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**204708Orig1s000**

**PHARMACOLOGY REVIEW(S)**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION**

Application number: 204708  
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Product: MIRVASO (brimonidine tartrate) Gel, 0.5%  
Indication: Facial erythema of rosacea  
Applicant: Galderma Research and Development, Inc.,  
Cranbury, NJ  
Review Division: Dermatology and Dental Products  
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# 1 Executive Summary

## 1.1 Introduction

Brimonidine tartrate is an alpha adrenergic receptor agonist. Brimonidine tartrate ophthalmic solutions, 0.1%, 0.15%, 0.2%, and 0.5%, (ALPHAGAN<sup>®</sup> and ALPHAGAN P<sup>®</sup>) have been approved for the treatment of glaucoma and ocular hypertension [NDAs 20613 (discontinued), 20490 (discontinued), 21262, and 21770]. The sponsor intends to develop MIRVASO (brimonidine tartrate) Gel, 0.5% for the treatment of facial erythema of rosacea through the 505(b)(2) regulatory pathway. The sponsor proposed to rely upon the Agency's finding of safety and effectiveness for the approved listed drug ALPHAGAN<sup>®</sup>, 0.2%, (NDA 20613) to support some nonclinical portions of this application. The listed drug was discontinued from marketing, but not for reasons of safety or effectiveness. In their clinical bridge study the sponsor used a generic drug product (ANDA 76260) as the comparator.

## 1.2 Brief Discussion of Nonclinical Findings

Brimonidine tartrate is a relatively selective alpha-2 alpha adrenergic receptor agonist. The therapeutic effect of brimonidine tartrate on facial erythema of rosacea might be due to its vasoconstriction activity.

The sponsor proposed to rely upon the Agency's finding of safety for the approved listed drug ALPHAGAN<sup>®</sup> ophthalmic solution, 0.2% to support some nonclinical portions of this 505(b)(2) application. The systemic exposure of once daily maximum clinical use of MIRVASO Gel, 0.5% (b)(4) applied to the entire face) was less than that of brimonidine tartrate ophthalmic solution 0.2% at its approved dose of 1 drop into each eye TID.

In addition to relying upon the Agency's finding of safety on the listed drug, including information regarding genetic toxicity, reproductive toxicity, and oral carcinogenicity, the sponsor also conducted pivotal repeat dose dermal toxicity studies in rats and minipigs, a photo-carcinogenicity study in hairless mice, a dermal rat carcinogenicity study, and several special toxicology studies.

In a chronic dermal toxicity study in minipigs, topical doses of 0 (water), 0 (vehicle), 1.2, 3.6, and 20 mg/kg/day brimonidine tartrate (0.06%, 0.18%, and 1% gel, 2 ml/kg) were administered once daily for 39 weeks. There were no significant treatment-related effects on body weight, ophthalmology, cardiovascular parameters, hematology, clinical chemistry, urinalysis, gross pathology, or histopathology. The NOAEL was identified as the high dose, 20 mg/kg/day (1% gel, 2 ml/kg/day).

In a 57-week dermal toxicity study in rats, topical doses of 0 (water), 0 (vehicle), 5.4, 30, and 60 mg/kg/day brimonidine tartrate (0.18%, 1%, and 2% gel, 3 ml/kg) were administered till Week 14. All the animals were put on a ~3-week dosing holiday due to decreases in body weight gain. When the study resumed, doses were reduced to 1.1,

6, and 12 mg/kg/day for males (dose volume reduced to 0.6 ml/kg), but remained unchanged for females. Treatment-related mortality was noted in high dose males and females. Body weight gain was lower in mid dose and high dose males, and in females at all dose levels. Lymphoid depletion in thymus was noted at high dose. Considering the dosing holiday and the decrease in body weight gain seen at all dose levels, a NOAEL was not identified in this study.

In the two chronic dermal toxicology studies, the 39-week dermal minipig study is considered more relevant in the safety assessment due to the similarity between human skin and minipig skin. In addition, the treatment duration of the dermal rat study (57 weeks) was much longer than the duration of a typical chronic toxicology study in rodents (6 months). In the dermal rat study, there were no significant histopathological findings except lymphoid depletion noted only at high dose. The multiple of human exposure based on AUC comparison between the NOAEL in the chronic dermal minipig study and the maximum clinical dose is 11.

A series of *in vitro* and *in vivo* genotoxicity tests were conducted with brimonidine tartrate and revealed no genotoxic potential. There was no concern for genotoxicity for brimonidine tartrate.

In a 21-month oral (diet) mouse carcinogenicity study and a 24-month oral (diet) rat carcinogenicity study, no drug-related carcinogenic effects were observed at oral doses up to 2.5 mg/kg/day in mice or up to 1 mg/kg/day in rats.

In a dermal rat carcinogenicity study with MIRVASO gel, brimonidine tartrate was administered at topical doses up to 5.4 mg/kg/day (0.18% gel) in males and 60/21.6 mg/kg/day (2% gel during Days 1-343 and 0.72% gel thereafter) in females once daily for 24 months. No drug-related carcinogenic effects were observed in this study. The multiple of human exposure is 512, when comparing  $AUC_{0-24h}$  obtained at the high dose tested in this study with that in human subjects obtained under maximum clinical use conditions.

In a 12-month dermal photo-carcinogenicity study, topical doses of 0% (vehicle), 0.18%, 1% and 2% brimonidine tartrate gel were administered to hairless albino mice once daily, five days per week, with concurrent exposure to simulated sunlight. No drug-related adverse effects were observed in this study. The results of this study suggest that topical treatment with MIRVASO Gel would not enhance photo-carcinogenesis.

Brimonidine tartrate was not teratogenic when administered during gestation at oral doses up to 2.5 mg/kg/day in pregnant rats and up to 5 mg/kg/day in pregnant rabbits. Reproduction and fertility studies in rats with brimonidine tartrate demonstrated no adverse effects on male or female fertility at oral doses up to 1 mg/kg/day.

Brimonidine tartrate gel (up to 2%) did not show irritancy or phototoxicity in hairless mice. MIRVASO Gel 0.5% is a nonirritant to rabbit eye. Brimonidine tartrate gel 2.0% did not show a skin sensitization potential in guinea pigs.

The toxicity profile of brimonidine tartrate gel has been well characterized. Based on the Agency's finding of safety and conducted nonclinical studies with brimonidine tartrate gel, overall there was no significant safety concern for MIRVASO Gel, 0.5%, at the proposed clinical dose. No postmarketing requirement is recommended for this NDA.

### 1.3 Recommendations

#### 1.3.1 Approvability

NDA 204708 for MIRVASO (brimonidine tartrate) Gel, 0.5% is approvable from a pharmacological/toxicological perspective, provided that the recommended changes in the label described in Section 1.3.3 are incorporated into the MIRVASO Gel label.

#### 1.3.2 Additional Non Clinical Recommendations

None.

#### 1.3.3 Labeling

It is recommended that the underlined wording be inserted into and the ~~strikeout~~ wording be deleted from the MIRVASO Gel label reproduced below. The pharmacologic class designation for MIRVASO is alpha adrenergic agonist. This is an established pharmacologic class.

### HIGHLIGHTS OF PRESCRIBING INFORMATION INDICATIONS AND USAGE

MIRVASO (brimonidine tartrate) Gel, (b) (4) % is an alpha (b) (4) adrenergic agonist indicated for the topical treatment of facial erythema of rosacea in adults 18 years of age or older.

#### 8.1 Pregnancy

(b) (4) Pregnancy Category B.

There are no adequate and well-controlled studies of MIRVASO Gel in pregnant women. In animal studies, brimonidine crossed the placenta and entered into the fetal circulation to a limited extent. MIRVASO Gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Brimonidine tartrate was not teratogenic when given at oral doses up to 2.5 mg/kg/day in pregnant rats during gestation days 6 through 15 and 5 mg/kg/day in pregnant rabbits during gestation days 6 through 18. (b) (4)

(b) (4)

### 8.3 Nursing Mothers

It is not known whether brimonidine tartrate is excreted in human milk, although in animal studies, brimonidine tartrate (b) (4) has been shown to be excreted in breast milk (b) (4)

Because of the potential for serious adverse reactions from MIRVASO Gel in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

### 12.1 Mechanism of Action

Brimonidine is a relatively (b) (4) selective alpha-2 adrenergic agonist (b) (4)

Topical facial application of (b) (4) MIRVASO Gel may reduce erythema through direct vasoconstriction.

### 13.1 Carcinogenesis. Mutagenesis. Impairment of Fertility

(b) (4)

In a 21-month oral (diet) mouse carcinogenicity study and a 24-month oral (diet) rat carcinogenicity study, no drug-related neoplasms were observed in mice at oral doses of brimonidine tartrate up to 2.5 mg/kg/day or in rats at oral doses of brimonidine tartrate up to 1 mg/kg/day.

In a dermal rat carcinogenicity study with MIRVASO gel, brimonidine tartrate was administered to Wistar rats at topical doses of 0.9 (0.03% gel), 1.8 (0.06% gel), and 5.4 mg/kg/day (0.18% gel) in males and 5.4 (0.18% gel), 30 (1% gel) during Days 1-

343/10.8 (0.36% gel) thereafter, and 60 (2% gel) during Days 1-343/21.6 mg/kg/day (0.72% gel) thereafter in females once daily for 24 months. No drug-related neoplasms were observed in this study.

In a 12-month dermal photo-carcinogenicity study, topical doses of 0% (MIRVASO Gel vehicle), 0.18%, 1% and 2% brimonidine tartrate gel were administered to hairless albino mice once daily, five days per week, with concurrent exposure to simulated sunlight. No drug-related adverse effects were observed in this study. The results of this study suggest that topical treatment with MIRVASO Gel would not enhance photo-carcinogenesis.

Brimonidine tartrate was not mutagenic or clastogenic in a series of *in vitro* and *in vivo* studies, including the Ames test, a chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells, and three studies in CD1 mice (a host-mediated assay, a cytogenetic study, and a dominant lethal assay).

Reproduction and fertility studies in rats with brimonidine tartrate demonstrated no adverse effects on male or female fertility at oral doses up to 1 mg/kg/day.

## 2 Drug Information

### 2.1 Drug

CAS Registry Number: 70359-46-5; 79570-19-7

Generic Name: Brimonidine tartrate

Code Name: COL-118, CD07805/47

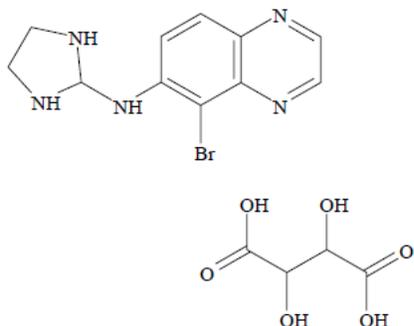
Chemical Name:

- (1) 5-bromo-N-(4, 5-dihydro-1H-imidazol-2-yl)-6-quinoxalinamine L-tartrate
- (2) 5-bromo-N-(4, 5-dihydro-1H-imidazol-2-yl)-6-quinoxalinamine (2R, 3R)-2,3-dihydroxybutanedioate (1:1)
- (3) 5-bromo-6-(2-imidazolylideneamino) quinoxaline L-tartrate

Molecular Formula/Molecular Weight:

C<sub>11</sub>H<sub>10</sub>BrN<sub>5</sub>•C<sub>4</sub>H<sub>6</sub>O<sub>6</sub> / 442.24/292.14 (as base)

Structure or Biochemical Description:



Pharmacologic Class: alpha adrenergic agonist (an established class)

## 2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA 20490	Alphagan (brimonidine tartrate ophthalmic solution/drops 0.5%), discontinued, by Allergan
NDA 20613	Alphagan (brimonidine tartrate ophthalmic solution/drops 0.2%), discontinued, by Allergan
NDA 21262	Alphagan P (brimonidine tartrate ophthalmic solution/drops 0.15%), by Allergan
NDA 21770	Alphagan P (brimonidine tartrate ophthalmic solution/drops 0.1%), by Allergan
ANDA 76260	Brimonidine tartrate ophthalmic solution/drops 0.2%, by Bausch and Lomb
IND 74841	COL-118 (brimonidine tartrate) topical gel, by Galderma Research and Development

## 2.3 Drug Formulation

The composition of MIRVASO (brimonidine tartrate) Gel, 0.5%, is listed in the following table.

Components	Function	Percent (w/w)	mg/g	Reference to Quality Standards
<b>Active Component</b>				
Brimonidine tartrate	Active ingredient	0.5	5	In-house <sup>a</sup>
<b>Excipients</b>				
(b) (4)	(b) (4)			NF
(Carbomer Homopolymer Type B)				NF
Methylparaben				NF
Phenoxyethanol				NF
Glycerin				USP
Titanium dioxide				USP
Propylene glycol				USP
Sodium hydroxide				NF
Purified water				USP

Qs=Quantum satis (as much needed to achieve target); NF=National Formulary; USP=United States Pharmacopeia.

<sup>a</sup> No monograph for brimonidine tartrate exists in the USP or European Pharmacopoeia (Ph. Eur.).

*Note:* The MIRVASO Gel contains 0.5% brimonidine tartrate, equivalent to 0.33% brimonidine (base).

## 2.4 Comments on Novel Excipients

There are no novel excipients. All the inactive ingredients are below approved levels listed in the FDA's database of inactive ingredients in approved drug products.

## 2.5 Comments on Impurities/Degradants of Concern

None.

## 2.6 Proposed Clinical Population and Dosing Regimen

Clinical population: Patients with facial erythema of rosacea, 18 years of age and older.  
Dosing regimen: Apply a small pea-size amount once daily to each of the five areas of the face (i.e., forehead, chin, nose, each cheek) avoiding the eyes and lips.

The maximum clinical dose that has been tested in a maximum use clinical PK study was 1 g MIRVASO Gel, 0.5%, applied to the entire face once daily for 29 days.

## 2.7 Regulatory Background

Brimonidine tartrate gel was initially developed by CollaGenex Pharmaceuticals, Inc., under the code name COL-118. The sponsor acquired the company in April 2008 and subsequently changed the code name to CD07805/47.

Exec CAC meetings were conducted on 01/28/2008, 03/03/2009, and 03/26/2013.

Division meetings conducted under IND 74841 were:

PreIND meeting 08/09/2006, Guidance meeting 10/31/2007, End of Phase 2 meeting 03/10/2008, Guidance meeting 12/03/2008, Guidance meeting 04/27/2010, PreNDA meeting 05/16/2012, and Guidance meeting 06/27/2012.

### 3 Studies Submitted

#### 3.1 Studies Reviewed

##### Pharmacokinetic studies:

1. Full validation of an LC-MS/MS assay for brimonidine in rat sodium heparin plasma (Study# RDS.03.VRE.34198)
2. Bioanalytical method for determination of CD07805 in minipig plasma samples by HPLC with ESI-MS/MS detection – Validation (Study# RDS.03.VRE.34213)

##### Repeat Dose Toxicology Studies:

1. Thirteen-week topical range-finding study of COL-118 in hairless mice, with or without simulated sunlight (Study# IYA00018, Sponsor Ref# RDS.03.SRE.12627)
2. A 90-day repeat dose dermal study in rats with a 4-week interim biopsy and a 4-week recovery period (Study# MB 07-15233.03)
3. CD07805/47: A 13-week dermal dose range-finding study in rats (Study# 1505-005, Sponsor Ref# RDS.03.SPR.12648)
4. CD07805/47: A 57-week dermal chronic study in rats (Study# 1505-002, Sponsor Ref# RDS.03.SRE.12626)
5. A 13-week toxicity study of brimonidine tartrate administered by dermal application to Göttingen minipigs with a 4-week recovery period (Study# IYA00006)
6. CD07805/47: 39-week topical (dermal application) toxicity study in the Göttingen minipig (Study# AA84352, Sponsor Ref# RDS.03.SRE.12694)

##### Carcinogenicity Studies:

1. Twelve-month topical study to determine the influence of CD07805/47 and CD07805/47 vehicle on photocarcinogenesis in hairless mice (Study# IYA00019, Sponsor Ref# RDS.03.SRE.12629)
2. CD07805/47: A 2-year dermal carcinogenicity study in Wistar Han rats (Study# 1628-003, Sponsor Ref# RDS.03.SPR.12667)

##### Special toxicology studies:

1. Single administration topical primary irritancy and phototoxicity screening test of COL-118 in hairless mice (Study# IYA00013)
2. CD07805/47 0.5% Gel: Primary eye irritation study in rabbits (Study# C96585, Sponsor Ref# RDS.03.SRE.12734)

3. Delayed contact dermal sensitization test-Buehler method (Study# MB 07-15969.06)

### **3.2 Studies Not Reviewed**

None.

### **3.3 Previous Reviews Referenced**

- Nonclinical review, IND 74841, by Dr. Kumar Mainigi, dated 08/23/2007
- Nonclinical review, IND 74841, by Dr. Paul Brown, dated 02/07/2008
- Nonclinical reviews, IND 74841, by this reviewer, dated 03/05/2009, 07/29/2010, 09/24/2010, 12/08/2010, 09/28/2011, 05/10/2012, and 03/01/2012

## **4 Pharmacology**

### **4.1 Primary Pharmacology**

No pharmacology data were submitted to the NDA. Brimonidine tartrate is a relatively selective alpha-2 adrenergic receptor agonist, which was primarily used in the treatment of open-angle glaucoma and ocular hypertension. In the eye, alpha-2 adrenergic receptor agonists reduce aqueous humor production by ciliary body and hence decrease intraocular pressure.

Brimonidine tartrate, as an alpha adrenergic receptor agonist, has vasoconstriction activity. This activity may lead to reduction in erythema in patients with rosacea.

### **4.2 Secondary Pharmacology**

None.

### **4.3 Safety Pharmacology**

No safety pharmacology data were submitted to the NDA. Previous review under IND 74841 (dated 08/23/2007) indicated that in humans, brimonidine exhibited minimal side effects on heart rate and blood pressure. Its effect on the function of central nervous system is also minimal.

## **5 Pharmacokinetics/ADME/Toxicokinetics**

### **5.1 PK/ADME**

No PK studies were performed with MIRVASO Gel. The sponsor has developed and validated bioanalytical methods to quantify brimonidine in rat and minipig plasma samples to perform toxicokinetic analyses in dermal toxicity studies. An LC-MS/MS

assay was validated for the measurement of brimonidine in rat plasma (limit of quantification: 0.025 ng/ml). A HPLC with ESI-MS/MS assay was validated for the measurement of brimonidine in minipig plasma (limit of quantification: 0.025 ng/ml).

According to Dr. An-Chi Lu, the clinical pharmacology reviewer, the maximum clinical dose tested in a maximum use clinical PK trial was 1 g MIRVASO Gel, 0.5%, applied to the entire face once daily for 29 days. The maximum systemic exposure was achieved on Day 18 of the trial (after the 15<sup>th</sup> application), with  $C_{max}$  of  $46.2 \pm 61.5$  pg/ml and  $AUC_{0-24h}$  of  $417.3 \pm 263.6$  pg•hr/ml. The systemic exposure of once daily maximum clinical use of MIRVASO Gel, 0.5% (1 g applied to face) was less than that of brimonidine tartrate ophthalmic solution 0.2% at its approved dose of 1 drop into each eye TID. The ratio of  $AUC_{0-24h}$  between MIRVASO Gel and brimonidine tartrate ophthalmic solution was 71% on Day 18 and 63% on Day 32 (refer to the clinical pharmacology review for this NDA).

## 5.2 Toxicokinetics

Included in toxicology studies.

# 6 General Toxicology

## 6.1 Single-Dose Toxicity

None.

## 6.2 Repeat-Dose Toxicity

1. A 90-day repeat dose dermal study in rats with a 4-week interim biopsy and a 4-week recovery period (Study# MB 07-15233.03)

In a 90-day dermal toxicity study, Wistar rats (10/sex/group) received daily topical applications of 0.3 ml of the test material (gel and cream vehicle, 0.2%, 1.0%, and 2.0% gel and cream) on two pre-shaved dorsal sites each of ~10% body surface area (BSA), with gel (or gel vehicle) applied on one site and cream (or cream vehicle) applied on the opposite site at the same concentration. The vehicle composition was not described in the study report (all test materials were provided by the sponsor and used as received). On Day 7 the dose volume for high dose females was reduced to 0.15 ml and the treatment site was reduced to 5% BSA. On Day 91 surviving animals were sacrificed and histopathology was examined for skin only. At the end of treatment a significant decrease in body weight gain was noted in high dose animals (61% in males and 22% in females). No untreated control was included in this study. All groups including vehicle had some findings of erythema and edema at the treated sites. Almost all the findings were observed at the cream-treated site and only a few were observed at the gel-treated sites. However, the incidence of erythema and edema did appear to increase in the drug treated animals compared to vehicle control. However, this study did not include clinical chemistry, hematology or histopathology of any tissues other

than skin. Therefore, systemic toxicity was not assessed. It was not clear if the 2% gel alone would be tolerated since it was not tested alone. This study was not considered adequate to support dose selection for a dermal carcinogenicity study (refer to review under IND 74841, 02/07/2008).

2. CD07805/47: A 13-week dermal dose range-finding study in rats (Study# 1505-005, Sponsor Ref# RDS.03.SPR.12648)

A 2-year dermal carcinogenicity study was initiated without concurrence from the Exec CAC. Part of that study generated data for a 13-week dermal rat dose range-finding study to support dose selection for a subsequent 2-year dermal carcinogenicity study, using data obtained from 10 animals/sex/group, which were sacrificed after 13 weeks of treatment. The dosing of the remaining animals was continued till up to 57 weeks and the data were reported as a 57-week chronic dermal toxicity study (19 or 20/sex/group were designated for necropsy and the remaining animals were used as needed for TK analysis on Day 400/401).

In the 13-week dermal rat study, topical doses of 0 (vehicle control), 5.4, 30, and 60 mg/kg brimonidine tartrate (0.18%, 1.0%, and 2.0% gel applied to 20% BSA at a dose volume of 3 ml/kg) were administered to Wistar rats (10/sex/group) once daily for 13 weeks. The vehicle composition was not described in the study report (all test materials were provided by the sponsor and used as received). A water control group was added ~5 weeks after the study initiation. No mortality was noted in this study. No treatment-related dermal irritation was noted in this study. A significant dose-dependent decrease in body weight gain was noted in males over the treatment period at all dose levels (17%, 33%, and 44% for low, mid and high dose groups, respectively, compared with vehicle control). A dose-dependent decrease in body weight gain was not noted in females, but a body weight gain decrease of 12% and 8% was noted in mid and high dose females when compared with vehicle control. A dose-dependent decrease in food consumption was noted in males but not in females. An increase in neutrophil count was noted in males (47%, 122%, and 105% for low, mid, and high dose groups) and females (87% and 114% for mid and high dose groups), when compared with vehicle control. An increase in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels was noted in males (21%, 47%, and 48% in low, mid, high dose groups for AST and 57% in mid and high dose groups for ALT) and females (33% and 62% in mid and high dose groups for AST and 50% in high dose group for ALT), when compared with vehicle control. No treatment-related significant macroscopic and microscopic findings were noted.

The maximum tolerated dose (MTD) in rats in the 13-week study is considered lower than 5.4 mg/kg/day (0.18% gel applied at 3 ml/kg) in males, based on significant body weight gain decrease at all dose levels. The MTD in females is considered close to the high dose tested, 60 mg/kg/day (2% gel applied at 3 ml/kg), based on minimal decrease in body weight gain (around 10%), plus significant alterations in clinical pathological parameters, such as the elevation of AST and ALT levels.

Systemic exposure to the test drug as indicated by AUC<sub>0-24</sub> was similar between male and female rats. There is no big difference between AUC<sub>0-24</sub> values in mid and high dose groups (refer to review under IND 74841, 03/05/2009).

Dose level	Sex	AUC <sub>0-24</sub> (ng.hr/ml)	C <sub>max</sub> (ng/ml)	T <sub>max</sub> (hr)
0.18%	M	386	63.7	4.0
	F	319	23.2	12.0
1%	M	2820	276	12.0
	F	2090	139	8.0
2%	M	2000	110	2.0
	F	2810	252	2.0

3. CD07805/47: A 57-week dermal chronic study in rats (Study# 1505-002, Sponsor Ref# RDS.03.SRE.12626)

The initial doses were described above in the 13-week dermal rat toxicity study. Due to decreases in body weight gain, male animals in the vehicle control, low dose, mid dose, and high dose groups were placed on a dosing holiday from Day 96 through Day 119. All animals in the water control group, and all females in the vehicle control, low dose, mid dose, and high dose groups were placed on a dosing holiday from Day 98 to Day 119. Following the dosing holiday, the dose volume for all males was reduced to 0.6 ml/kg for the remainder of the study, whereas the dose volume for all females remained unchanged (3 ml/kg).

Significant treatment-related mortality is noted at high dose (4/20 in males and 13/20 in females). The cause of death in most incidences was undetermined. Histopathological findings in the early deaths included gastro-intestinal ulceration in one high dose female, squamous cell carcinoma in one high dose male (in the treated skin region), uterus tumors in 2 water control females, and schwannoma in one low dose female. No significant dermal irritation was noted. Mean body weight gain over the entire treatment period was 24% and 32% lower in mid dose and high dose males, and was 19%, 14%, and 15% lower in low dose, mid dose, and high dose females, respectively, compared to the vehicle control group. At the end of treatment, a significant increase in neutrophil count was noted in mid dose and high dose males (57% and 88%) and in all treated females (65%, 139%, and 183% at low dose, mid dose, and high dose, respectively). Histopathology showed one mid dose male and two high dose males had primary hemangiosarcomas in the mesenteric lymph nodes. Minimal to severe generalized lymphoid depletion in thymus was noted in high dose males and females.

The carcinogenic potential of the test drug is evaluated in a 2-year dermal carcinogenicity study in rats (reviewed in Section 8). Considering the dosing holiday and the decrease in body weight gain seen at all three dose levels, a NOAEL is not identified in this study.

The TK parameters on Days 89 and 401 were measured (see the copied table below):

Day	Treatment (% CD07805/47)	Sex	AUC <sub>0-24</sub> (hr•ng/mL)	C <sub>max</sub> (ng/mL)	T <sub>max</sub> (hr)
89	0.18	M	386	63.7	4.00
		F	319	23.2	12.0
	1	M	2820	276	12.0
		F	2090	139	8.00
	2	M	2000	110	2.00
		F	2810	252	2.00
401	0.18	M	42.6	3.58	4.00
		F	208	27.2	2.00
	1	M	145	14.0	1.00
		F	964	57.7	4.00
	2	M	507	65.2	8.00
		F	2440	309	8.00

The increase in AUC was approximately dose proportional from low dose to mid dose. Day 89 AUC in mid dose and high dose animals were comparable. There was no drug accumulation when comparing AUC values on Day 89 and Day 401 in females (no dose change). The decrease in AUC values in males was due to the dose decrease after the dosing holiday (refer to review under IND 74841, 03/01/2012).

4. A 13-week toxicity study of brimonidine tartrate administered by dermal application to Göttingen minipigs with a 4-week recovery period (Study# IYA00006)

Topical doses of 0 (vehicle), 20, 100, and 200 mg/day brimonidine tartrate (5 g 0.2%, 1.0%, and 2.0% gel and 5 g 0.2%, 1.0%, and 2.0% cream, applied to the left and right dose sites, respectively, 10% BSA in total) were administered to minipigs (3/sex/group) once daily for 13 weeks, followed by a 4-week recovery period (2/sex/group for vehicle control and high dose groups). The vehicle composition was not described in the study report (all test materials were provided by the sponsor and used as received). Hematology and clinical chemistry was not examined in this study. Only skin (treated and untreated) was examined for histology. No mortality was observed. No significant effects on body weight were noted. Dermal observations (erythema, edema, blanching, desquamation, and scab) were generally seen in all groups, including control, and were not dose-related. There were no significant histopathological findings at the left dosing sites (gel). Inflammation, parakeratosis, pustules, epidermal hyperplasia, and/or epidermal hypergranulosis were noted in both cream- and vehicle cream-treated sites on Days 29 and 92. No significant histology findings were noted after the treatment-free period.

The cream formulation caused more dermal irritation (a vehicle effect) than the gel formulation. A dermal NOAEL was not identified and systemic toxicity was not adequately evaluated in this study (refer to review under IND 74841, 07/29/2010).

5. CD07805/47: 39-week topical (dermal application) toxicity study in the Göttingen minipig (Study# AA84352, Sponsor Ref# RDS.03.SRE.12694)

Topical doses of 0 (water), 0 (vehicle: same as the clinical vehicle), 1.2, 3.6, and 20 mg/kg/day brimonidine tartrate (0.06%, 0.18%, and 1% gel, applied to ~10% BSA, at 2 ml/kg) were administered to minipigs (4/sex/group) once daily, 6 hr per day, for 39 weeks. No mortality was noted. There were no significant treatment-related effects on body weight, food consumption, ophthalmology, cardiovascular parameters, hematology, clinical chemistry, urinalysis, gross pathology, or histopathology. The NOAEL was identified as the high dose tested, 20 mg/kg/day (1% gel applied at 2 ml/kg/day), under the study conditions.

TK analysis was conducted for blood samples collected on the first day of dosing (referred by the sponsor as Day 0) and on Day 272. Due to the high variability in individual plasma concentrations and numerous BLQ values, the TK interpretation is limited. The systemic exposure to brimonidine tartrate was higher on Day 272 than on Day 0. On Day 272, the systemic exposure increased with dose between 3.6 and 20 mg/kg/day. The TK parameters are shown in the copied table below (refer to reviews under IND 74841, 03/01/2012 and 05/10/2012).

Mean toxicokinetic parameters from treated groups were as follows:

Occasion	Dose (mg/kg/day)	Concentration (%)	Sex	C <sub>max</sub> (ng/mL)	T <sub>max</sub> <sup>a</sup> (h)	AUC <sub>0-24h</sub> (ng.h/mL)
Day 0	1.2	0.06	Male	NC1	NC1	NC1
			Female	NC2	NC2	NC2
	3.6	0.18	Male	NC1	NC1	NC1
			Female <sup>b</sup>	0.719	14	6.48
	20	1	Male	0.360	14	4.61
			Female	0.089	13	1.12
Day 272	1.2	0.06	Male	NC3	NC3	NC1
			Female	0.123	8	1.81
	3.6	0.18	Male	0.135	2.25	1.45
			Female	0.137	0.5	1.32
	20	1	Male	1.91	0 <sup>c</sup>	4.78
			Female	0.689	1.25	6.03

NC1: Not possible to calculate since 3 out of 4 animals presented only few or no quantifiable concentrations.

NC2: Not possible to calculate since all concentrations were BLQ for 3 out of 4 animals.

NC3: Values not calculated in the bioanalytical and toxicokinetic phase report.

<sup>a</sup>: Median values.      <sup>b</sup>: Only 2 animals with quantifiable concentrations.

<sup>c</sup>: Corresponding to 24h after the day 271 dosing.

- Thirteen-week topical range-finding study of COL-118 in hairless mice, with or without simulated sunlight (Study# IYA00018, Sponsor Ref# RDS.03.SRE.12627)

This study was conducted for the dose selection for a 12-month photocarcinogenicity study. Topical doses of 0 (untreated), 0 (vehicle), 0.18%, 1%, and 2% brimonidine tartrate gel were administered to Crl:SKH1-*hr* albino hairless mice (6/sex/group), with or without simulated sunlight exposure (see the two copied design tables below). The vehicle composition was not described in the study report (all test materials were provided by the sponsor and used as received).

Group	Mice per Sex per Group	Descriptor	Concentration (%)	Administration Volume (mcL/mouse)	Mouse Number	
					Male	Female
1	6	Untreated	N/A	N/A	1201 - 1206	1301, 3093, 1303 - 1306
2	6	Vehicle	0	200	1207 - 1212	1307 - 1312
3	6	COL-118	0.18	100	1213 - 1218	1313 - 1318
4	6	COL-118	1	100	1219 - 1224	1319 - 1324
5	6	COL-118	2	100	1225 - 1230	1325 - 1330
6	6	COL-118	2	200	1231 - 1236	1331 - 1336
7	6	Untreated	N/A	N/A	1237 - 1242	1337 - 1342
8	6	Vehicle	0	200	1243 - 1248	1343 - 1348
9	6	COL-118	0.18	100	1249 - 1254	1349 - 1354
10	6	COL-118	1	100	1255 - 1260	1355 - 1360
11	6	COL-118	2	100	1261 - 1266	1361 - 1366
12	6	COL-118	2	200	1267 - 1272	1367 - 1372

Group 1: Neither formulation administration nor UVR exposure.

Groups 2 through 6: Formulation administration only.

Group 7: UVR exposure only.

Groups 8 through 12: Both formulation administration and UVR exposure.

N/A - Not applicable

Group	Administration and UVR Exposure Mondays, Wednesdays, Fridays		Administration and UVR Exposure Tuesdays, Thursdays		RBU Per Week
	Formulation Pre-UVR	UVR (RBU)	UVR (RBU)	Formulation Post-UVR	
1	No	N/A	N/A	No	0
2 through 6	Yes	N/A	N/A	Yes	0
7	No	120	120	No	600
8 through 12	Yes	120	120	Yes	600

Group 1: Neither formulation administration nor UVR exposure.

Groups 2 through 6: Formulation administration only.

Group 7: UVR exposure only.

Groups 8 through 12: Both formulation administration and UVR exposure.

RBU: Robertson-Berger Units. A measure of effectiveness for UVR; 400 RBU approximates one minimal erythema dose in previously untanned human skin.

N/A - Not applicable

A 6.5 kilowatt xenon long arc, water cooled burner was used to generate simulated sunlight irradiation. The UVR dose level, 600 RBU per week, was based on the anticipated UVR dose level that was used in the chronic study designed to detect enhancement of photocarcinogenesis. Historical data indicate that this UVR dose level

produces a tumor median latent period that permits detection of photocarcinogenesis enhancement within the response range of the test system.

The test article or vehicle formulations were administered and the appropriate mice were irradiated once daily, 5 days per week, for 12 weeks and 4 days on Week 13. Formulation was administered to the back and sides (approximately 25 cm<sup>2</sup>) of appropriate mice 1 hr before daily UVR exposure on Monday, Wednesday and Friday, and 1 hr after UVR exposure on Tuesday and Thursday.

By Day 4 the groups (Groups 6 and 12) treated with 2% gel at a dose volume of 200 µl, with or without UVR exposure, showed adverse clinical signs including hyperactivity, hyperreactivity, dehydration, decreased motor activity, cold to touch, dyspnea, ataxia and/or hunched posture. The two groups were terminated on Day 8.

One male in Group 6 and two males in Group 11 died early and necropsy did not reveal obvious cause of death. All other mice survived to scheduled sacrifice. At the end of study, no significant treatment-related effects on body weight were noted. Repeat topical administration of brimonidine tartrate at concentrations of 0.18%, 1% or 2% at a dose volume of 100 µl resulted in no significant adverse skin reactions, with or without UVR exposure. Skinfold thickness measurements did not identify any adverse effects, with or without UVR exposure. Groups of mice treated with 1% and 2% gel at a dose volume of 100 µl exhibited hyperactivity and hyperreactivity, but the extent of these reactions were not to a degree that would adversely affect the photocarcinogenesis response in a full study.

*Reviewer's comment:* Per the ICH M3(R2) guidance document, we no longer recommend conduct of photocarcinogenicity studies for topical drug products. However, the recommendation for conduct of a photocarcinogenicity study with this drug product was made prior to implementation of the ICH M3(R2) guidance document so the dose range-finding study and subsequent photocarcinogenicity study are reviewed in this document.

## 7 Genetic Toxicology

The following genetic toxicology information is contained in the ALPHAGAN<sup>®</sup> (brimonidine tartrate ophthalmic solution, 0.2%, NDA 20613/S-018, year 2001) label.

“Brimonidine tartrate was not mutagenic or cytogenic in a series of in vitro and in vivo studies including the Ames test, chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells, a host-mediated assay and cytogenic studies in mice, and dominant lethal assay.”

The genetic toxicology information for brimonidine tartrate is considered better presented in the label for ALPHAGAN<sup>®</sup> P (brimonidine tartrate ophthalmic solution, 0.1% and 0.15%, NDAs 21262/S-020 and 21770/S-004, year 2010).

### “13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Brimonidine tartrate was not mutagenic or clastogenic in a series of in vitro and in vivo studies including the Ames bacterial reversion test, chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells, and three in vivo studies in CD1 mice: a host-mediated assay, cytogenetic study, and dominant lethal assay.”

## 8 Carcinogenicity

The following carcinogenicity information is contained in the ALPHAGAN<sup>®</sup> (brimonidine tartrate ophthalmic solution, 0.2%, NDA 20613/S-018, year 2001) label.

“No compound-related carcinogenic effects were observed in either mice or rats following a 21-month and 24-month study, respectively. In these studies, dietary administration of brimonidine tartrate at doses up to 2.5 mg/kg/day in mice and 1.0 mg/kg/day in rats achieved ~77 and 118 times, respectively, the plasma drug concentration estimated in humans treated with one drop ALPHAGAN<sup>®</sup> into both eyes 3 times per day.”

Study #1 (refer to review under IND 74841, 03/01/2012)

Title: Twelve-month topical study to determine the influence of CD07805/47 and CD07805/47 vehicle on photocarcinogenesis in hairless mice (Study# IYA00019, Sponsor Ref# RDS.03.SRE.12629)

Topical doses of 100 µl 0 (vehicle), 0.18%, 1%, and 2% brimonidine tartrate gel were administered to Crl:SKH1-*hr* albino hairless mice (36/sex/group), with or without simulated sunlight exposure, once daily, five days per week, for 12 months (see the copied dose table below). The vehicle was the same as the clinical vehicle.

Group	Mice/ Sex/ Group	CD07805/47 Concentration (%)	Formulation Administration Volume (mL/mouse)	UVR Exposure RBU/Week
1	36	0 (Vehicle)	100	600
2	36	0.18	100	600
3	36	1	100	600
4	36	2	100	600
5	36	NA	None	600
6	36	NA	None	1200

UVR: Ultraviolet Radiation. RBU: Robertson-Berger Units NA: Not Applicable

On Monday, Wednesday and Friday of each week, mice were exposed to UV 1 hr after the completion of formulation administration. On Tuesday and Thursday of each week, mice were administered formulations 1 hr after UVR exposure. After the completion of 40 weeks of formulation administration and UV exposure, mice were maintained for up to an additional 12 weeks, for a total of 52 weeks, with sacrifice of surviving mice in

Week 53. The source of radiation was a 6.5 kilowatt xenon log arc lamp with a (b) (4) to mimic solar simulated light.

The dose selection was based on the result of a dose range-finding study (described above in Section 6.2). The selected doses are considered acceptable. The selected concentrations are the same as tested in the 2-year dermal rat carcinogenicity study for females.

The UV radiation dose is also considered acceptable. The lower UVR control level was 600 RBU per week. Accumulated historic data indicate that this level produces an appropriate tumor median latent period for comparison with other groups. The higher control level was 1200 RBU per week; a significant decrease in median tumor latent period is produced by this dose level. The test level of UVR (600 RBU per week) was selected to permit detection of enhanced photocarcinogenesis within the response range of the test system and in the presence of a test article that is neither protective nor phototoxic.

There were no gender differences in survival. High UV calibration group was early terminated in Week 41 according to tumor burden criteria. All other groups were sacrificed on schedule. The number of mice sacrificed early due to individual tumor burden was significantly lower in the groups treated with 1% or 2% brimonidine tartrate gel, compared to the vehicle control group. The number of mice with erythema, flaking, wrinkling, thickening and white raised area(s) was significantly reduced in the groups treated with 1% or 2% brimonidine tartrate gel, compared to the vehicle control group.

#### **Adequacy of Carcinogenicity Study**

The photocarcinogenicity study was adequately conducted.

#### **Appropriateness of Test Models**

The test model was appropriate for this study.

#### **Evaluation of Tumor Findings**

Only skin tumors were evaluated in this study, which was the primary objective of the study. Mice in the untreated high UVR group developed skin tumors significantly earlier than mice in the untreated low UVR group. Treatment with vehicle did not have significant effects on photocarcinogenesis, as compared to the untreated low UVR group. Topical treatment with brimonidine tartrate gel formulations did not cause enhancement of UV-induced photocarcinogenesis, as compared to the vehicle control group. On the contrary, treatment with brimonidine tartrate gel formulations showed a dose-dependent protection effect against the UV-induced photocarcinogenic response; the onset of skin tumors was delayed and the tumor yield was reduced in a dose-dependent manner, as compared to the vehicle control group. There were no significant differences in tumor development between sexes in groups treated with brimonidine tartrate formulations.

Tumor data were evaluated in terms of median onset, prevalence, and tumor yield. The median onset and tumor yield results are shown in the following tables.

#### Unbiased median week to tumor for tumors $\geq 1$ mm

Dose Group	1	2	3	4	5	6
CD07805/47 Formulation	vehicle	0.18%	1%	2%	None	None
UVR Exposure (RBU/week)	600	600	600	600	600	1200
Sex combined median (weeks)	40.5	48.0	NA*	NA	40.5	26.0
Males median (weeks)	42.0	48.0	NA	NA	44.0	26.5
Females median (weeks)	39.0	47.5	NA	NA	40.0	25.0

\*Not achieved (> 52 weeks)

#### Tumor yield (average number of $\geq 1$ mm tumors per survivor)

Dose Group	1	2	3	4	5	6*
CD07805/47 Formulation	vehicle	0.18%	1%	2%	None	None
UVR Exposure (RBU/week)	600	600	600	600	600	1200
Time	Week 52	Week 52	Week 52	Week 52	Week 41	Week 41
Sex combined	4.57	2.40	0.85	0.49	0.89	7.61
Males	3.34	2.10	0.73	0.43	0.49	6.78
Females	6.00	2.66	0.55	0.55	1.29	8.00

\*Group 6 was sacrificed according to group tumor burden criteria in Week 41.

## Study #2

### **Background:**

The sponsor submitted a 2-year dermal rat carcinogenicity protocol (SPA) for review on 12/20/2007. This protocol did not receive concurrence from the Exec CAC as there was no adequate dose-ranging data to support dose selection. The following Exec CAC recommendations and conclusions were relayed to the sponsor on 01/30/2008:

- *The Committee did not have adequate data on which to base a dosage recommendation. The sponsor should conduct a 90 day dose range finding study in an appropriate species in which each animal is treated with only one test article, using the intended clinical vehicle and an untreated control. Complete clinical chemistry and histopathology should be included. The study should test the maximum feasible dose. The study should be GLP compliant.*
- *Once completed, a study report of the dose range finding study along with a complete carcinogenicity protocol should be submitted for review as a special protocol. Individual animal data should be included. The carcinogenicity protocol should include an untreated control group as well as vehicle control. After submission of the protocol, the exec-CAC will give its feedback.*

As described above in Section 6.2, the sponsor initiated a 2-year dermal carcinogenicity study without receiving concurrence from the Exec CAC. Part of that study generated data for a 13-week dermal rat dose range-finding study and the dose range-finding study was submitted with a new 2-year dermal carcinogenicity study protocol (SPA) on 01/21/2009. A second Exec CAC meeting was conducted and the following recommendations and conclusions were relayed to the sponsor on 03/05/2009:

- *The Committee recommended doses of 0 (untreated control), 0 (vehicle control), 0.18%, 1.0%, and 2.0% COL-118 gel, applied once daily to 20% BSA at 3 ml/kg for female rats, based on MTD (decreased body weight gain).*
- *The Committee recommended doses of 0 (untreated control), 0 (vehicle control), 0.03%, 0.06%, and 0.18% COL-118 gel, applied once daily to 20% BSA at 3 ml/kg, for male rats, based on MTD (decreased body weight gain).*
- *The sponsor should notify the Agency if there is excessive mortality and prior to changing dosing or terminating any dose groups.*

Subsequently the sponsor initiated the 2-year dermal rat carcinogenicity study following the Exec CAC's recommendations. On 09/15/2010, the sponsor submitted a request for study protocol modification, based on an increase in mortality in mid dose and high dose females at Week 41 of the study (shown in the following table).

		Group 1 water	Group 2 Placebo	Group 3 0.03%	Group 4 0.06%	Group 5 0.18%
Male	Surviving animals (No.)	57	57	58	59	60
	Surviving rate	95%	95%	97%	98%	100%

		Group 1 water	Group 2 Placebo	Group 3 0.18%	Group 4 1%	Group 5 2%
Female	Surviving animals (No.)	59	59	60	55	47
	Surviving rate	98%	98%	100%	92%	78%

The mortality rate at Week 41 was higher in mid dose (8%) and high dose females (22%) than that in the two control groups (2%). Such an increase was not seen in males. After receiving concurrence from the Exec CAC, the following comments were relayed to the sponsor on 09/24/2010:

- *The study should continue without an off-treatment period. There is no need to change the time for TK blood sample collection (at Week 52).*
- *The concentrations of COL-118 gel for mid dose and high dose female rats should be lowered to 0.36% and 0.72%, respectively. The dosing volume should be kept unchanged (3 ml/kg).*
- *If the trend of decreasing survival continues to be seen in female rats after lowering the mid dose and high dose, you should notify the Executive Carcinogenicity Assessment Committee (through the Division) to obtain additional guidance.*

On 04/14/2011 (SD 75 under IND 74841), the sponsor stated that they decided to accept FDA's recommended doses, but as these concentrations were not immediately available, these new concentrations need to be specifically manufactured. During this interim time period, the sponsor decided to dilute the formulations currently available at the CRO (b)(4), USA) with the corresponding vehicle. The dosing of the mid and high dose females was changed, starting on Day 344 (Week 49). New manufactured formulations were used from Day 428. The sponsor cancelled the TK blood sampling scheduled at Week 52. A TK sampling was performed during Week 43, before the change of the concentrations, to document systemic exposures in all animals. Subsequently, an additional TK sampling was performed during Week 66.

On 09/08/2011 the sponsor submitted another request for study protocol modification based on the survival rate in the high dose female groups observed at Week 92 (shown in the following table).

		Group 1 water	Group 2 Placebo	Group 3 0.03%	Group 4 0.06%	Group 5 0.18%
Male	Surviving animals (No.)	48	45	51	47	55
	Surviving rate	80%	75%	85%	78%	92%

		Group 1 water	Group 2 Placebo	Group 3 0.18%	Group 4 1%	Group 5 2%
Female	Surviving animals (No.)	45	41	48	41	33
	Surviving rate	75%	68%	80%	68%	55%

A slightly higher mortality rate was seen in high dose females. After receiving concurrence from the Exec CAC, the following comments were relayed to the sponsor on 10/05/2011:

- *The study should continue without further modification for the present.*
- *Dosing of the high dose female group should stop if the number of animals in that group should decline to 20, but treatment of other groups should continue. A given treatment group (within a gender) should be terminated and subjected to necropsy per the protocol if the number of surviving animals in that group declines to 15. If the study has reached at least 100 weeks of treatment by the time a given treatment group declines to 15, then all groups of that gender may be sacrificed at that time (but treatment of the other gender would continue). If no group declines to 15 animals, then the study should continue until the scheduled terminal sacrifice. You should notify the Executive Carcinogenicity Assessment Committee (through the Division) prior to termination of any group.*

The dermal carcinogenicity study was completed on 09/27/2012.

**Study title:** CD07805/47: A 2-year dermal carcinogenicity study in Wistar Han rats

Study no.: 1628-003, Sponsor Ref# RDS.03.SPR.12667  
 Study report location: SD 1, NDA 204708 (SAS tumor dataset located in SD 2, NDA 204708)

Conducting laboratory and location: (b) (4)

Date of study initiation: 09/29/2009

GLP compliance: Yes

QA statement: Yes

Drug, lot #, and % purity: CD07805/47 vehicle gel, lot# 053\*09, 014\*10, 017\*10  
 CD07805/47 gel, 0.03%, lot# 054\*09  
 CD07805/47 gel, 0.06%, lot# 055\*09  
 CD07805/47 gel, 0.18%, lot# 057\*09, 058\*09, 015\*10  
 CD07805/47 gel, 0.36%, lot# 038\*10  
 CD07805/47 gel, 0.72%, lot# 039\*10  
 CD07805/47 gel, 1%, lot# 060\*09  
 CD07805/47 gel, 2%, lot# 061\*09

CAC concurrence: Yes

**Key Study Findings**

An increased incidence of mortality was noted during the first year of the study in females treated with 1% and 2% gel. Doses therefore were lowered to 0.36 and 0.72% gel for mid dose and high dose females on Day 343 and thereafter. Survival at the end of the study was generally >50%, with the exception of the high dose female group (40%). Survival rate at the end of the study was acceptable for study interpretation.

No significant dermal irritation was noted in this study. Body weight was lower in high dose males and all treated female groups, compared to controls. No significant test article-related effects on hematology parameters were noted.

A complete list of tissues was examined histopathologically. No significant test article-related non-neoplastic findings were noted. No significant test article-related neoplastic findings were noted in this study. CD07805/47 gel was not carcinogenic when administered topically to rats at concentrations up to 0.18% in males and 2/0.72% in females, once daily for 2 years. Day 457 AUC<sub>0-24</sub> values were 215 ng•hr/ml in high dose males and 1070 ng•hr/ml in high dose females, respectively.

**Adequacy of Carcinogenicity Study**

This carcinogenicity study was adequately conducted.

**Appropriateness of Test Models**

The test model was appropriate for this study.

## Evaluation of Tumor Findings

There were no biologically significant test article-related neoplastic findings, under the study conditions.

*Note:* The evaluation of this dermal carcinogenicity study received CAC concurrence during the CAC meeting on 03/26/2013 (refer to Appendix I for the CAC meeting minutes).

## Methods

Doses: Refer to the dose table below.  
For males: 0 (water control), 0 (vehicle control), 0.9, 1.8, and 5.4 mg/kg/day (0.03%, 0.06%, and 0.18% gel)  
For females: 0 (water control), 0 (vehicle control), 5.4, 30, and 60 mg/kg/day until Day 343; 0, 0, 5.4, 10.8, and 21.6 mg/kg/day thereafter (0.18%, 1%, and 2% gel until Day 343; 0.18%, 0.36%, and 0.72% gel thereafter)

Frequency of dosing: Once daily for up to 104 weeks  
Dose volume: 3 ml/kg, applied to 20% BSA  
Route of administration: Dermal, unoccluded. The dosing sites were gently wiped with a Wypall® or equivalent, wet with tap water to remove any residual material, prior to the next application.

Formulation/Vehicle: Clinical vehicle (See Section 2.3)  
Basis of dose selection: MTD (refer to Exec CAC recommendations)  
Species/Strain: Wistar Han [CrI:WI(Han)] rats  
Number/Sex/Group: 60 for main study animals  
Age: 6 weeks  
Animal housing: The animals were individually housed in suspended, stainless steel, wire-mesh type cages. During the study, if animals developed lesions attributable to the wire mesh cage bottoms, the animals were transferred to solid bottom caging until the lesions and/or symptoms had healed or regressed sufficiently for the animals to be returned to wire mesh bottomed cages.

Paradigm for dietary restriction: None  
Dual control employed: No  
Interim sacrifice: None  
Satellite groups: TK animals (refer to the dose table below)  
Deviation from study protocol: The doses were modified for mid dose and high dose females from Day 343 to the end of treatment. Time for TK sampling was modified (refer to the background of the study)

Dose table:

*Reviewer's comment:* The placebo control referenced in the table and/or figures below refers to the vehicle control.

Group Assignments				
Group Number	Male (% concentration)	Female (% concentration)	Number of Animals	
			Male	Female
Main Study				
1	0 (water control)	0 (water control)	60	60
2	0 (placebo control)	0 (placebo control)	60	60
3	0.03	0.18	60	60
4	0.06	1/0.36 <sup>c</sup>	60	60
5	0.18	2/0.72 <sup>c</sup>	60	60
Toxicokinetic				
6	0 (water control)	0 (water control)	4 <sup>a</sup>	4 <sup>a</sup>
7	0 (placebo control)	0 (placebo control)	4 <sup>a</sup>	4 <sup>a</sup>
8	0.03	0.18	12 <sup>b</sup>	12 <sup>b</sup>
9	0.06	1/0.36 <sup>c</sup>	12 <sup>b</sup>	12 <sup>b</sup>
10	0.18	2/0.72 <sup>c</sup>	12 <sup>b</sup>	12 <sup>b</sup>
	Sentinels		25	25
<sup>a</sup> One additional animal included as a possible replacement animal. <sup>b</sup> Three additional animals included as possible replacement animals. <sup>c</sup> Dose concentrations were reduced beginning on Day 344.				

## Observations and Results

### Mortality

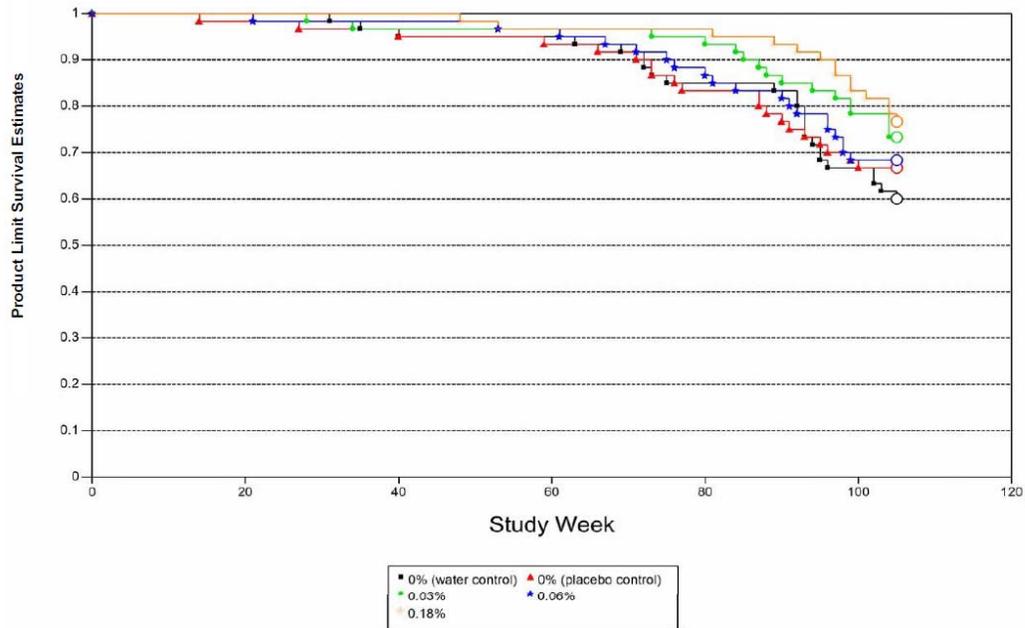
Cumulative survival rate at the end of study:

For males: 62%, 67%, 73%, 68%, and 78%, for water control, vehicle control, low dose, mid dose, and high dose groups, respectively

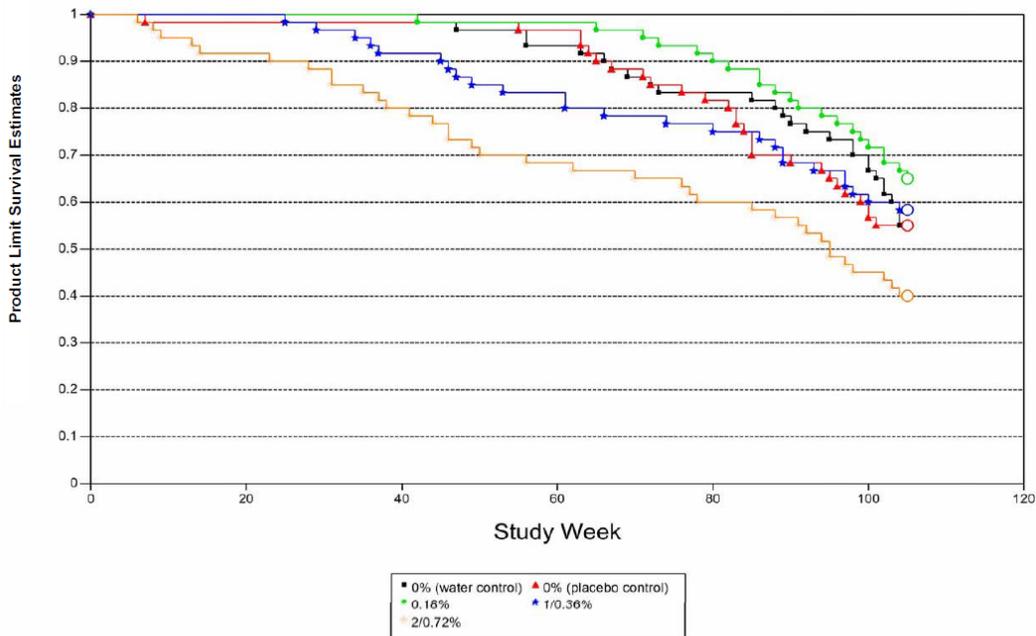
For females: 55%, 55%, 67%, 58%, and 40%, for water control, vehicle control, low dose, mid dose, and high dose groups, respectively

An increased incidence of mortality was noted during the first year of the study in females treated with 1% and 2% gel. Once these doses were reduced to 0.36 and 0.72% gel, from Week 50, mortality occurred at comparable rates among all groups. Survival at the end of study was generally >50% (more than 30 survivors per group), with the exception of the high dose female group where the survival was 40% (24 survivors) at Week 104. However, survival in this group at week 92 was 55% (33 survivors). Overall, survival rate at the end of the study was considered acceptable for study interpretation (refer to the statistical review, by Dr. Min Min, for survival rate analysis).

Survival rates for males:



Survival rates for females:



### Clinical Signs

A detailed clinical examination of each animal was performed weekly at 1-2 hr postdose for all main study animals. On occasion, clinical observations were recorded at unscheduled intervals for all animals. Decreased activity, clonic convulsions,

hypersensitivity to touch and vocalization were noted among females treated with 1% and 2% gel. After dose decrease for the two groups, no dose-related pattern for the adverse clinical signs was evident.

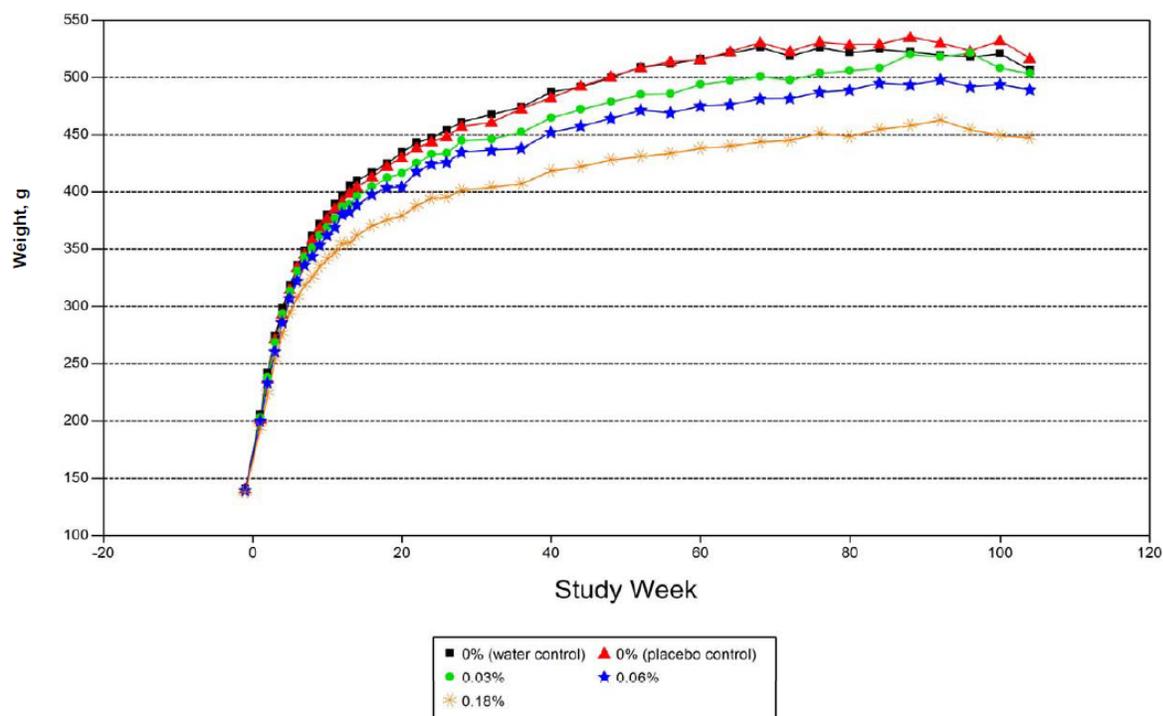
### Skin irritation evaluation

Evaluation of skin irritation was conducted weekly for main study animals. There was no significant test article-related evidence of erythema or edema.

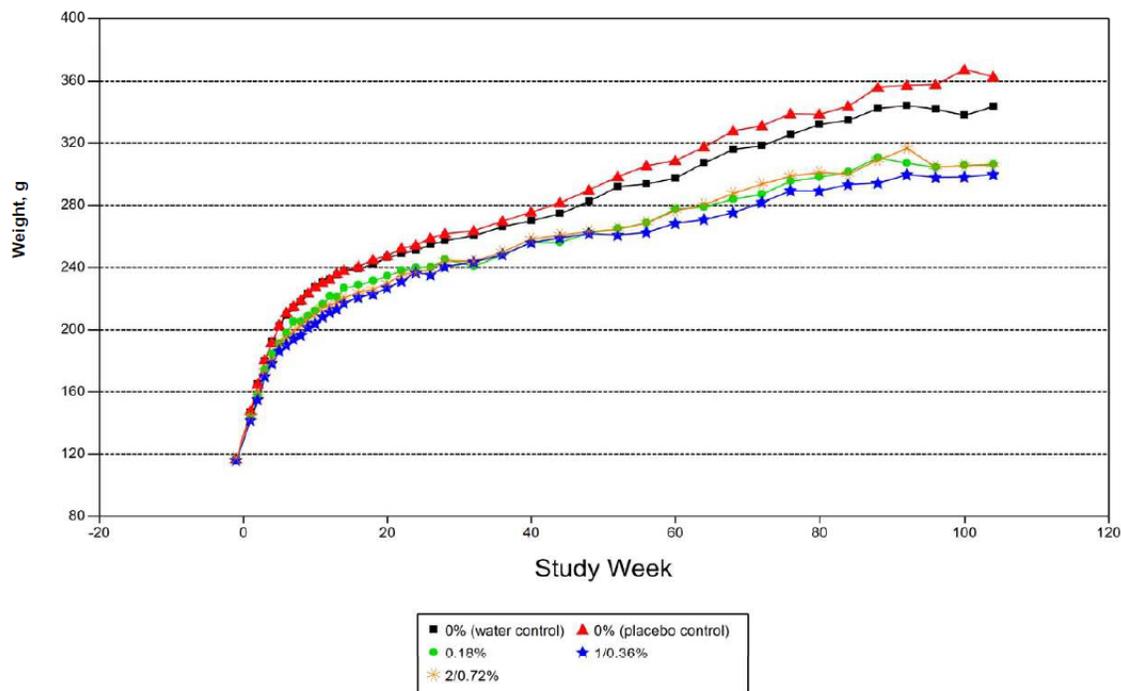
### Body Weights

Body weight was measured weekly for the first 14 weeks, every two weeks until Week 28, and every 4 weeks thereafter. Body weight in high dose males was lower over the duration of treatment, compared to both the water and vehicle controls (15-18%). In females, body weight was lower in all treated groups over the duration of treatment (16-25%), compared to both the water and vehicle controls.

Group mean body weight for males:



Group mean body weight for females:



## Feed Consumption

Food consumption was measured weekly for the first 14 weeks, every two weeks until Week 28, and every 4 weeks thereafter. Food consumption was generally lower among males at 0.06 and 0.18% for most of the treatment period. Food consumption was also lower among females at 1% and 0.18% during the first two months of the study (not dose-dependent). By ~Week 10, food consumption was generally higher in the females compared to either the water or vehicle controls.

## Hematology

Hematology were conducted on all main study animals at termination and on all animals euthanized earlier. No significant test article-related effects on hematology parameters were identified in either sex at any dose level.

## Gross Pathology

No significant test article-related macroscopic observations were noted in either sex.

## Histopathology

Peer Review: Yes.

All tissues listed below were examined for all main study animals.

Adrenals, aorta, bone marrow, brain, clitoral glands, coagulating glands, epididymides, eyes, gastrointestinal tract [esophagus, stomach (glandular and nonglandular),

duodenum, jejunum, ileum, cecum, colon, and rectum], gross lesions, Harderian glands, heart, joint (tibiofemoral), kidneys, lacrimal glands, larynx, liver, lungs, lymph nodes, mammary gland (female only), nasal tissue (levels A, B, C, and D), optic nerves, ovaries, pancreas, Peyer's patch, pharynx, pituitary, preputial glands, prostate, salivary glands, sciatic nerves, seminal vesicles, skeletal muscle, skin (treated and untreated), spinal cord, spleen, testes, thymus, thyroid and parathyroid glands, tissue masses, tongue, trachea, ureters, urinary bladder, uterus with cervix, vagina, and Zymbal's glands.

### Neoplastic:

The tumor incidence data were analyzed by Dr. Min Min. A pair-wise comparison test was conducted for water control group vs. vehicle control group. Pair-wise comparison tests were also conducted for vehicle control group vs. low dose group, vehicle control group vs. mid dose group, and vehicle control group vs. high dose group. In addition, a dose response relation test (trend analysis) was conducted using a poly-k method with the vehicle control group (zero dose), low, mid, and high dose groups. As recommended by this reviewer, in addition to the analysis of each individual tumor types seen in this study, Dr. Min analyzed the following combinations of organs/tumors:

For male rats:

- Combine lymphoma seen in all organs
- Combine hemangioma and hemangiosarcoma seen in all organs
- Adrenal: combine adenoma and carcinoma
- Liver: combine adenoma and carcinoma
- Lymph node: combine same type of tumors seen in different area of lymph nodes in different animals, e.g., combining histiocytic sarcoma seen in different lymph nodes (but if the same tumor was seen in different lymph nodes in the same animal, count as 1)
- Pancreas: combine adenoma and carcinoma
- Skin, subcutis: combine fibroma and fibrosarcoma
- Thyroid gland: combine adenoma and carcinoma originated from the same cell type

For female rats:

In addition to the combinations mentioned above for male rats

- Mammary gland: combine adenoma and adenocarcinoma
- Pituitary gland: combine adenoma and carcinoma
- Uterus with cervix: combine adenoma and adenocarcinoma; combine stromal polyp and stromal sarcoma

According to the Haseman-Lin-Rahman criteria, for a single species study, statistical significance levels are  $p \leq 0.05$  (5%) for rare tumors (with a historical control incidence less than 1%) and  $p \leq 0.01$  (1%) for common tumors. The following table (copied from Dr. Min's review) displays the tumor incidence results that had at least one test that achieved a nominal  $p \leq 0.05$  level of significance.

**Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or Pair-wise Comparisons**

		0 mg	5 mg	20 mg	40 mg				
		Cont	Low	Med	High	P_Val ue	P_Val ue	P_Val ue	P_Val ue
Organ Name	Tumor Name	N=60	N=60	N=60	N=60	Dos Resp	C vs. L	C vs. M	C vs. H
Female cavity, abdomi n SCHWANNOMA 0 0 0 2 [47] [52] [44] [36]									
						0.040	.	.	0.185

From Dr Min’s analysis, the only statistically significant finding was the incidence of schwannoma in abdominal cavity in high dose females (incidence 2/60). The incidence of schwannoma in high dose females was statistically significant in the trend analysis (p value = 0.04), but not in the pair-wise comparison with the vehicle control (p = 0.185). Usually for a neoplastic finding considered to be biologically significant, statistical significance should be achieved in both the trend analysis and pair-wise comparison test. No statistical significance was achieved in any tumor types in test article-treated males, either in the trend analysis or in pair-wise comparisons. There were no significant findings in pair-wise comparisons between the water control and vehicle control groups in either sex.

The finding of schwannoma in abdominal cavity in high dose females is considered biologically insignificant, based on the following considerations:

- The incidence of 2/60 did not achieve statistical significance in pair-wise comparison with the vehicle control.
- Schwannoma was also noted in abdominal cavity in the vehicle control group in males, with an incidence of 1/60.
- In the 57-week dermal toxicity study in Wistar rats (See Section 6.2), schwannoma was also seen in one low dose female, but not in mid dose or high dose groups (no dose response).
- Dietary carcinogenicity studies have been conducted for brimonidine tartrate. No compound-related carcinogenic effects were observed in either a 21-month dietary mouse carcinogenicity study (doses up to 2.5 mg/kg/day) or a 24-month dietary rat carcinogenicity study (doses up to 1.0 mg/kg/day).

Overall, there were no significant test article-related neoplastic findings in either sex.

Non Neoplastic:

No significant test article-related non-neoplastic findings were noted in either sex. Non-neoplastic findings were of the type typically seen in rats of this strain and age. All were considered incidental and not related to test article administration.

**Toxicokinetics**

TK parameters were measured for the blood samples collected on Days 1, 296, and 457 (see the copied table below).

Day	Sex	Dose (%)	Dose (mg/kg/day)	AUC <sub>0-24</sub> (hr•ng/mL)	C <sub>max</sub> (ng/mL)	t <sub>1/2</sub> (hr)	T <sub>max</sub> (hr)
1	Male	0.03	0.9	14.0	3.03	6.71	1.00
		0.06	1.8	15.0	3.62	10.7	1.00
		0.18	5.4	50.3	6.58	6.38	1.00
	Female	0.18	5.4	83.5	8.64	16.9	2.00
		1	30	132	8.84	33.5	1.00
		2	60	393	31.3	NC	8.00
296	Male	0.03	0.9	42.9	5.11	6.57	1.00
		0.06	1.8	68.8	6.06	17.8	1.00
		0.18	5.4	170	13.6	14.3	1.00
	Female	0.18	5.4	492	36.7	NC	8.00
		1	30	1420	89.0	NC	2.00
		2	60	3350	185	NC	8.00
457	Male	0.03	0.9	22.5	5.35	9.83	1.00
		0.06	1.8	74.6	5.96	8.09	1.00
		0.18	5.4	215	23.0	9.00	1.00
	Female	0.18	5.4	294	37.3	21.4	1.00
		0.36**	10.8	407	51.2	8.34	2.00
		0.72**	21.6	1070	60.6	NC	8.00

\*\*Concentration was lowered on Day 344.

NC = not calculated

Systemic exposure to brimonidine tartrate increased in approximate proportion to the increase in concentration in gel in both sexes on all study days. Systemic exposure to brimonidine tartrate was higher on Days 296 and 457 than on Day 1 in both male and females. No significant increase in exposure was noted in males between Day 296 and Day 457. The exposure in mid dose and high dose females was lower on Day 457, compared to Day 296, due to dose decrease.

### Dosing Solution Analysis

Dosing formulations were evaluated for homogeneity, concentration, and stability.

Dosing Formulation Analysis Sample Collection – Feasibility Study						
Sample Type	Concentrations Sampled (%)	Stratum	Number of Samples per Concentration			Sample Quantity (g)
			Collected	Analyzed	Backup	
Homogeneity Analyses <sup>a, b</sup>	0.36 and 0.72	Top	6	2	4	1
		Middle <sup>c</sup>	6	2	4	1
		Bottom	6	2	4	1
Stability Analysis (8 Day) <sup>a, b, d</sup>	0.36 and 0.72	Middle	6	2	4	1
Stability Analysis (15 Day) <sup>a, b, d</sup>	0.36 and 0.72	Middle	6	2	4	1
<sup>a</sup> The samples, including backup samples, were stored at room temperature pending analyses or final disposition. <sup>b</sup> Samples collected following 30, 60, and 90 minutes of mixing. <sup>c</sup> Samples collected for zero timepoint stability. <sup>d</sup> Only samples collected after 60 minutes of mixing were analyzed. The samples collected following 30 and 90 minutes of mixing were discarded.						

For all the measurements average recovery was in the range of 97.5-110.6% of nominal concentrations. The dosing accuracy is acceptable.

## 9 Reproductive and Developmental Toxicology

No reproductive or developmental toxicity studies were conducted with MIRVASO Gel.

The following information is contained in the ALPHAGAN<sup>®</sup> (brimonidine tartrate ophthalmic solution, 0.2%, NDA 20613/S-018, year 2001) label.

“Pregnancy: Teratogenic Effects: Pregnancy Category B

Reproductive studies performed in rats with oral doses of 0.66 mg base/kg revealed no evidence of harm to the fetus due to ALPHAGAN<sup>®</sup>. Dosing at this level produced 100 times the plasma drug concentration level seen in humans following multiple ophthalmic doses.

There are no adequate and well-controlled studies in pregnant women. In animal studies, brimonidine crossed the placenta and entered into the fetal circulation to a limited extent. ALPHAGAN<sup>®</sup> should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.”

“Reproductive studies performed in rats with oral doses of 0.66 mg base/kg revealed no evidence of impaired fertility due to ALPHAGAN<sup>®</sup>.”

More detailed information regarding reproductive and developmental toxicity of brimonidine tartrate is presented in the label for ALPHAGAN<sup>®</sup> P (brimonidine tartrate

ophthalmic solution, 0.1% and 0.15%, NDAs 21262/S-020 and 21770/S-004, year 2010).

#### “8.1 Pregnancy

Pregnancy Category B: Teratogenicity studies have been performed in animals. Brimonidine tartrate was not teratogenic when given orally during gestation days 6 through 15 in rats and days 6 through 18 in rabbits. The highest doses of brimonidine tartrate in rats (2.5 mg/kg/day) and rabbits (5.0 mg/kg/day) achieved AUC exposure values 360- and 20-fold higher, or 260- and 15-fold higher, respectively, than similar values estimated in humans treated with ALPHAGAN<sup>®</sup> P 0.1% or 0.15%, 1 drop in both eyes three times daily.

There are no adequate and well-controlled studies in pregnant women; however, in animal studies, brimonidine crossed the placenta and entered into the fetal circulation to a limited extent. Because animal reproduction studies are not always predictive of human response, ALPHAGAN<sup>®</sup> P should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.”

#### “13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Reproduction and fertility studies in rats with brimonidine tartrate demonstrated no adverse effect on male or female fertility at doses which achieve up to approximately 125 and 90 times the systemic exposure following the maximum recommended human ophthalmic dose of ALPHAGAN<sup>®</sup> P 0.1% or 0.15%, respectively.”

In the submission the sponsor provided a one-page abstract of reproductive and developmental toxicity studies for brimonidine tartrate [Angelov et al., Allergan Inc., 1996. Reproductive and developmental safety studies with brimonidine (ALPHAGAN<sup>™</sup>), Investigative Ophthalmology and Visual Science Annual Meeting]. The following information is contained in the abstract:

“Methods: In a fertility and reproduction study, male and female rats were administered brimonidine by oral gavage at doses of 0.01-1.0 mg/kg/day. Male rats were treated for 10 days prior to and during mating, and females were treated for 14 days prior to mating and through gestation and lactation. In the teratology studies, rats and rabbits were treated during the gestation period. Doses used were 0.1-2.5 mg/kg/day for rats and 0.25-5.0 mg/kg/day for rabbits. In the perinatal and postnatal study, pregnant rats were treated from gestation day 16 through lactation day 20. Offspring through two generations were delivered and reared. Doses used in this study were 0.01-1.0 mg/kg/day.

Results: In all studies, systemic pharmacologic effects, characterized by sedation and decreased body weight gain were observed in the highest dose groups. *Fertility and reproduction*: There were no treatment-related effects in the reproductive indices (mating and fertility, natural deliveries, and litter observations) even at the highest dose which produces plasma concentrations ( $C_{max}$ ) ~180 times higher than the human concentrations. *Teratology*: In rats and rabbits, there were no teratogenic effects. In rats, the mean maximum plasma concentration in females receiving the highest oral

dose of 2.5 mg/kg/day was 333 times the human concentration. In rabbits, the mean maximum plasma concentration in females receiving the highest oral dose of 5.0 mg/kg/day was 24 times the human concentration. *Perinatal and postnatal*: There was no indication of impaired behavior, fertility, or reproductive capabilities in the parental or the resulting 2 generations, and growth and development of second generation offspring appeared normal through lactation. The highest dose in this study produces plasma concentrations ~180 times higher than the human concentrations.”

It appears the summary information was from the inventor of the listed drug (Allergan Inc.). Peri- and post-natal developmental studies are not described in the ALPHAGAN<sup>®</sup> label. The sponsor did not provide a right of reference letter from the inventor to authorize them use the nonclinical data contained in previous NDAs for ALPHAGAN<sup>®</sup> and ALPHAGAN P<sup>®</sup> ophthalmic solutions. Under the 505(b)(2) regulation, the sponsor can only rely upon the Agency’s finding of safety and effectiveness, as is reflected in the approved labeling for the listed drug. Therefore, additional information regarding peri- and post-natal developmental toxicity of brimonidine tartrate should not be added to the MIRVASO Gel label.

“Oral dose of 0.66 mg base/kg” was used in the ALPHAGAN<sup>®</sup> label to describe the fertility study. To make the dose consistent in the MIRVASO Gel label, instead of using 0.66 mg base/kg, the high dose of brimonidine tartrate in the fertility study is recorded as 1 mg/kg in the MIRVASO Gel label.

## 10 Special Toxicology Studies

1. Single administration topical primary irritancy and phototoxicity screening test of COL-118 in hairless mice (Study# IYA00013)

To test the primary irritancy potential of brimonidine tartrate gel, single topical doses of 0, 8, 40, and 80 mg/kg brimonidine tartrate (100 µl vehicle, 0.2%, 1%, and 2% gel, respectively, applied to 25 cm<sup>2</sup> BSA) were administered to Crl:SKH1-*hr* hairless mice (3/group). The vehicle composition was not described in the study report (all the test materials were provided by the sponsor and used as received). Mice were examined for clinical observations and test article effects at time points up to three days postdose. To test the phototoxicity potential of brimonidine tartrate gel, the same single doses of brimonidine tartrate gel were administered to Crl:SKH1-*hr* hairless mice (6/group). 8-methoxypsoralen (8-MOP) was used as a positive control. After 60 ± 10 min, all mice were exposed to UV irradiation for 30 ± 5 min, which is equivalent to a dose of 0.5 minimal erythema dose (MED). A 6.5 kw long-arc xenon lamp was used to generate simulated sunlight irradiation (290-790 nm). Mice were examined for clinical observations and test article effects at time points up to three days postdose.

No mortality was seen in this study. Modest dose-dependent body weight loss (up to 5%) was noted in both study phases. Brimonidine tartrate gel (up to 2%) did not show irritancy or phototoxicity in hairless mice, under the study conditions (refer to review under IND 74841, 12/08/2010).

2. CD07805/47 0.5% Gel: Primary eye irritation study in rabbits (Study# C96585, Sponsor Ref# RDS.03.SRE.12734)

0.1 ml brimonidine tartrate gel, 0.5%, was applied by instillation into the left eye of each of three New Zealand White rabbits. Scoring of irritation effects was performed at 1, 24, 48 and 72 hr postdose. The lot number of the formulation (0373.0056) indicated that it is the clinical formulation.

No abnormal finding was observed in any animal at any time point. Brimonidine tartrate gel 0.5% is classified as a “nonirritant” to rabbit eye (refer to review under IND 74841, 03/01/2012).

3. Delayed contact dermal sensitization test-Buehler method (Study# MB 07-15969.06)

Brimonidine tartrate gel 2.0% was tested in guinea pigs for its skin sensitization potential using the method of Ritz & Buehler. The formulation composition was not described in the study report (the test material was provided by the sponsor and used as received). For induction application, 0.4 ml brimonidine tartrate gel 2.0% was applied topically (occluded) to Hartley Albino guinea pigs (15/sex) for 6 hr, once per week for 3 weeks. Five males and five females were not treated in the induction period and served as naive control. Two weeks after the last induction dose, all animals were challenged with the same dose (0.4 ml 2.0% brimonidine tartrate gel). Skin reactions of the animals were recorded at 24 and 48 hr following patch removal. The sensitivity of guinea pigs to a positive control, 85% hexylcinnamaldehyde (HCA) is confirmed in this laboratory (every six months).

All animals appeared normal during the observation period. There were no treatment-related body weight changes. Erythema was not observed at 24 or 48 hr after patch removal in any animal, in the induction period or at challenge. Brimonidine tartrate gel 2.0% did not show a skin sensitization potential, under the study conditions (refer to review under IND 74841, 12/08/2010).

## 11 Integrated Summary and Safety Evaluation

Brimonidine tartrate is a relatively selective alpha-2 alpha adrenergic receptor agonist. Brimonidine tartrate ophthalmic solutions in different strengths have been approved for the treatment of glaucoma and ocular hypertension. The therapeutic effect of brimonidine tartrate on facial erythema of rosacea might be due to its vasoconstriction activity.

The sponsor proposed to rely upon the Agency’s finding of safety for the approved listed drug ALPHAGAN® ophthalmic solution, 0.2% to support some nonclinical portions of this 505(b)(2) application. Because the listed drug was discontinued from marketing

(not for reasons of safety or effectiveness), a generic drug product was used as the comparator in the clinical bridge study. The systemic exposure of once daily maximum clinical use of MIRVASO Gel, 0.5% (1 g applied to the face) was less than that of brimonidine tartrate ophthalmic solution 0.2% at its approved dose of 1 drop into each eye TID.

In addition to relying upon the Agency's finding of safety on the listed drug, including information regarding genetic toxicity, reproductive toxicity, and oral carcinogenicity, the sponsor also conducted repeat dose dermal toxicity studies in rats and minipigs, a photo-carcinogenicity study in hairless mice, a dermal rat carcinogenicity study, and several special toxicology studies.

In a chronic dermal toxicity study in minipigs, topical doses of 0 (water), 0 (vehicle: clinical vehicle), 1.2, 3.6, and 20 mg/kg/day brimonidine tartrate (0.06%, 0.18%, and 1% gel, 2 ml/kg) were administered once daily for 39 weeks. There were no significant treatment-related effects on body weight, ophthalmology, cardiovascular parameters, hematology, clinical chemistry, urinalysis, gross pathology, or histopathology. The NOAEL was identified as the high dose, 20 mg/kg/day (1% gel, 2 ml/kg/day).

In a 57-week dermal toxicity study in rats, topical doses of 0 (water), 0 (vehicle: not described), 5.4, 30, and 60 mg/kg/day brimonidine tartrate (0.18%, 1%, and 2% gel, 3 ml/kg) were administered till Week 14. All the animals were put on a ~3-week dosing holiday due to decreases in body weight gain. When the study resumed, doses were reduced to 1.1, 6, and 12 mg/kg/day for males (dose volume reduced to 0.6 ml/kg), but remained unchanged for females. Treatment-related mortality was noted in high dose males and females. Body weight gain over the entire treatment period was lower in mid dose and high dose males, and in females at all dose levels, compared to the vehicle control group. Lymphoid depletion in thymus was noted in high dose males and females. Considering the ~3-week dosing holiday and the decrease in body weight gain seen at all three dose levels, a NOAEL was not identified in this study.

In the two chronic dermal toxicology studies, the 39-week dermal minipig study is considered more relevant in the safety assessment due to the similarity between human skin and minipig skin. In addition, the treatment duration of the dermal rat study (57 weeks) was much longer than the duration of a typical chronic toxicology study in rodents (6 months). In the dermal rat study, there were no significant histopathological findings except lymphoid depletion noted only at high dose. The multiples of human exposure based on AUC comparison between the NOAEL/low dose in the animal studies and the maximum clinical dose (1 g/day 0.5% gel) is shown below.

Duration of toxicity study	Species	Route	NOAEL (mg/kg/day)	AUC <sub>0-24h</sub> (ng•hr/ml)	Multiples of human exposure**
57-week	rat	Dermal	5.4/1.1 or 5.4*	Male: 42.6	101
				Female: 208	495
39-week	minipig	Dermal	20	Male: 4.78	11
				Female: 6.03	14

\*NOAEL was not identified. In this study, 5.4/1.1 mg/kg/day was the low dose tested in males and 5.4 mg/kg/day was the low dose tested in females.

\*\*Comparing to the mean  $AUC_{0-24h}$  (0.42 ng•hr/ml) obtained under maximum clinical use conditions (1 g MIRVASO Gel, 0.5%, applied to face once daily for 29 days, 0.08 mg/kg/day brimonidine tartrate for a 60 kg subject)

A series of *in vitro* and *in vivo* genotoxicity tests were conducted with brimonidine tartrate, including the Ames test, a chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells, and three studies in CD1 mice: a host-mediated assay, a cytogenetic study, and a dominant lethal assay. Brimonidine tartrate was negative in all these tests. There was no concern for genotoxicity for brimonidine tartrate.

Oral (diet) carcinogenicity studies have been conducted with brimonidine tartrate. In a 21-month oral mouse carcinogenicity study and a 24-month oral rat carcinogenicity study, no drug-related carcinogenic effects were observed at oral doses up to 2.5 mg/kg/day in mice or up to 1 mg/kg/day in rats.

In a dermal rat carcinogenicity study with MIRVASO gel, brimonidine tartrate was administered to Wistar rats at topical doses up to 5.4 mg/kg/day (0.18% gel) in males and 60/21.6 mg/kg/day (2% gel during Days 1-343 and 0.72% gel thereafter) in females once daily for 24 months. No drug-related carcinogenic effects were observed in this study. The Exec CAC has reviewed this study and concluded that this study was acceptable. The multiples of human exposure are 512 and 2548, for male and female rats, respectively, when comparing  $AUC_{0-24h}$  obtained at the high dose tested in this study (Day 457 value, 215 and 1070 ng•hr/ml in males and females, respectively) with that in human subjects obtained under maximum clinical use conditions (0.42 ng•hr/ml).

In a 12-month dermal photo-carcinogenicity study, topical doses of 0% (MIRVASO Gel vehicle), 0.18%, 1% and 2% brimonidine tartrate gel were administered to hairless albino mice once daily, five days per week, with concurrent exposure to simulated sunlight. No drug-related adverse effects were observed in this study. The results of this study suggest that topical treatment with MIRVASO Gel would not enhance photo-carcinogenesis.

Brimonidine tartrate was not teratogenic when given at oral doses up to 2.5 mg/kg/day in pregnant rats during gestation days 6 through 15 and up to 5 mg/kg/day in pregnant rabbits during gestation days 6 through 18. Reproduction and fertility studies in rats with brimonidine tartrate demonstrated no adverse effects on male or female fertility at oral doses up to 1 mg/kg/day.

Brimonidine tartrate gel (up to 2%) did not show irritancy or phototoxicity in hairless mice. MIRVASO Gel 0.5% is classified as a “nonirritant” to rabbit eye. Brimonidine tartrate gel 2.0% did not show a skin sensitization potential in guinea pigs.

The toxicity profile of brimonidine tartrate gel has been well characterized. Based on the Agency’s finding of safety and conducted nonclinical studies with brimonidine tartrate gel, overall there was no significant safety concern for MIRVASO Gel, 0.5%, at the proposed clinical dose. The animal multiples of human exposure based on AUC comparison are not presented in the MIRVASO Gel label because AUC values obtained

in the reproductive toxicity studies and oral carcinogenicity studies were not provided in the ALPHAGAN<sup>®</sup> label.

This NDA is approvable from a pharmacology/toxicology perspective. No postmarketing requirement is recommended for this NDA.

## 12 Appendix/Attachments

Appendix I: Executive CAC meeting minutes

### Executive CAC

**Date of Meeting:** March 26, 2013

**Committee:** David Jacobson-Kram, Ph.D., OND IO, Chair  
Paul Brown, Ph.D., OND, IO, Member  
Albert Defelice, Ph.D., DCRP, Alternate Member  
Barbara Hill, Ph.D., DDDP, Supervisor  
Jianyong Wang, Ph.D., DDDP, Presenting Reviewer

**Author of Draft:** Jianyong Wang, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations.

**NDA #:** 204708

**Drug Name:** MIRVASO (brimonidine tartrate) Gel, 0.5%

**Sponsor:** Galderma Research and Development, Inc., Cranbury, NJ

### Background:

MIRVASO Gel, 0.5% is an alpha adrenergic receptor agonist being developed for the treatment of facial erythema of rosacea. The sponsor originally submitted a 2-year dermal rat carcinogenicity protocol for review on 12/20/2007. This protocol did not receive Exec CAC concurrence because there was no adequate dose-ranging data to support dose selection. The sponsor initiated a 2-year dermal rat carcinogenicity study without receiving Exec CAC concurrence. Part of that study generated data for a 13-week dermal rat dose range-finding study and the dose range-finding study was submitted with a new 2-year dermal carcinogenicity study protocol on 01/21/2009. The Exec CAC meeting recommendations and conclusions were relayed to the sponsor on 03/05/2009. The sponsor initiated the 2-year dermal rat carcinogenicity study following the Committee's recommendations.

On 09/15/2010, the sponsor submitted a request for study protocol modification, based on an increase in mortality in mid dose and high dose females at Week 41 of the study. The sponsor was advised to reduce the concentrations of brimonidine tartrate gel for the mid and high dose females on 09/24/2010. On 09/08/2011, the sponsor submitted

another request for study protocol modification based on a low survival rate noted in the high dose female group at Week 92. The sponsor was provided with guidance on appropriate dose group termination criteria on 10/05/2011. The 2-year dermal rat carcinogenicity study was completed on 09/27/2012. The final study report was submitted to NDA 204708 on 10/25/2012.

### Rat Carcinogenicity Study:

In a 2-year dermal rat carcinogenicity study, topical doses of 0 (water control), 0 (vehicle control), 0.9, 1.8, and 5.4 mg/kg/day brimonidine tartrate (0.03%, 0.06%, and 0.18% gel applied to 20% BSA once daily at 3 ml/kg) were administered to males. Initially topical doses of 0 (water control), 0 (vehicle control), 5.4, 30, and 60 mg/kg/day brimonidine tartrate (0.18%, 1%, and 2% gel applied to 20% BSA once daily at 3 ml/kg) were administered to females. Due to higher mortality rate noted in mid dose and high dose female groups, topical doses for mid dose and high dose females were reduced to 10.8 and 21.6 mg/kg/day (0.36%, and 0.72% gel applied to 20% BSA once daily at 3 ml/kg), respectively, on Day 343 and thereafter. The vehicle gel contained (b) (4), methylparaben (b) (4), phenoxyethanol (b) (4), glycerin (b) (4), titanium dioxide (b) (4), propylene glycol (b) (4), sodium hydroxide (b) (4), and purified water (b) (4).

After dose reduction for mid dose and high dose females, mortality occurred at comparable rates among all groups. At the end of study survival rate was higher than 50% in all groups except the high dose female group (survival rate 40%). Survival rate at the end of the study was considered acceptable for study interpretation. Body weight in high dose males was lower over the duration of treatment, compared to both the water and vehicle controls (15-18%). In females, body weight was lower in all treated groups over the duration of treatment (16-25%), compared to both the water and vehicle controls. There was no significant test article-related skin irritation. There were no significant test article-related effects on hematology parameters.

For histopathological examination, a complete list of tissues was examined for all main study animals. There were no significant test article-related non-neoplastic findings in either sex. There were no significant findings in the pair-wise comparison between the water and vehicle control groups in either sex. No statistical significance was achieved in any tumor types in treated males, either in the trend analysis or in pair-wise comparisons to vehicle control. The only statistically significant finding was the incidence of schwannoma in abdominal cavity in high dose females (incidence 2/60). The incidence of schwannoma in high dose females was statistically significant in the trend analysis ( $p$  value = 0.04), but not in the pair-wise comparison to vehicle control ( $p$  = 0.185). Schwannoma was also noted in abdominal cavity in the male vehicle control group, with an incidence of 1/60. Dietary carcinogenicity studies have been conducted for brimonidine tartrate. No compound-related carcinogenic effects were observed in either a 21-month dietary mouse carcinogenicity study (doses up to 2.5 mg/kg/day) or a 24-month dietary rat carcinogenicity study (doses up to 1.0 mg/kg/day). The finding of schwannoma in abdominal cavity in high dose females in this study is considered

biologically insignificant. Overall there were no significant test article-related neoplastic findings, under the study conditions.

**Executive CAC Recommendations and Conclusions:**

- The Committee concluded that the study was acceptable.
- The Committee concurred that there were no drug-related neoplasms in the dermal rat carcinogenicity study.

David Jacobson-Kram, Ph.D.  
Chair, Executive CAC

cc:\n  
/Division File, DDDP  
/B. Hill, Supervisor, DDDP  
/J. Wang, P/T reviewer, DDDP  
/D. Williams, Project Manager, DDDP  
/A. Seifried, OND IO

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JIANYONG WANG  
04/24/2013

BARBARA A HILL  
04/25/2013

## PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

**NDA Number:** 204708

**Applicant:** Galderma Research and  
Development, Inc., Cranbury, NJ

**Stamp Date:**  
10/25/2012

**Drug Name:** Mirvaso  
(brimonidine tartrate) Gel, 0.5%

**NDA Type:** 505(b)(2)

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		This is an electronic CTD submission.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		In addition to submitted repeat dose dermal toxicity studies, a 12-month photocarcinogenicity study in hairless mice, a 2-year dermal rat carcinogenicity study, and special toxicology studies, the sponsor proposes to rely upon the Agency's finding of safety on Alphagan 0.2% ophthalmic solution (NDA 20613) to support this NDA.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	X		
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?	X		
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?	X		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		

File name: 5\_Pharmacology\_Toxicology Filing Checklist for NDA\_BLA or Supplement  
010908

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR  
NDA/BLA or Supplement**

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?		X	The multiples of maximum recommended human dose were not provided in Section 8.1 and were incomplete in Section 13.1. The labeling for these two sections needs to be modified.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)			It is not applicable to this NDA.
11	Has the applicant addressed any abuse potential issues in the submission?			It is not applicable to this NDA.
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			This NDA is not to support a Rx to OTC switch.

**IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? YES**

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

N/A.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None at this time.

Jianyong Wang 11/27/2012  
 \_\_\_\_\_  
 Reviewing Pharmacologist Date

Barbara Hill see sign-off date  
 \_\_\_\_\_  
 Team Leader/Supervisor Date

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JIANYONG WANG  
11/28/2012

BARBARA A HILL  
11/28/2012