ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
Release Date: 12/09/2013

ClinicalTrials.gov ID: NCT01199965

Study Identification

Unique Protocol ID:	MAP0004-CL-P203
Brief Title:	Pharmacokinetics & Tolerability Study of MAP0004 in Smoking and Non-Smoking Adult Volunteers
Official Title:	An Open-Label, 2-Period, Crossover Phase 2 Study Comparing the Pharmacokinetics and Tolerability of Dihydroergotamine Mesylate (DHE) Delivered Intravenously (DHE 45) and by Oral Inhalation (MAP0004) in Smoking and Non-Smoking Adult Volunteers
Secondary IDs:	

Study Status

Record Verification:	December 2013
Overall Status:	Completed
Study Start:	January 2010
Primary Completion:	April 2010 [Actual]
Study Completion:	April 2010 [Actual]

Sponsor/Collaborators

Sponsor:	Allergan
Responsible Party:	Sponsor
Collaborators:	MAP Pharmaceuticals, Inc., a wholly owned subsidiary of Allergan

Oversight

FDA Regulated?:	Yes

Applicable Trial?:	Section 801 Clinical Trial? No Delayed Posting? No
IND/IDE Protocol?:	No
Review Board:	Approval Status: Approved Approval Number: 09/WSE02/55 Board Name: South East Wales Research Ethics Committee Panel B Board Affiliation: South East Wales Research Ethics Committee Panel B Phone: 02920 376823 Email: carl.phillips@bsc.wales.nhs.uk
Data Monitoring?:	No
Plan to Share Data?:	
Oversight Authorities:	United States: Institutional Review Board United Kingdom: Medicines and Healthcare Products Regulatory Agency

Study Description

Brief Summary:	Compare the pharmacokinetics of Dihydroergotamine Mesylate (DHE) delivered by oral inhalation (MAP0004) or Intravenous (IV) DHE in smokers versus non-smokers. Identify whether there are clinically significant differences in the tolerability of MAP0004 between smokers and non-smokers.
Detailed Description:	

Conditions

Conditions:	Healthy Subjects
Keywords:	

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 1/Phase 2
Intervention Model:	Crossover Assignment
Number of Arms:	2
Masking:	Open Label

Allocation:	Randomized
Endpoint Classification:	Pharmacokinetics Study
Enrollment:	47 [Actual]

Arms and Interventions

Arms	Assigned Interventions
IV DHE then MAP0004 Smokers and non-smokers received Intravenous Dihydroergotamine Mesylate (IV DHE) at Visit 2 followed by MAP0004 7-11 days later at Visit 3.	Drug: MAP0004 1.0mg MAP0004 via inhalation at Visit 2 or 3 as per protocol Drug: IV DHE IV DHE administered at Visit 2 or 3 as per protocol Other Names: • D.H.E.45®
MAP0004 then IV DHE Smokers and non-smokers received MAP0004 at Visit 2 followed by Intravenous Dihydroergotamine Mesylate (IV DHE) 7-11 days later at Visit 3.	Drug: MAP0004 1.0mg MAP0004 via inhalation at Visit 2 or 3 as per protocol Drug: IV DHE IV DHE administered at Visit 2 or 3 as per protocol Other Names: • D.H.E.45®

Outcome Measures

[See Results Section.]

Eligibility

Minimum Age:	18 Years
Maximum Age:	45 Years
Gender:	Both
Accepts Healthy Volunteers?:	Yes
Criteria:	Major Inclusion Criteria:

1. Able to provide written informed consent
2. Male or Female subjects 18 to 45 years old
3. Female subjects who are practicing adequate contraception or who are sterile
4. Stable cardiac status
5. Normal rhythm or arrhythmia deemed clinically insignificant on ECG

Major Exclusion Criteria:

1. Contraindication to dihydroergotamine mesylate (DHE)
2. Use of any excluded concomitant medications within the 10 days prior to Visit 1 (See Section 5.5)
3. History of hemiplegic or basilar migraine
4. Participation in another investigational trial during the 30 days prior to Visit 1 or during this trial

Contacts/Locations

Study Officials:

Locations: United Kingdom
Simbec Research Limited
Merthyr Tydfil, Merthyr Tydfil, United Kingdom, CF48 4DR

References

Citations:

Links:

Study Data/Documents:

Study Results

Participant Flow

Pre-Assignment Details	All smoking and non-smoking subjects received both MAP0004 and Intravenous (IV) Dihydroergotamine (DHE).

Reporting Groups

	Description
Smokers	Currently smoking at least 10 cigarettes/day for at least 1 year with a positive urinary cotinine result.
Non-smokers	Never smoked or total exposure <1 pack year and at least 12 months since last cigarette with a negative urinary cotinine result at screening.

Overall Study

	Smokers	Non-smokers
Started	23	24
Completed	22	24
Not Completed	1	0

Baseline Characteristics

Reporting Groups

	Description
Smokers	Currently smoking at least 10 cigarettes/day for at least 1 year with a positive urinary cotinine result.
Non-smokers	Never smoked or total exposure <1 pack year and at least 12 months since last cigarette with a negative urinary cotinine result at screening.

Baseline Measures

	Smokers	Non-smokers	Total
Number of Participants	23	24	47
Age, Continuous [units: years] Mean (Standard Deviation)	32.91 (7.1)	30.71 (8.8)	31.79 (8)
Gender, Male/Female [units: participants]			
Female	15	16	31
Male	8	8	16

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Cmax of Dihydroergotamine After MAP0004 and IV DHE Administration in Smokers Versus Non-smokers
Measure Description	The maximum concentration (Cmax) is the highest concentration of a drug measured in the plasma. Plasma is the clear portion of the blood. The Cmax of Dihydroergotamine is reported in picograms per milliliter (pg/ml).
Time Frame	48 hours
Safety Issue?	No

Analysis Population Description

Patients with available data at specified time points are included in the analysis population.

Reporting Groups

	Description
MAP0004 1.0mg Smokers	Currently smoking at least 10 cigarettes/day for at least 1 year with a positive urinary cotinine result and receiving MAP0004 at either Visit 2 or 3.
MAP0004 1.0mg Non-smokers	Never smoked or total exposure <1 pack year and at least 12 months since last cigarette with a negative urinary cotinine result at screening and receiving MAP0004 at either Visit 2 or 3.
IV DHE 1.0mg Smokers	Currently smoking at least 10 cigarettes/day for at least 1 year with a positive urinary cotinine result and receiving IV DHE at either Visit 2 or 3.
IV DHE 1.0mg Non-smokers	Never smoked or total exposure <1 pack year and at least 12 months since last cigarette with a negative urinary cotinine result at screening and receiving IV DHE at either Visit 2 or 3.

Measured Values

	MAP0004 1.0mg Smokers	MAP0004 1.0mg Non-smokers	IV DHE 1.0mg Smokers	IV DHE 1.0mg Non-smokers
Number of Participants Analyzed	22	24	22	24
Cmax of Dihydroergotamine After MAP0004 and IV DHE Administration in Smokers Versus Non-smokers [units: pg/ml] Geometric Mean (Standard Deviation)	1282.059 (636.138)	2550.727 (1297.097)	60046.128 (49580.385)	48428.635 (43894.253)

2. Primary Outcome Measure:

Measure Title	AUC(0-48) of Dihydroergotamine After MAP0004 and IV DHE Administration in Smokers and Non-smokers
Measure Description	The AUC(0-48) is the area under the plot of plasma concentration of drug against time after drug administration. Dihydroergotamine AUC(0-48) is reported in picograms times hour per milliliter (pg*h/ml).
Time Frame	48 hours
Safety Issue?	No

Analysis Population Description

Patients with available data at specified time points are included in the analysis population.

Reporting Groups

	Description
MAP0004 1.0mg Smokers	Currently smoking at least 10 cigarettes/day for at least 1 year with a positive urinary cotinine result and receiving MAP0004 at Visit 2 or 3.
MAP0004 1.0mg Non-smokers	Never smoked or total exposure <1 pack year and at least 12 months since last cigarette with a negative urinary cotinine result at screening and receiving MAP0004 at Visit 2 or 3.
IV DHE 1.0mg Smokers	Currently smoking at least 10 cigarettes/day for at least 1 year with a positive urinary cotinine result and receiving IV DHE at Visit 2 or 3.
IV DHE 1.0mg Non-smokers	Never smoked or total exposure <1 pack year and at least 12 months since last cigarette with a negative urinary cotinine result at screening and receiving IV DHE at Visit 2 or 3.

Measured Values

	MAP0004 1.0mg Smokers	MAP0004 1.0mg Non-smokers	IV DHE 1.0mg Smokers	IV DHE 1.0mg Non-smokers
Number of Participants Analyzed	23	24	22	24
AUC(0-48) of Dihydroergotamine After MAP0004 and IV DHE Administration in Smokers and Non-smokers [units: pg*h/ml] Geometric Mean (Standard Deviation)	3014.968 (1136.162)	4148.750 (1533.861)	11049.027 (3744.094)	11731.639 (3167.828)

Reported Adverse Events

Time Frame	[Not specified]
Additional Description	All 24 non-smoking subjects who received MAP0004 and IV DHE and 23 smoking subjects who received MAP0004 and 22 of the 23 smoking subjects received IV DHE were included in the adverse event analysis.

Reporting Groups

	Description
MAP0004 1.0mg Smokers	Currently smoking at least 10 cigarettes/day for at least 1 year with a positive urinary cotinine result and receiving MAP0004 at either Visit 2 or 3.
MAP0004 1.0mg Non-smokers	Never smoked or total exposure <1 pack year and at least 12 months since last cigarette with a negative urinary cotinine result at screening and receiving MAP0004 at either Visit 2 or 3.

	Description
IV DHE 1.0mg Smokers	Currently smoking at least 10 cigarettes/day for at least 1 year with a positive urinary cotinine result and receiving IV DHE at either Visit 2 or 3.
IV DHE 1.0mg Non-smokers	Never smoked or total exposure <1 pack year and at least 12 months since last cigarette with a negative urinary cotinine result at screening and receiving IV DHE at either Visit 2 or 3.

Serious Adverse Events

	MAP0004 1.0mg Smokers	MAP0004 1.0mg Non-smokers	IV DHE 1.0mg Smokers	IV DHE 1.0mg Non-smokers
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	0/23 (0%)	0/24 (0%)	0/22 (0%)	0/24 (0%)

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	MAP0004 1.0mg Smokers	MAP0004 1.0mg Non-smokers	IV DHE 1.0mg Smokers	IV DHE 1.0mg Non-smokers
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Total	4/23 (17.39%)	8/24 (33.33%)	15/22 (68.18%)	22/24 (91.67%)
Gastrointestinal disorders				
Diarrhoea [A] †	0/23 (0%)	0/24 (0%)	1/22 (4.55%)	2/24 (8.33%)
Nausea [A] †	1/23 (4.35%)	0/24 (0%)	5/22 (22.73%)	9/24 (37.5%)
Vomiting [A] †	0/23 (0%)	0/24 (0%)	2/22 (9.09%)	5/24 (20.83%)
General disorders				
Chest discomfort [A] †	0/23 (0%)	0/24 (0%)	2/22 (9.09%)	3/24 (12.5%)
Fatigue [A] †	0/23 (0%)	1/24 (4.17%)	2/22 (9.09%)	0/24 (0%)
Feeling hot [A] †	0/23 (0%)	0/24 (0%)	0/22 (0%)	2/24 (8.33%)
Infections and infestations				
Rhinitis [A] †	0/23 (0%)	2/24 (8.33%)	0/22 (0%)	1/24 (4.17%)
Musculoskeletal and connective tissue disorders				
Back pain [A] †	1/23 (4.35%)	1/24 (4.17%)	2/22 (9.09%)	0/24 (0%)

	MAP0004 1.0mg Smokers	MAP0004 1.0mg Non-smokers	IV DHE 1.0mg Smokers	IV DHE 1.0mg Non-smokers
	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)	Affected/At Risk (%)
Neck pain [A] †	0/23 (0%)	2/24 (8.33%)	1/22 (4.55%)	4/24 (16.67%)
Pain in extremity [A] †	0/23 (0%)	0/24 (0%)	3/22 (13.64%)	2/24 (8.33%)
Nervous system disorders				
Dizziness [A] †	1/23 (4.35%)	1/24 (4.17%)	6/22 (27.27%)	2/24 (8.33%)
Headache [A] †	2/23 (8.7%)	2/24 (8.33%)	6/22 (27.27%)	10/24 (41.67%)
Paraesthesia [A] †	0/23 (0%)	2/24 (8.33%)	1/22 (4.55%)	2/24 (8.33%)
Respiratory, thoracic and mediastinal disorders				
Epistaxis [A] †	0/23 (0%)	0/24 (0%)	0/22 (0%)	2/24 (8.33%)
Vascular disorders				
Flushing [A] †	0/23 (0%)	0/24 (0%)	2/22 (9.09%)	5/24 (20.83%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA (11.1)

Limitations and Caveats

[Not specified]

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

A disclosure restriction on the PI is that the sponsor can review results communications prior to public release and can embargo communications regarding trial results for a period that is less than or equal to 90 days from the time submitted to the sponsor for review. The sponsor cannot require changes to the communication and cannot extend the embargo.

Results Point of Contact:

Name/Official Title: VP, Scientific Affairs
Organization: MAP Pharmaceuticals Inc., a wholly owned subsidiary of Allergan

Phone: 650-386-3100
Email: dkellerman@mappharma.com