer Part No.	Ingredient Name	Weight per Section	No. of Sections
216.14	6036004	Lactose DC Type 2	237.8 kg	1
47.00	6005137	Microcrystalline Cellulose 102	51.7 kg	1
47.00	6034115	Starch 1500	51.7 kg	1
0.300	6001030	Colloidal Silicon Dioxide	0.3300 kg	1
1.56	6023090	Magnesium Stearate	1.716 kg	1
Coating Material				
9.36*	50949409	Opadry II 85F18422 White	4.290 kg*	3
* Included at a 25% overage for process losses				

2.1.P.3.3 Description of Manufacturing Process and Process Controls

The manufacturing process is described below. A summary, in the form of a flow chart is shown as Figure 1.

1) The Lactose DC type 2, Microcrystalline Cellulose 102, Silica Dioxide and Starch 1500 are passed through an 850 micron screen into a suitable container.

2) The sieved powders from step 1 are blended in a 1100L IBC.

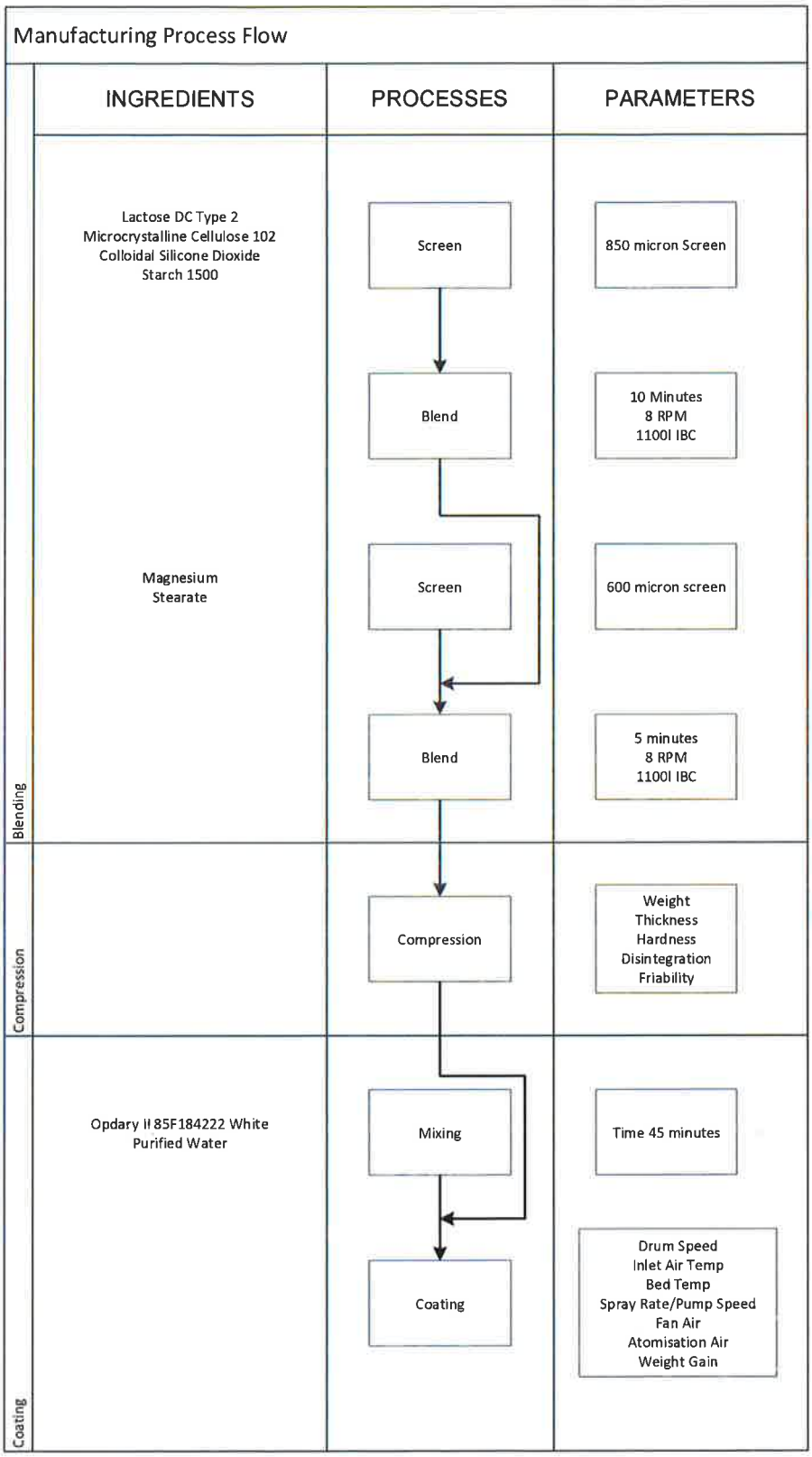
3) The Magnesium Stearate is passed through a 600 micron screen and added to the blended powders from step 2.

4) The bulk from step 3 is blended for 5 minutes

5) The blended powder from step 4, is compressed into tablets on a rotary compression machine.

6) The compressed tablet cores are coated in a traditional tablet coater to a target weight gain of 3% w/w

Figure 1 Flow Diagram of Manufacturing Process



2.1.P.3.4 Controls of Critical Steps and Intermediates

Information not required

2.1.P.3.5 Process Validation and/or Evaluation

Data are not required.

2.1.P.4 CONTROL OF EXCIPIENTS

2.1.P.4.1 Specifications

Excipients used in manufacturing of drug product are widely used in manufacture of pharmaceutical formulation.
The pharmacopoeial excipients will be tested in accordance with the relevant monograph in the current editions of Ph. Eur. and the excipients which are not official in Ph. Eur. will be tested with the in-house specification and method of analysis.

Excipients	Reference to standards@
Lactose DC Type 2	Ph. Eur.
Microcrystalline Cellulose 102	Ph. Eur.
Starch 1500	Ph. Eur.
Colloidal Silicon Dioxide	Ph. Eur.
Magnesium Stearate	Ph. Eur.
Purified Water	Ph. Eur.
Opadry II 85F18422 white	In-house

@ Always current version of Ph. Eur./In-house specification shall be followed.

All excipients used in formulation are procured from one of the approved suppliers, but other qualified supplier can also be used.

The specification followed by the drug product manufacturer for Opadry II 85F18422 white is as follows:

Accord-UK Ltd
Whuddon Valley
Barnstaple, Devon
EX32 8NS, United Kingdom
T: +44 (0) 1271 385200
F: +44 (0) 1271 346106
www.accord-healthcare.co.uk

Opadry White 85F18422; Specification

Test	Limits
Appearance	White powder.
Identification: a) By Colour Test Titanium dioxide	A yellow / orange colour should be produced.
Dispersion	a. Foreign matter – should be absent. b. Undispersed pigments: not more than 2 specks should be observed. c. Small, soft, uniform size particles (if observed): they should easily break. d. Hard lumps (if observed): they should disperse in water.
Ash	35.80 – 43.80%

David Ardern PS Analytical Support Team Leader

2.1.P.4.2 Analytical Procedures

The Ph. Eur. excipients will be tested in accordance with the relevant monograph in the current edition of European Pharmacopoeia and the excipients which are not official in Ph. Eur. will be tested with the in-house method of analysis.

The methods of analysis followed by the drug product manufacturer for Opadry II 85F18422 white are provided below:

01. Appearance:

Reference: Inhouse

Spread the sample over a piece of white card. Note the colour of the powder.

02. Ash:

Reference: Inhouse

Heat a platinum crucible to redness for 10 minutes, allow to cool in a dessicator and weighing. Record the weight W_1. Place about 1.0 g of the substance being examined in the crucible. Record the weight W_2. Ignite at about 775- 825°C for 15 minute. Cool and weigh, again ignite for 15 minute and repeat this procedure until two successive weighings do not differ by more than 0.5 mg. Record the weight W_3

Calculate the ash as follows:

$$\% \text{ Ash} = \frac{(W_3 - W_1) \times 100}{(W_2 - W_1)}$$

Where
W_1 : Weight of platinum crucible in g
W_2 : Weight of platinum crucible with sample in g
W_3 : Weight of platinum crucible with residue in g

03. Dispersion:

Reference: Inhouse

Place about 10.0 g of powder sample on to 600 micrometer testing sieve. (US Sieve no. 30)

Shake sieve to allow the powder to fall through.

Check the following in the material that has been retained on the sieve.

A) Foreign matter : Should be absent
B) Undispersed pigments: Not more than 2 specks should be observed.
C) Small, soft, uniform size particles (If observed): They should easily break.
D) Hard lumps (If observed): They should disperse in water.

04. Identification:

Titanium dioxide:

Reference: Inhouse

Procedure:

Test solution: Mix 0.500 g substance being examined with 5 g of anhydrous sodium sulphate in a crucible, mix the contents and add 5.0 mL of sulphuric acid and boil vigorously, until ash is obtained. Cool it, add 10.0 mL slowly a cooled mixture of water: sulphuric acid (30: 10). Cool again and transfer into 100 mL volumetric flask and dilute to volume with water. Filter the solution with Whatman No.1 filter paper.

To 5.0 mL of above filtrate solution, add 0.5 mL of strong hydrogen peroxide solution (30%).

A yellow /orange colour should be produced.

2.1.P.4.3 Validation of Analytical Procedures

Not applicable.

2.1.P.4.4 Justification of Specifications

Not applicable.

2.1.P.4.5 Excipients of Human or Animal Origin

None of the excipients are of animal or human origin.

2.1.P.4.6 Novel Excipients

No novel excipients are employed in the manufacture of Hydroxychloroquine sulfate tablets.

2.1.P.5 CONTROL OF PLACEBO PRODUCT

2.1.P.5.1 Specification(s)

Table 5 Specification for Hydroxychloroquine Sulfate Placebo Tablets

Tests	Specification		Method reference
	Release	Shelf life	
Description	White to off-white, plain, 9mm, round, biconvex, film-coated tablets	White to off-white, plain, 9mm, round, biconvex, film-coated tablets	081
Description Comparison	Tablets are visually similar to Hydroxychloroquine Sulfate 200mg film coated tablets	Tablets are visually similar to Hydroxychloroquine Sulfate 200mg film coated tablets	1858
Thickness	4.40 -4.70mm	4.40 -4.70mm	083
Disintegration	Not more than 15 minutes	Not more than 15 minutes	087
Absence of Hydroxychloroquine	Less than 0.05% (LOQ)	Less than 0.05% (LOQ)	1850
Microbial examination *	A) Microbial enumeration test: i) Total Aerobic Microbial Count: Not more than 10^3 cfu /g ii) Total Combined Yeasts and Moulds Count: Not more than 10^2 cfu /g B) Test for specified micro-organism: i) *Escherichia coli*: Should be absent	A) Microbial enumeration test: i) Total Aerobic Microbial Count: Not more than 10^3 cfu /g ii) Total Combined Yeasts and Moulds Count: Not more than 10^2 cfu /g B) Test for specified micro-organism: i) *Escherichia coli*: Should be absent	Ph. Eur. <2.6.12 & 2.6.13>

2.1.P.5.2 Analytical Procedures

The compendial procedures used for testing are performed in accordance with compendial requirements.
The in-house analytical methods are described below.

2.1.P.5.2.1 Related Substances method 1850

Absence of Hydroxychloroquine is proven by testing as per the related substances procedure for Hydroxychloroquine 200mg tablets. This uses a pH3.5 buffer/acetonitrile gradient HPLC chromatography system. The column used is a Kromasil 100-5-C18, 250 x 4.6 mm, 5□m. Twenty whole tablets are sonicated for 15 minutes in acetonitrile/water (20/80), filtered and quantified against a Hydroxychloroquine sulfate reference standard.

2.1.P.7 CONTAINER CLOSURE SYSTEM

PVC 250µm film thermosealed to a 25 µm aluminium sheet.

2.1.P.8 STABILITY

A qualitative comparison of the test product and placebo formulations is shown below.

Name of Ingredient	Test Product	Placebo
Hydroxychloroquine Sulfate	✓	x
Lactose	✓	✓
Starch	✓	✓
Povidone K30	✓	x
Magnesium Stearate	✓	✓
Microcrystalline Cellulose 102	X	✓
Colloidal Silicon Dioxide	x	✓
Opadry II 85F18422 white	✓	✓

The placebo formulation comprises Lactose, Starch and Magnesium Stearate in common with the test product. In addition it contains Microcrystalline Cellulose 102 and Colloidal Silicon Dioxide. These are both common pharmaceutical excipients used in many Accord-UK Ltd tablet formulations with a shelf life of ≥36 months.

The shelf life of the test product is 30 months in line with the registered shelf life. The ingredients used in the placebo formulation provide confidence in the stability of the physical characteristics of the tablets. It is not expected that the physical appearance of the placebo tablets will deteriorate over a 30 month shelf life. For the purposes of this blinded study the placebo will be given a 30 month shelf life in line with the test product.

Amendment to shelf life

MA variation to replace Intas Pharmaceuticals Limited, India with Accord-UK Limited as Finished Product Manufacturer was approved 30/04/2020 and included a reduction in shelf life to 24 months.

The Clinical Trial Authorisation submission to AIFA was approved 24/04/2020 with a shelf life of 12 months to cover the duration of the study.

For the purposes of this IMPD, the shelf life is reduced from 30 months to 12 months to cover the duration of the study.