CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY IND REVIEW AND EVALUATION

Application number:	NDA 22474
Supporting document/s:	SDN 145
Sponsor's letter date:	05 September, 2014
CDER stamp date:	09 September, 2014
Product:	ella® (Ulipristal acetate)
Indication:	Emergency Contraceptive
Sponsor:	HRA Pharma
Review Division:	Division of Reproductive and Urologic Products
Reviewers:	Drs. Deepa Rao D.V.M., Ph.D., and Lynnda Reid, Ph.D
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1 Executive Summary

1.1 Introduction

Ella® is an approved marketed drug for emergency contraception. The active ingredient is ulipristal acetate, a selective progestin receptor modulator (SPRM) with mixed progesterone receptor agonist/antagonist and anti-glucocorticoid activities. The anti-progestational pharmacological activity on the hypothalamic-pituitary-gonadal axis has been targeted to treat women desiring emergency contraception for up to 120 hours following unprotected sexual intercourse.

The sponsor has now submitted carcinogenicity studies in rats and mice impacting INDs (b) (4) . Review of data from these studies also impacts Section 13 of the label for the approved marketed drug ella®.

1.2 Brief Discussion of Nonclinical Findings

Data from the two year rat carcinogenicity study reveals the presence of adrenocortical adenomas in the intermediate dose group of female rats that is statistically significant. This incidence of adrenocortical adenomas in female rats could not be definitively ruled out as a treatment-related effect based on the biological plausibility of variable dose-response effects due to agonist/antagonist activity of endocrine modulators. No other drug-related tumors were noted in female or male rats.

Data from the 26 week transgenic mouse study did not reveal any drug-related neoplasms in male or female mice.

1.3 Recommendations

1.3.1 Clinical Study (ies) Safe to Proceed: Yes

1.3.3 Additional Recommendation(s) (Non-hold comments/advice to sponsor) *if any.*

Section 13 of the label will be updated to include information from the results of the carcinogenicity studies.

8 Carcinogenicity

8.1 Two Year Oral Carcinogenicity Study in Rats

Study title: PGL4001: 104 Week Oral (Gavage) Administration Carcinogenicity Study in the Sprague Dawley Rat

Study no.:	8211643
Study report location:	EDR: S0065 Module 4.2.3.4.1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	24 August, 2009 (Day 1 dosing)
GLP compliance:	Yes, UK-MHRA and OECD regulations
QA statement:	Included
Drug, lot #, and % purity:	PGL4001, Lots 2 and 8, 98.6% purity
CAC concurrence (doses):	Following the ECAC protocol review, (b) (4) the recommended doses of 1, 3, and 10 mg/kg/day in male and female rats based on greater than 25-fold AUC ratios of rodent to human exposure.

Key Study Findings

Adequacy of Carcinogenicity Study

- Doses used were based on recommendations made by ECAC in response to the carcinogenicity protocol assessment request (DAARTS IND (b) (4), Dr. Adele Seifried dated July 15, 2009).

- Actual multiples of clinical exposure achieved in this study (based on $AUC_{(0\text{-}t)}$) in male and female rats were 0.5, 5, 23 and 0.4, 5, and 31 times the clinical dose of 30 mg in humans for doses used at 1, 3, and 10 mg/kg/day.

- The study was terminated early due to morbidity and mortality across all groups. The incidence of morbidity and mortality in the water control group (Dose Group 1) was higher than all other groups. Termination of study in both sexes was based on ECAC survival/termination criteria being achieved in the water control group (Dose Group 1). Sponsor consulted with the non-clinical reviewer prior to termination of the studies (DAARTS IND (b) (4) Dr. Jeffrey Bray dated May 10, 2011). All female groups were terminated commencing Week 99 and all male groups were terminated commencing in Week 100. No clear explanation for early mortality in both sexes was provided by the sponsor.

- Dose-related gender differences in body weight gain were noted. Males showed a dose-related decrease in body weight gain with corresponding reductions in food consumption. Females showed an initial increase in body weight gain with corresponding increases in food consumption, followed by a decrease in body weight after week 28 with no significant corresponding changes in food consumption compared to controls.

- Statistical analysis of tumor data was conducted by the sponsor. No statistical analysis was completed at the FDA at this time.

Key Tumor Findings

There are no obvious dose-related increased incidences of tumors in PGL4001 treated animals. Statistically significant findings (based on sponsor-conducted statistical analysis) include an increase in adrenal cortical adenomas and pituitary adenomas/carcinomas in the intermediate dose group females administered 3 mg/kg/day. Both these tumors show a decrease in incidence at the high dose of 10 mg/kg/day, and no statistically significant dose-related trends were noted for either of these tumors.
In females, the incidence of benign thymomas is higher than the concurrent control (no tumors), the historical control incidence (provided by the sponsor), and also higher than historical incidences published for Sprague-Dawley rats (McMartin et al, 1992, and Brix et al, 2005). This was not found to be statistically significant (sponsor conducted analysis).

Neoplastic incidence of interstitial cell adenoma in the testis is considered to be generally comparable to the background historical control incidence provided by the sponsor, and below the background incidence in control Sprague-Dawley rats (McMartin et al, 1992).

All other tumor incidences are considered to be sporadic or incidental, not dose-related, and comparable with the concurrent controls, and/or historical control incidence (provided by the sponsor), and/or comparable to background control incidences for Sprague-Dawley rats (McMartin et al, 1992; Brix et al, 2005). Based on the above criteria for evaluation, all other tumor incidences were considered to unlikely related to the administration of PGL4001.

Appropriateness of Test Models

The duration of study, test species/strain, route of exposure appears adequate.

Methods

Doses:	1, 3 and 10 mg/kg/day
Frequency of dosing:	Once daily
Dose volume:	5 mL/kg
Route of administration:	Oral Gavage
Formulation/Vehicle:	PGL4001 (also known as VA-2914 and CDB-2914) in Aqueous Suspending Vehicle (98.7% water, 0.9% w/v NaCl, 0.9% v/v Benzyl Alcohol, 0.4% v/v polyoxethylene sorbitan monooleeate, 0.5% w/v carboxymethylcellulose).
Basis of dose selection:	Based on ECAC recommendations (Response to Carcinogenicity Protocol Assessment Request –Final CAC Report – IND (b) (4), July 15, 2009)
Species/Strain:	Sprague-Dawley Rats
Number/Sex/Group:	60/sex/group, 5 groups

Dose Group 1	Water Control	60/sex
Dose Group 2	Vehicle Control	60/sex
Dose Group 3	1 mg/kg/day	60/sex
Dose Group 4	3 mg/kg/day	60/sex
Dose Group 5	10 mg/kg/day	60/sex

Age:	~ 6 weeks old at start of dosing
Animal housing:	Cage-housing (in groups of 5)
Paradigm for dietary restriction:	Not restricted. Ad libidum access to food and water
Dual control employed:	Yes, Group 1 was water control and Group 2 was vehicle control
Interim sacrifice:	No
Satellite groups:	For toxicokinetics, 9 per sex at 1, 3, and 10 mg/kg/day and 3 per sex for Group 1 (water control)
Deviation from study protocol:	Dosing Deviations (Appendix 1)

Observations and Results

Mortality

Although the studies were terminated early in both sexes, with a higher incidence of mortality in both sexes of the water control group (Dose Group 1) compared to PGL 4001 treated groups. The incidence and spectrum of histopathological findings is similar between decedents and rats surviving to terminal kill. Statistical analysis of tumor data between the two control groups revealed no statistically significant differences. It is unlikely that mortality was due to PGL 4001.

Reviewer Comment: *No explanation on the cause of early deaths in the water control group was provided. It is not known how the mortality/morbidity rate*

compares to site-specific (laboratory) historical control data for Sprague-Dawley rats.

Table 1: Survival Data in Males and Females

Survival Data										
Dose (mg/kg)	**Males**					**Females**				
	Gp 1	Gp 2	Gp 3	Gp 4	Gp 5	Gp 1	Gp 2	Gp 3	Gp 4	Gp 5
Decedents*	40	35	33	29	28	40	35	33	31	21
Survived to T-Sac	20	25	27	31	32	20	25	27	29	39
% Survival to T-Sac	**33%**	**42%**	**45%**	**52%**	**53%**	**33%**	**42%**	**45%**	**48%**	**65%**

*Decedents – includes animals found dead, killed moribund, and accidental deaths

Figure 1: Group Survival – males

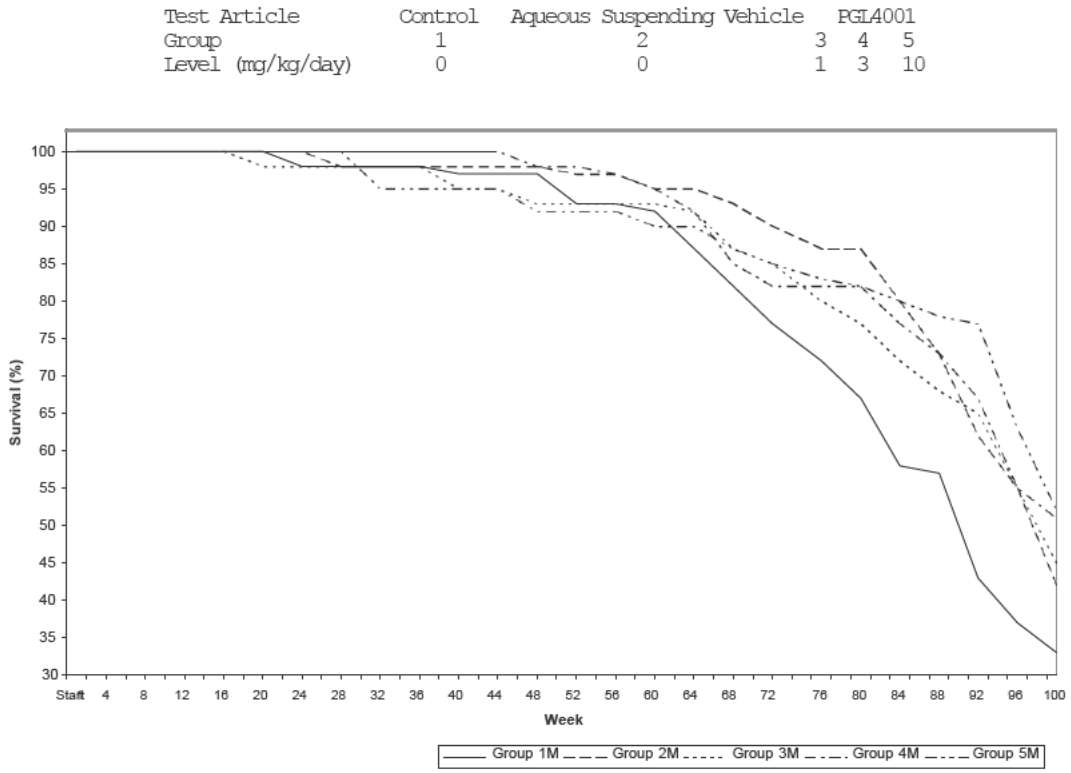
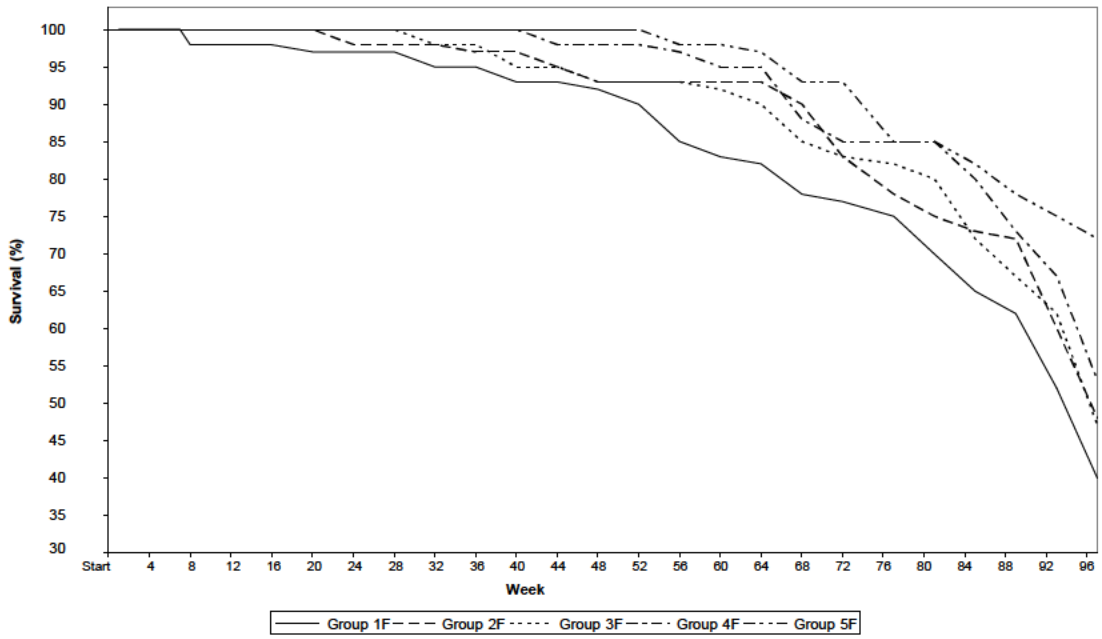


Figure 2: Group Survival – females

Test Article	Control	Aqueous Suspending Vehicle	PGL4001	
Group	1	2	3	4	5
Level (mg/kg/day)	0	0	1	3	10



Clinical Signs

No adverse clinical signs were noted.

Body Weights

Body weight gains were significantly decreased in male rats treated with 10 mg/kg compared to vehicle controls starting from approximately Week 8. At Week 52, males treated with 10 mg/kg/day showed a reduction of body weight gain of approximately 32% compared with Group 2 vehicle control, and -21% compared with Group 1 water control. At termination, the difference was approximately -18% lower compared with the Group 2 vehicle control, and -7% compared with Group 1 water control.

Females treated with 10 mg/kg/day showed an increase in body weight gain of +67% (increased absolute body weights of approximately +12%) compared with Group 2 vehicle controls up to Week 28. Thereafter, gains were reduced. At termination, body weight gains were decreased by approximately -12% in rats treated with 10 mg/kg/day compared with Group 2 vehicle control, but, there were no differences in bodyweights compared with Group 1 water control.

Figure 3: Group Mean Body Weights – Males

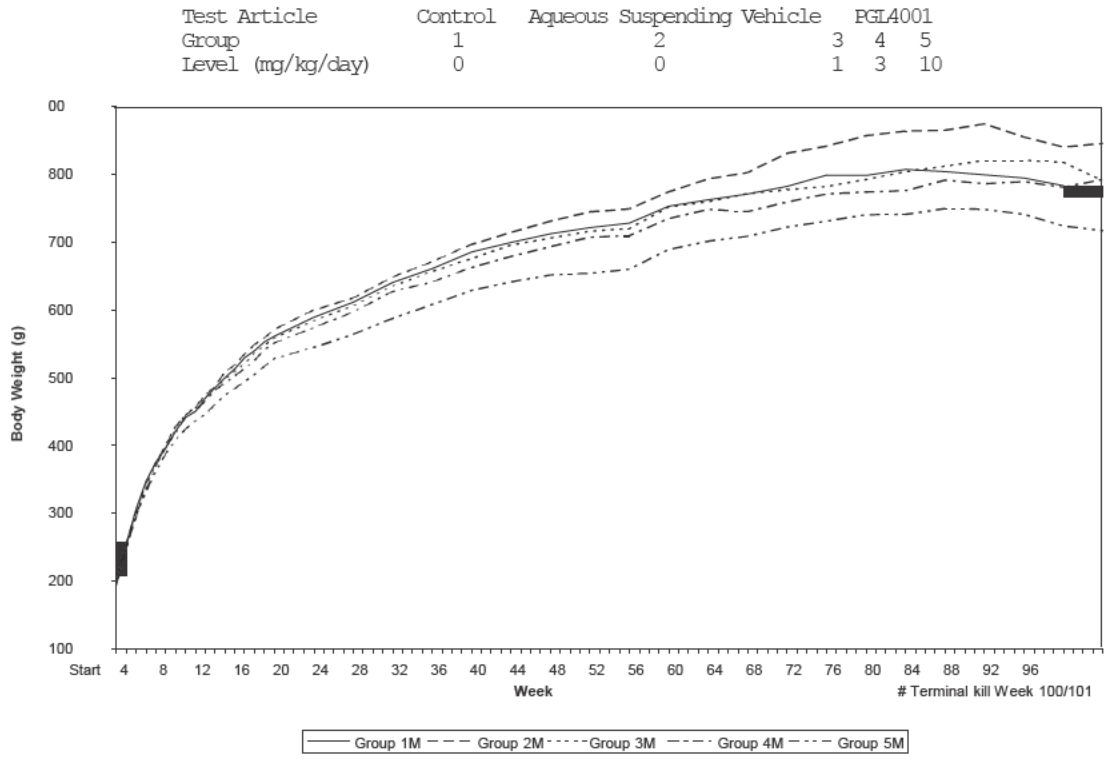
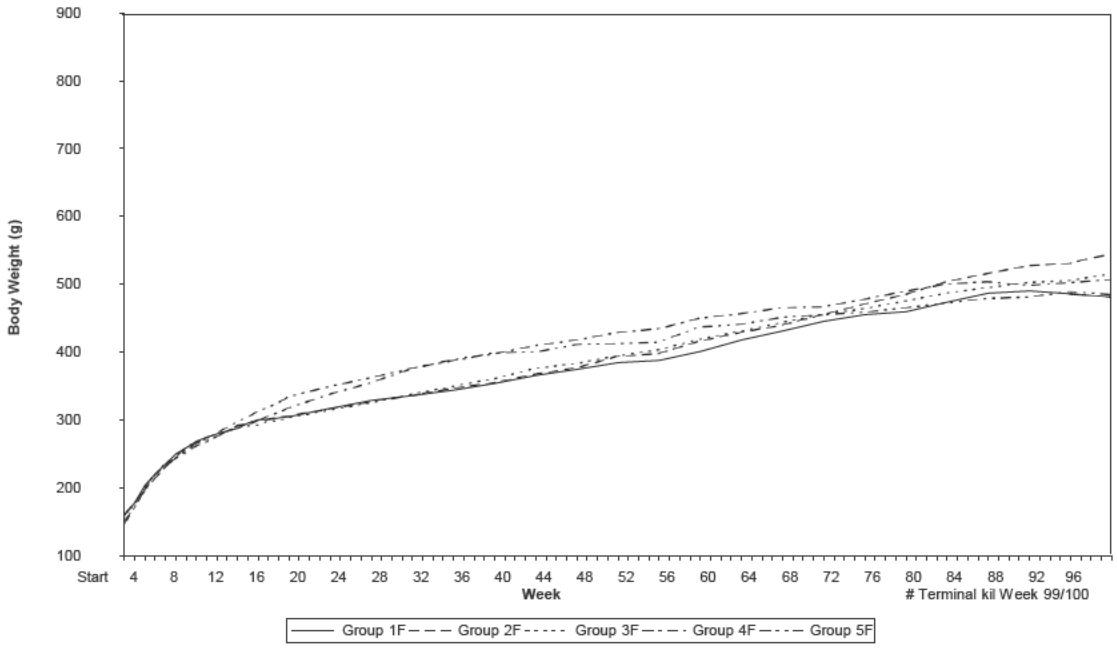


Figure 4: Group Mean Body Weights – Females



Food Consumption

Males treated with 10 mg/kg/day showed minor but significant reductions in food consumption over the entire treatment period compared with Group 2 vehicle controls.

Females treated with 10 mg/kg/day showed minor increases in food consumption from Week 9 (achieving statistical significance from Weeks 14 to 28), but thereafter consumptions were similar to controls.

Figure 5: Group Mean Food Consumption over Selected Intervals

Test Article		Control	Aqueous Suspending Vehicle		PGL4001	
Group		1	2	3	4	5
Level (mg/kg/day)		0	0	1	3	10

		Mean food consumption (g/animal/week) for Group:						
Week		1M	2M	3M	4M	5M	Statistics	
1-13	Mean	193.3	195.3	195.2	193.9	188.6	DR*	A SD
		5.55	6.79	6.67	7.69	7.57		
14-28	Mean	199.1	201.1	199.2	196.3	187.0**		A SD
		5.96	10.89	10.06	10.77	9.30		
32-52	Mean	200.8	202.9	200.8	196.9	190.9*		A SD
		7.85	10.23	11.67	11.14	8.24		
56-96	Mean	197.9	202.0	192.0	190.8*	182.0***		A SD
		7.62	11.94	10.56	10.16	10.67		
56-100	Mean	197.5	202.0	191.4	190.1*	181.4***		A SD
		7.45	12.20	10.73	9.77	10.09		
1-96	Mean	196.5	199.4	196.1	194.1	186.9**		A SD
		5.15	8.83	7.85	9.14	8.10		
1-100	Mean	196.5	199.8	195.8	193.8	186.6***		A SD
		5.23	9.10	7.91	9.09	7.97		
Week		1F	2F	3F	4F	5F	Statistics	
1-13	Mean	137.1	141.4	133.7	139.4	142.4		A SD
		7.43	8.98	9.21	9.51	8.95		
14-28	Mean	134.8	140.0	134.2	145.0	152.0**		A SD
		5.96	8.39	9.82	9.86	7.52		
32-52	Mean	142.7	150.1	144.3	152.5	153.1		A SD
		11.00	12.00	13.90	11.45	10.86		
56-96	Mean	145.7	151.7	147.4	146.2	143.9	DR*	A SD
		7.15	9.88	7.35	5.59	9.12		
1-96	Mean	139.8	144.9	139.0	144.4	146.3		A SD
		6.89	8.87	8.88	7.96	8.03		

* P<0.05
** P<0.01
*** P<0.001
DR = significant dose response test (Groups 2,3,4,5)

A = ANOVA, dose response and Dunnett's

Gross Pathology

Changes in gross pathology seen in the lungs included pale areas or pale foci in both sexes, with an increased incidence in females given 10 mg/kg. Changes in other organs included prostate (small), ovary (small), and pituitary (large).

Table 2: Group Incidence of Selected Macroscopic Findings

		Males					Females				
		1M	2M	3M	4M	5M	1F	2F	3F	4F	5F
Tissue and finding	Level (mg/kg/day)	0	0	1	3	10	0	0	1	3	10
Lungs	No. examined:	20	25	27	31	32	20	25	27	29	39
Pale focus		7	4	6	5	7	1	-	1	4	8
Pale area		2	1	4	3	6	3	2	3	8	13
Ovaries		0	0	0	0	0	20	25	27	29	39
Small		-	-	-	-	-	-	1	5	3	9
Prostate		20	25	27	31	32	0	0	0	0	0
Small		-	-	2	2	5	-	-	-	-	-
Pituitary		20	25	27	31	32	20	25	27	29	39
Large		2	4	3	3	3	**9**	**10**	**12**	**16**	**22**

Histopathology

Peer Review

External peer review was not completed and stated as “Not required” by the sponsor.

Neoplastic

Group incidences of neoplastic data for evaluating potential neoplasms are summarized in the reviewer generated table below. Historical control tumor incidence data was provided by the sponsor for carcinogenicity studies conducted in Sprague-Dawley Rats between 2007 and 2013. When available, other published data for historical control tumor incidence data for carcinogenicity studies conducted in Sprague-Dawley Rats have also been included (McMartin et al, 1992; Brix et al, 2005).

Table 3: Summary of Group Incidences of Neoplastic Data (Reviewer generated)

		Males (dose in mg/kg/day)						Females (dose in mg/kg/day)				
		Group 1	Group 2	Group 3	Group 4	Group 5		Group 1	Group 2	Group 3	Group 4	Group 5
Organ and Finding		**Vehicle Control**	**Water Control**	**1**	**3**	**10**		**Vehicle Control**	**Water Control**	**1**	**3**	**10**
ADRENAL GLAND	**# examined**	**60**	**60**	**60**	**60**	**60**		**60**	**60**	**60**	**60**	**60**
Cortical Adenoma (All)		0	2 (3.3%)	1 (1.7%)	1 (1.7%)	1 (1.7%)		1 (1.7%)	2 (3.3%)	2 (3.3%)	**10 (16.7%)***	1 (1.7%)
Control Incidence - Cortical Adenoma	***9/717 or 1.3% (Sponsor); 1.6% (McMartin et al, 1992)***							***15/718 or 2% (Sponsor); 4.6% (McMartin et al, 1992); 0.5% (Brix et al, 2005)***				
**** indicates statistical significance based pair-wise comparison with control group***												
Benign Phaeochromocytoma (All)		4 (16%)	9 (15%)	6 (10%)	7 (11.7%)	7 (11.7%)		1 (1.7%)	2 (3.3%)	1 (1.1%)	2 (3.3%)	1 (1.7%)
Control Incidence - Benign Phaeochromocytoma	***104/717 or 14.5% (Sponsor); 19% (McMartin et al, 1992)***							***19/718 or 2.6% (Sponsor); 5.3% (McMartin et al, 1992); 7.6% (Brix et al, 2005)***				
Malignant Phaeochromocytoma (All)		1 (1.7%)	2 (3.3%)	0	2 (3.3%)	1 (1.7%)		0	0	1 (1.7%0	0	0
Control Incidence - Malignant Phaeochromocytoma	***19/717 or 2.7% (Sponsor); 1.9% (McMartin et al, 1992)***							***2/718 or 0.27% (Sponsor); 0.9% (McMartin et al, 1992); 0.3% (Brix et al, 2005)***				
Benign + Malignant Phaeochromocytoma (All)		5 (8.3%)	11 (18.3%	6 (10%)	9 (15%)	8 (13.3%)		1 (1.7%)	2 (3.3%)	2 (3.3%)	2 (3.3%)	1 (1.7%)

Control Incidence - Benign + Malignant Phaeochromocytoma	***123/717 or 17.2% (Sponsor); 20.9% (McMartin et al, 1992)***							***21/718 or 2.9% (Sponsor); 6.2% (McMartin et al, 1992); 7.9% (Brix et al, 2005)***				
TESTIS												
Interstitial Cell Adenoma (All)		0	1 (2.9%)	1 (2.9%)	0	3 (5%)						
Control Incidence - Interstitial Cell Adenoma	***20/720 or 2.8% (Sponsor); 6.5% (McMartin et al, 1992)***											
PITUITARY												
Pituitary Adenoma (All)		28 (46.7%)	28 (46.7%)	15 (25%)	25 (42.4%)	18 (30.5%)		31 (51.7%)	37 (61.7%)	34 (56.7%)	**44 (73.4%)***	29 (48.3%)
Historical Control Incidence-Pituitary Adenoma		***322/720 or 44.7% (Sponsor); 62.2% (McMartin et al, 1992)***						***463/720 or 64.3% (Sponsor); 84.7% (McMartin et al, 1992); 41.2% (Brix et al, 2005)***				
Pituitary Carcinoma (All)		0	0	0	0	0		1 (1.7%)	0	1 (1.7%)	0	0
Historical Control Incidence-Pituitary Carcinoma		***1/720 or 0.1% (Sponsor); 1.4% (McMartin et al, 1992)***						***11/720 or 1.5% (Sponsor); 3.4% (McMartin et al, 1992); 0.3% (Brix et al, 2005)***				
Pituitary Adenoma + Carcinoma		28 (46.7%)	28 (46.7%)	15 (25%)	25 (42.4%)	18 (30.5%)		32 (53.4%)	37 (61.7%)	35 (58.4%)	**44 (73.4%)***	29 (48.3%)
Historical Control Incidence-Pituitary Adenoma +Carcinoma		***323/720 or 44.8% (Sponsor); 63.6% (McMartin et al, 1992)***						***463/720 or 64.3% (Sponsor); 88.1% (McMartin et al, 1992); 41.5% (Brix et al, 2005)***				
**** indicates statistical significance based pair-wise comparison with control group***												

THYROID											
C-cell Adenoma (All)		4 (6.7%)	3 (5%)	2 (3.4%)	3 (5%)	5 (8.4%)		2 (3.4%)	3 (5%)	5 (8.4%)	4 (6.7%)	5 (8.4%)
Historical Control Incidence - C-cell Adenoma		***56/699 or 8% (Sponsor); 6.5% (McMartin et al, 1992)***						***44/713 or 6.2% (Sponsor); 5.9% (McMartin et al, 1992); 26.2% (Brix et al, 2005)***				
C-cell Carcinoma (All)		2 (3.4%)	1 (1.7%)	0	0	0		0	0	0	0	0
Historical Control Incidence - C-cell Carcinoma		***13/699 or 1.9% (Sponsor); 0.9% (McMartin et al, 1992)***						***2/713 or 0.3% (Sponsor); 1.7% (McMartin et al, 1992); 3.8% (Brix et al, 2005)***				
C-cell adenomas + carcinomas (All)		6 (10%)	4 (6.7%)	2 (3.4%)	3 (5%)	5 (8.4%)		2 (3.4%)	3 (5%)	5 (8.4%)	4 (6.7%)	5 (8.4%)
Historical Control Incidence - C-cell adenomas + carcinomas		***69/699 or 9.9% (Sponsor)***						***46/713 or 6.5% (Sponsor)***				
Follicular Cell Adenoma (All)		3 (5%)	0	2 (3.4%)	0	2 (3.4%)		0	1 (1.7%)	1 (1.7%)	1 (1.7%)	0
Historical Control Incidence - Follicular Cell Adenoma		***23/699 or 3.3% (Sponsor); 3.9% (McMartin et al, 1992)***						***6/713 or 0.8% (Sponsor); 1.9% (McMartin et al, 1992); 0.5% (Brix et al, 2005)***				
Follicular Cell Carcinoma (All)		0	0	1 (1.7%)	0	1 (1.7%)		0	0	0	0	1 (1.7%)
Historical Control Incidence - Follicular Cell Carcinoma		***3/699 or 0.4% (Sponsor); 2.2% (McMartin et al, 1992)***						***0/713 (Sponsor); 1.4% (McMartin et al, 1992)***				
Follicular Cell adenomas + carcinomas (All)		3 (5%)	0	3 (5%)	0	3 (5%)		0	1 (1.7%)	1 (1.7%)	1 (1.7%)	1 (1.7%)
Historical Control Incidence - Follicular Cell Adenoma + Carcinoma		***26/699 or 3.7% (Sponsor)***						***6/713 or 0.8% (Sponsor)***				

THYMUS												
Thymoma	**# examined**							**58**	**57**	**56**	**59**	**55**
Benign Thymoma (All)								0	0	0	**1 (1.7%)***	**3 (5.5%)***
Control Incidence - Benign Thymoma								***17/693 or 2.5% (Sponsor); 0.6% (McMartin et al, 1992); 0.3% (Brix et al, 2005)***				
Malignant Thymoma(All)								0	0	1 (1.8%)	0	0
Control Incidence - Malignant Thymoma								***1/693 or 0.1% (Sponsor)***				
Benign + Malignant Thymoma (All)								0	0	1 (1.8%)	**1 (1.7%)***	**3 (5.5%)***
Control Incidence - Benign + Malignant Thymoma								***18/693 or 2.6% (Sponsor)***				
**** indicates statistical significance based pair-wise comparison with control group***												

Non Neoplastic

Treatment-related non-neoplastic findings were observed in the reproductive system (mammary gland, ovary, uterus, vagina, seminal vesicle, prostate), endocrine system (adrenal, pituitary), and thymus, muscle, liver, pancreas and lungs.
A summary of non-neoplastic changes is shown in the table below:

Table 4: Group Incidence of Selected Non-Neoplastic Findings

Mammary

		Males					Females				
		1M	2M	3M	4M	5M	1F	2F	3F	4F	5F
Tissue and finding	Level (mg/kg/day)	0	0	1	3	10	0	0	1	3	10
Mammary gland	No. examined:	9	19	9	14	24	20	25	27	28	39
Cystic change	Grade -	9	17	9	13	21	17	15	10	10	11
	1	-	-	-	1	3	2	1	1	1	4
	2	-	1	-	-	-	**1**	**6**	**11**	**12**	**14**
	3	-	1	-	-	-	-	2	2	5	10
	4	-	-	-	-	-	-	1	2	-	-
	5	-	-	-	-	-	-	-	1	-	-
Acinar hyperplasia	Grade -	9	19	9	14	24	9	7	24	20	34
	1	-	-	-	-	-	3	5	2	5	5
	2	-	-	-	-	-	6	9	1	2	-
	3	-	-	-	-	-	1	4	-	-	-
	4	-	-	-	-	-	1	-	-	1	-
Atypical hyperplasia	Grade -	9	19	9	14	24	16	22	25	28	39
	1	-	-	-	-	-	4	2	2	-	-
	2	-	-	-	-	-	-	1	-	-	-

Ovary

		Males					Females				
		1M	2M	3M	4M	5M	1F	2F	3F	4F	5F
Tissue and finding	Level (mg/kg/day)	0	0	1	3	10	0	0	1	3	10
Ovary	No. examined:	0	0	0	0	0	20	25	27	29	39
Acyclic-follicular	Grade -						12	16	7	4	1
	present						**8**	**9**	**20**	**25**	**38**

Uterus

		Males					Females				
		1M	2M	3M	4M	5M	1F	2F	3F	4F	5F
Tissue and finding	Level (mg/kg/day)	0	0	1	3	10	0	0	1	3	10
Uterus	No. examined:	0	0	0	0	0	20	25	27	28	39
Cystic glands	Grade -						16	21	12	14	21
	1						**2**	**1**	**10**	**13**	**10**
	2						**1**	**3**	**5**	**1**	**6**
	3						-	-	-	-	1
	4						1	-	-	-	1

Vagina

		Males					Females				
		1M	2M	3M	4M	5M	1F	2F	3F	4F	5F
Tissue and finding	Level (mg/kg/day)	0	0	1	3	10	0	0	1	3	10
Vaginal Mucification	No. examined:	0	0	0	0	0	20	25	27	29	39
	Grade -						**4**	**6**	**14**	**19**	**23**
	1						2	6	5	5	7
	2						7	7	5	5	5
	3						6	5	2	-	4
	4						1	1	1	-	-

Seminal Vesicle and Prostate

Tissue and finding	Level (mg/kg/day)	Males 1M 0	2M 0	3M 1	4M 3	5M 10	Females 1F 0	2F 0	3F 1	4F 3	5F 10
Seminal vesicle	No. examined:	20	25	27	31	32	0	0	0	0	0
contraction	Present	**1**	**2**	**5**	**10**	**16**					
Prostate											
Contraction	Present	-	-	**1**	**3**	**11**					

Adrenal and Pituitary

Tissue and finding	Level (mg/kg/day)	Males 1M 0	2M 0	3M 1	4M 3	5M 10	Females 1F 0	2F 0	3F 1	4F 3	5F 10
Adrenal	No. examined:	20	25	27	31	32	20	25	27	29	39
Focal medullary hyperplasia	Grade -	17	19	21	27	24	19	22	24	24	29
	1	1	3	2	3	4	**1**	**3**	**3**	**2**	**9**
	2	1	1	2	-	2	-	-	-	2	1
	3	1	2	2	1	2	-	-	-	1	-
Pituitary											
Diffuse hyperplasia	Grade -	20	25	26	30	32	19	19	20	24	16
	1	-	-	-	-	-	**1**	**3**	**1**	**1**	**8**
	2	-	-	1	1	-	**-**	**3**	**5**	**1**	**12**
	3	-	-	-	-	-	**-**	**-**	**1**	**3**	**3**
Focal hyperplasia	Grade -	10	11	7	18	11	11	19	19	26	33
	1	3	6	5	10	8	6	-	4	-	1
	2	4	7	11	3	11	2	4	-	2	5
	3	3	1	4	-	2	1	2	4	1	-

Thymus, Muscle, Liver, and Lung

Tissue and finding	Level (mg/kg/day)	Males 1M 0	2M 0	3M 1	4M 3	5M 10	Females 1F 0	2F 0	3F 1	4F 3	5F 10
Thymus	No. examined:	19	24	25	31	31	18	23	25	29	37
Medullary hyperplasia	Grade -	19	23	24	31	30	16	23	22	24	30
	1	-	1	1	-	1	2	-	3	3	2
	2	-	-	-	-	-	-	-	-	-	2
	3	-	-	-	-	-	-	-	-	1	3
	4	-	-	-	-	-	-	-	-	1	-
Skeletal muscle atrophy	No. examined:	20	25	27	31	32	20	25	27	29	39
	Grade -	7	5	4	4	7	9	8	10	10	8
	1	7	12	15	16	17	**11**	**16**	**16**	**19**	**29**
	2	3	7	5	8	3	-	1	1	-	2
	3	3	1	2	3	4	-	-	-	-	-
	4	-	-	1	-	1	-	-	-	-	-
Liver	No. examined:	20	25	27	31	32	20	25	27	29	39
Bile duct hyperplasia	Grade -	8	9	12	9	3	11	19	16	11	11
	1	11	11	8	16	11	7	**6**	**9**	**13**	**15**
	2	**1**	**5**	**7**	**5**	**14**	**2**	-	**2**	**5**	**10**
	3	-	-	-	**1**	**4**	-	-	-	-	**3**
Pancreas	No. examined:	20	25	27	31	32	20	25	27	29	39
Lobular atrophy	Grade -	18	19	18	15	18	13	22	26	21	32
	1	**1**	**5**	**8**	**10**	**11**	6	1	-	8	7
	2	**1**	**1**	**1**	**4**	**3**	1	2	-	-	-
	3	-	-	-	1	-	-	-	-	-	-
	4	-	-	-	-	-	-	-	1	-	-
	5	-	-	-	1	-	-	-	-	-	-

Lung	No. examined:	20	25	27	31	32	20	25	27	29	39
Foamy macrophages	Grade -	10	12	16	13	8	12	17	19	8	11
	1	10	12	10	12	17	4	7	4	12	14
	2	**-**	**1**	**1**	**6**	**7**	4	1	2	7	9
	3	-	-	-	-	-	-	-	2	1	5
	4	-	-	-	-	-	-	-	-	1	-

Key: - = finding not present, 1 = minimal, 2 = slight, 3 = moderate; 4 = moderately severe; 5 = severe

Integrated Evaluation of Potential Tumor Signals

Reproductive System:

Lesions in organs of the male and female reproductive systems generally reflect the pharmacological anti-progestin activity of PGL4001. No obvious dose-related neoplastic effects were noted.

Reproductive System: Females

Mammary Gland: Although histopathological diagnoses in the mammary gland include cystic changes, these were characterized by grossly dilated ducts without evidence of epithelial or glandular proliferation, lined by low cuboidal or flattened epithelium. Tumor incidences show an apparent dose-related decrease in the incidence of fibroadenomas in females given PGL4001.
Ovary: Gross pathology observations of small ovaries likely reflect the absence or marked reduction in size and number of corpora lutea suggesting acyclic follicular ovaries consistent with the anti-progestin pharmacological activity of PGL4001. Neoplastic incidences of one cystadenoma and one malignant granulosa cell tumor in the treated groups are considered sporadic or incidental.

Uterus: Histopathological changes in the uterus included cystic glands characterized by solitary or multiple cysts or dilated glands lined by flattened glandular epithelium. Neoplastic incidences of adenoma, adenocarcinoma and stromal polyp in control and treated groups are considered to be comparable to concurrent controls and/or historical background incidences (sponsor); while the incidences of one SCC (low dose group) is considered to be sporadic or incidental.

Vagina: Histopathological changes included vaginal mucification characterized by enlargement of the superficial cells of the vaginal epithelium with a clear cytoplasm containing mucus. No neoplastic changes in the vagina are noted.

Reproductive System: Males

Testis: Neoplastic incidence of interstitial cell adenoma in the testis is considered to be generally comparable to the background historical control incidence provided by the sponsor, and below the background incidence reported in control Sprague-Dawley rats (McMartin et al, 1992).

Seminal Vesicle: Histopathological changes included seminal vesicular contraction characterized by a reduction in size with little colloid in the lumen. No neoplastic changes in the seminal vesicles are noted.

Prostate: Statistically significant reduced prostate weights (relative to body weights) in animals given 10mg/kg/day, as well as gross observations of 'small' prostate reflect histopathological changes of contraction characterized by a reduction in size with little colloid in the lumen. No neoplastic changes in the prostate are noted.

Endocrine System

Lesions in the adrenal and pituitary generally reflect the pharmacological anti-progestin activity of PGL4001. Although no obvious dose-related neoplastic effects were noted, a treatment-related incidence of pituitary and adrenocortical adenomas by PGL4001 in the intermediate dose group in females cannot be definitively ruled out.
Adrenal Gland: Neoplastic incidences of cortical adenomas (no cortical carcinomas were noted), are considered to be comparable to concurrent controls and/or historical background incidences, *except for an increase in the incidence of cortical adenomas in the intermediate dose group in females (given 3 mg/kg/day of PGL4001). This increase in the intermediate dose group was also statistically significant (as conducted by the sponsor) by pair-wise comparison to the control vehicle group.* Benign and malignant phaeochromocytomas in treated and control groups are also considered to be comparable to concurrent controls and historical background incidences, and lower than reported historical incidences in Sprague-Dawley rats (*McMartin et al, 1992; Brix et al, 2005)*.

Typically, it can be sometimes challenging to differentiate hyperplasia from neoplasia in the adrenal cortex and medulla in rats. In this study, although an apparent dose-related increase in focal adrenal medullary hyperplasia was noted in females, no specific corresponding 'spike' was seen in the intermediate dose group. Histopathologically, focal medullary hyperplasia was characterized by focal or multifocal aggregates of medullary cells, usually with basophilic cytoplasm and more hyperchromatic nuclei than surrounding cells. There was no or minimal compression, with little alteration in architecture. Based on the morphological description and incidence of focal adrenal

medullary hyperplasia, the incidence of benign phaeochromocytoma in the intermediate dose group is unclear, and maybe a secondary effect of PGL4001.

For cortical adenomas, although non-neoplastic lesions (hypertrophy or hyperplasia) were not noted in the present 99-week study, based on lesions (hypertrophy of the zona fasiculata) noted in the 26-week study, and the anti-glucocorticoid pharmacological activity of PGL4001, a treatment-related incidence of cortical adenomas in the intermediate dose group cannot to be ruled out. However, there was no significant dose-related response and the incidence of cortical adenomas in the high dose group females was comparable to concurrent control incidences, within historical control incidences provided by the sponsor, as well as lower than published historical control incidences for Sprague-Dawley rats (McMartin et al, 1992).

Pituitary: Gross pathology observations of 'large' pituitaries noted in females reflect the histopathological changes of diffuse hyperplasia in the pituitary was characterized by a uniform field of mainly chromophobic cells in the pars distalis, and a diffusely basophilic appearance. Neoplastic incidence of pituitary adenomas is generally unremarkable compared to concurrent controls and historical control incidences (sponsor) and historical control incidence for Sprague-Dawley rats (McMartin et al, 1992). Although pituitary carcinomas were noted, they were comparable to the concurrent controls, and background incidences.

However, *an increase in the incidence of pituitary adenomas in the intermediate dose group in females (given 3 mg/kg/day of PGL4001) was noted. This increase in the intermediate dose group was also statistically significant (as conducted by the sponsor) by pair-wise comparison to the control vehicle group.* Similar to adrenal lesions, it can also be challenging to differentiate hyperplasia from neoplasia for pituitary lesions. Based on the anti-progestin pharmacological activity of PGL4001, a treatment-related incidence of pituitary adenomas in the intermediate dose group cannot be ruled out. *However, there was no significant dose-related response, and the incidence of pituitary adenomas in the high dose group was lower than concurrent control incidences, historical control incidences provided by the sponsor, as well as historical control incidences published for Sprague-Dawley rats (McMartin et al, 1992).*

Pancreas: Histopathological lesions in the pancreas included lobular atrophy characterized by increased prominence of ductular structures with atrophy of acinar structures and a variable inflammatory cell infiltrate. Incidences of islet cell adenoma and carcinoma in the control and treated groups were comparable to the incidence in concurrent controls and historical control incidence provided by the sponsor. The incidence of acinar cell adenoma in treated and control groups are considered to be incidental.

Neoplastic incidences of thyroid tumors (C-cell adenomas and carcinomas, and follicular cell adenomas and carcinomas) are considered to be comparable to concurrent controls and/or the historical control incidence provided by the sponsor and/or historical control incidences in Sprague-Dawley rats (McMartin et al, 1992; Brix et al, 2005).

Other Organ Systems

Thymus: Neoplastic findings of benign thymomas include a diffuse expansion of the medulla to a greater degree than hyperplasia, with focal loss of normal architecture and loss of the normal cortical rim. Since thymic medullary hyperplasia is considered part of a continuum of change with increasing severity to benign thymoma, the incidence of the non-neoplastic changes of moderate medullary hyperplasia appears to correlate with the dose-related increase in incidence of benign thymomas. However, this incidence of benign thymomas was not detected to be statistically significant (as conducted by the sponsor). In females, the incidence is higher than the concurrent control (no tumors), the historical control incidence (provided by the sponsor), and also higher than historical incidences published for Sprague-Dawley rats (McMartin et al, 1992, and Brix et al, 2005). Incidence of malignant thymoma is limited to one female in the mid-dose group.

Reviewer Comment: *The incidence stated in the sponsor's pathology report is apparently incorrect compared to the tumor data tables and historical control incidence data tables provided by the sponsor. It is unclear which data was used for statistical analysis by the sponsor since the incidence was found not to be statistically significant.*

Skeletal Muscle: Non-neoplastic histopathological changes in the skeletal muscle atrophy was characterized by fibers that were small and angular in cross-section, with prominent nuclei forming clusters. Surrounding fibers occasionally showed compensatory hypertrophy. Neoplastic incidences included hemangiosarcoma in treated and control groups which are considered to be sporadic or incidental.

Liver: Small but statistically significant increase in liver weights was likely reflected by non-neoplastic of bile duct hyperplasia characterized by bile duct proliferation. Bile ducts were surrounded by varying amounts of fibrous tissue and inflammatory cell infiltrates. The stroma was occasionally sclerotic and the ductules distorted. *Neoplastic changes included incidences of hepatocellular adenoma in treated and control groups and is considered to be sporadic or incidental.*

Lung: Non-neoplastic lesions include the presence of foamy macrophages in the lung characterized by small collections of alveolar macrophages with abundant foamy cytoplasm, particularly in sub-pleural or peribronchial areas. Often, the lesions were chronic, which had a granulomatous appearance, with cholesterol clefts in the histiocyte cytoplasm, perivascular lymphocyte accumulations and bronchiolo-alveolar hyperplasia of the alveolar epithelium. These non-neoplastic changes in the lung may reflect the gross pathology findings of pale area or pale foci and are likely due to secondary

inflammatory reaction to test article aspiration following oral gavage administration. Neoplastic incidence was limited to broncho-alveolar adenoma in one control female that is considered to be sporadic and incidental.

Toxicokinetics

Blood samples for toxicokinetics (0.5 mL nominal) were taken from all toxicokinetic animals on Day 1, during Weeks 13, 26 and 52 at 0.5, 1, 2, 4, 6 and 24 hours after dosing.

Male and female rats were exposed to 0.5, 5, 23 and 0.4, 5, and 31 times the clinical dose of 30 mg in humans. PGL4001 was absorbed in rats to reach maximum levels at sampling times of 0.5 to 1 hr post-dose. Half-life values for PGL4001 were between 1.53 and 8.10 hours, and between 2.61 and 9.33 hours for PGL4002 (the main metabolite of PGL4001). Half-life values at Week 52 were generally higher for both PGL4001 and PGL4002.

Toxicokinetic parameters at week 52 of dosing are summarized below.

Table 5: Toxicokinetic parameters at Week 52 of Dosing

	Male Rat			Female Rat		
Dose (mg/kg/day)	**1**	**3**	**10**	**1**	**3**	**10**
Multiple of Exposure (based on AUC)	0.5	5	22.5	0.4	5.4	30.7
Tmax (hr)	1	0.5	1	0.5	1	0.5
t1/2(hr)	5.2	6.4	7.9	5.6	8.1	7.9
Cmax (ng/mL)	59.1	582	1370	77.4	459	2510
AUC(0-t) (ng.hr/mL)	277	2720	12300	231	2940	16800

* based on AUC (0-t) of 548±259 ng.h/mL at a single clinical dose of 30 mg in humans (from PGL-H-504, DAARTS 5.3.3.1)

Systemic exposure was dose-related with evidence of accumulation of PGL4001 and to a lesser extent, PGL4002 in rat plasma following repeat dosing in all dose groups.

Systemic exposure of rats to PGL4001 was generally sex independent in groups 3 and 4 (1 mg/kg/day and 3 mg/kg/day, respectively), being similar in both genders on all sampling occasions. In group 5 (10 mg/kg/day) exposure of female rats was greater than exposure to male rats on all sampling occasions.

Dosing Solution Analysis (Stability, Homogeneity, and Concentration)

Formulations prepared for use in Weeks 1, 2, 8, and 12 of the study were analyzed for stability and homogeneity. The formulations were to be considered homogeneous if the coefficient of variation (CV) of the results was ≤ 6.0% (actual CV was between 0.14 and

1.07%). In addition the homogeneity results should be within ± 10% of the mean (actual results were between 99 and 103%). The formulations were to be considered stable if the mean of the results at each time point were ±10% of the mean at 0 hour. Actual results for each analysis were within these criteria.

Formulations prepared for use in Weeks 1, 13, 26, 39, 52, 65, 78, 91 and 102 of the study were analyzed to determine achieved concentration. The target range for the preparation of the formulations was 90 to 110% of nominal (actual concentrations were 98 to 107% of nominal). Test article was not detected in the control samples.

References:

Brix AE, Nyska A, Haseman JK, Sells DM, Jokinen MP, Walker NJ. Incidences of Selected Lesions in Control Female Harlan Sprague-Dawley Rats from Two-Year Studies Performed by the National Toxicology Program. Toxicologic Pathology, 33: 477-483, 2005

McMartin DN, Sahota PS, Gunson DE, Han Hsu H, Spaet RH. Neoplasms and Related Proliferative Lesions in Control Sprague-Dawley Rats from Carcinogenicity Studies. Historical Data and Diagnostic Considerations. Toxicologic Pathology, 20 (2): 212-225, 1992

8.2 26 Week Transgenic Mouse Study (Reviewed by Dr. Lynnda Reid)

Study title: PGL-4001 A 26 Week Oral Carcinogenicity Study in Transgenic Hemizygous CBYB6F1-TG(HRAS)2JIC Mice

Study no.:	HRA2914-488
Study report location:	EDR: S0065 Module 4.2.24
Conducting laboratory and location:	(b) (4)
Date of study initiation:	4/19/2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	PGL4001 C0605/1 08040 - 101.2% NMU 099K1262
CAC concurrence:	Yes (IND (b) (4) - 4/5/2011)

Key Study Findings:

Based on the data, PGL4001 is not considered to be carcinogenic up to the highest dose tested of 130 mg/kg. The NOAEL for this study was 45 mg/kg/day with corresponding AUC_{0-24} levels of 24,800 and 41,800 ng•h/mL in males and females, respectively. The associated AUC_{0-24} levels 130 mg/kg on Day 182 were 52,200 and 83,300 ng•h/mL in males and females, respectively, resulting in exposure multiples ~ 100 times greater than the maximum recommended human dose of 30 mg/day.
Note: AUC in females at the MRHD = 548±259 ng•h/mL

Adequacy of Carcinogenicity Study:

Study was adequate -

- Doses were based on recommendations by the ECAC
- Positive control, N-methyl=N-nitrosourea (NMU), performed as expected
- Acceptable dosing multiples were achieved

Appropriateness of Test Model

The Tg.rasH2 model is acceptable for the testing of both genotoxic and non-genotoxic compounds. Clinical route of administration was used.
The dose level of 75 mg/kg MNU was selected based on previously conducted studies to produce a high incidence of multiple tumor growth in the CB6F1/Jic-TgrasH2@Tac heterozygous mouse.

Evaluation of Tumor Findings

Methods

Doses:	PGL4001: 15, 45 or 130 mg/kg/day
Positive Control	NMU 7.5 mg/mL (75 mg/kg IP)
Frequency of dosing:	Daily
Dose volume:	10 mL/kg
Route of administration:	Oral Gavage
Formulation/Vehicle:	Aqueous Suspending Vehicle (ASV): 0.9% NaCl, 0.9% benzyl alcohol, 0.4% Tween® 80, 0.5% carboxymethylcellulose, 98.7% distilled water
Basis of dose selection:	Doses recommended by ECAC based on deaths in wild type mice at 400 mg/kg/day
Species/Strain:	CByB6F1-Tg(HRAS)2Jic (-/- homozygous c-Ha) Mice
Number/Sex/Group:	25/sex/group
Age:	8-9 weeks
Animal housing:	Individually housed
Paradigm for dietary restriction:	*ad libitum*
Dual control employed:	Vehicle and Water controls
Interim sacrifice:	No
Satellite groups:	TK: Controls - 6 control animals/sex/group; PGL4001 – 36 animals/sex/group
Deviation from study protocol:	None which affected study outcome

Observations and Results

Mortality – twice daily

Vehicle and Water Controls: One vehicle control male, 1 male and 1 female from the water control group were found dead or euthanized during the study.
NMU: 14 males and 16 females were found dead/euthanized on study. The majority of these animals were found to have tumors leading to their moribund status/death.

PGL4001: A total 11 animals were found dead/euthanized during the course of the study: 2 males and 3 females from the 15 mg/kg/day group, 1 male from the 45 mg/kg/day group, and 3 females from the 130 mg/kg/day group were found dead or euthanized during the course of the study. The causes of death for the main study animals were of the type commonly seen in studies utilizing mice of this strain.

	Sex	Water Control	Vehicle Control	NMU	15 mg/kg	45 mg/kg	130 mg/kg
Number/Sex/Group		25	25	25	25	25	25
Surviving to Terminal Necropsy	Males	24 (96%)	24 (96%)	11 (44%)	23 (92%)	24 (96%)	25 (100%)
	Females	24 (96%)	25 (100%)	9 (36%	23 (92%)	25 (100%)	22 (88%)
Premature Deaths	Males	1 (4%)	1 (4%)	14 (56%)	2 (8%)	1 (4%)	0
	Females	1 (4%)	0	16 (64%)	2 (8%)	0	3 (12%)
Day of premature deaths	Males	179	148	81-173	181, 184	179	-
	Females	126	-	32-175	102, 140	-	34, 101, 134

In the animals designated for toxicokinetics, 1 male from the 45 mg/kg/day group and 1 male from the 130 mg/kg/day groups died or were euthanized prior to their scheduled termination. There was no histology conducted on the toxicokinetic animals.

Clinical Signs – twice daily, detailed clinical observations and mass observations were conducted ~ 1 hour postdose each day during week 1 and once weekly thereafter

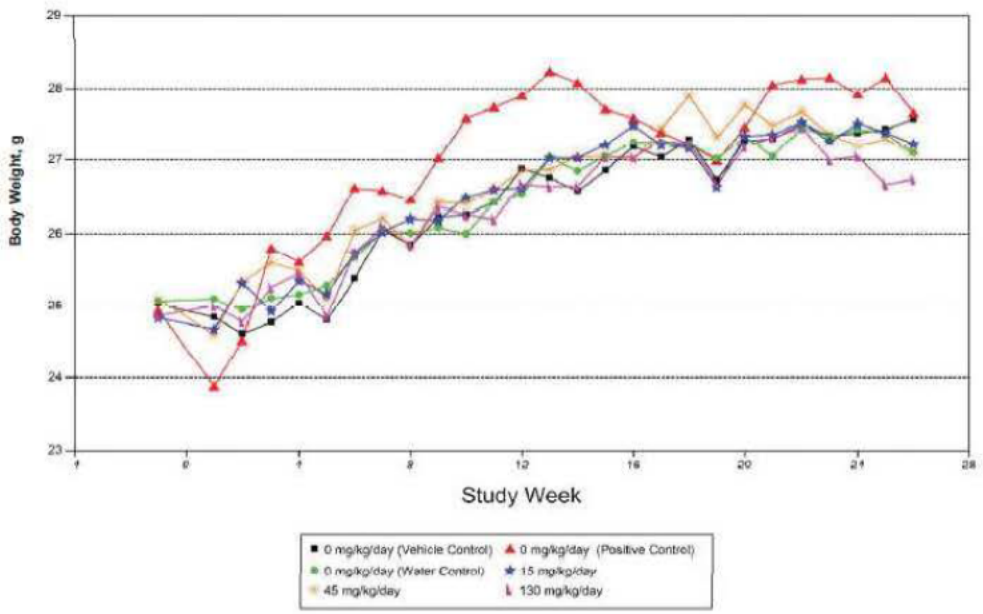
Clinical observations noted during the course of the study were either of a low incidence, sporadic in nature, lacked a dose response, or were observed concurrently in controls

There were increased observations of nodules in animals that received NMU, which correlated with an increased incidence of masses noted in these animals. There were no masses detected in animals that received water, vehicle, or test article during the course of the study.

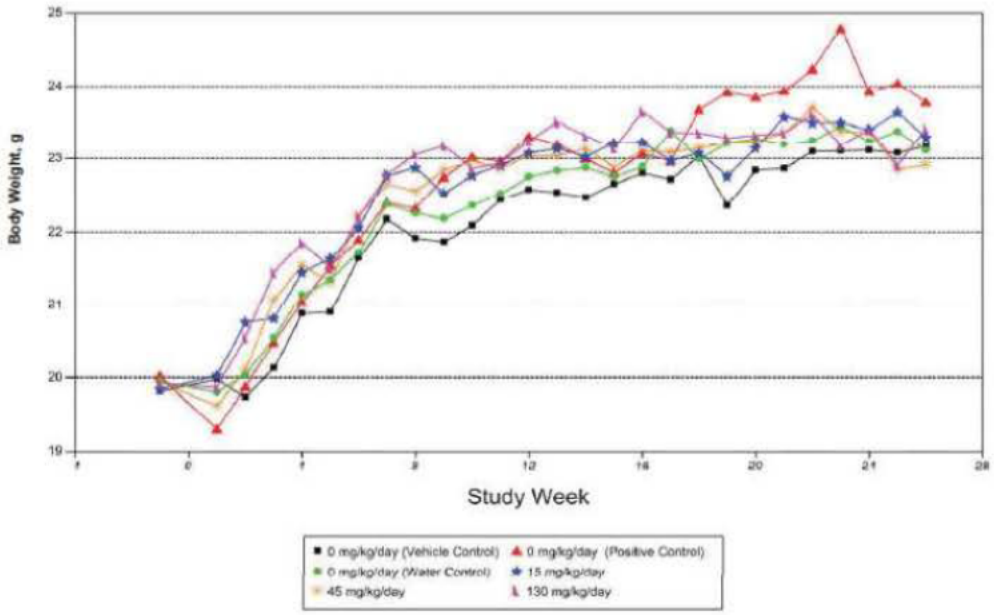
Body Weights - weekly

There were no significant PGL-4001 related effects on mean body weight for either males or females receiving test article. Males that received the positive control showed significant differences in mean body weight, from a 4% decrease early in the study to a 6% increase at Week 10. (See Graphs on following page)

Mean Body Weight Values - MALE



Mean Body Weight Values - FEMALE



Feed Consumption – recorded weekly

There were occasional statistically significant differences in mean food consumption values for animals that received PGL-4001 compared to controls; however, these differences were sporadic, of a small magnitude, and did not show a dose response.

Hematology – Blood samples were collected at terminal necropsy

There was a mild decrease in red cell mass (erythrocytes, hemoglobin, and hematocrit) in animals of both sexes receiving the positive control article and 130 mg/kg/day of the test article relative to vehicle control animals.
Animals at all PGL4001 dose levels exhibited minimal to mild increases in lymphocytes relative to vehicle controls. Animals receiving the positive control article exhibited mild to moderate increases in neutrophils relative to vehicle controls. Two individual female animals receiving the positive control article also had marked increases in atypical "blast" cells that were typical of acute leukemia.

Gross Pathology - termination

Increases in liver weights were seen in males and females at 45 mg/kg/day and 130 mg/kg that correlated with microscopic findings of minimal panlobular hepatocellular hypertrophy at 130 mg/kg/day. There was no increase in incidence of hepatic neoplasms in either males or females at any dose level compared to controls. Increases in thyroid/parathyroid gland weights were seen in males and females at 130 mg/kg/day and in females at 45 mg/kg/day with no microscopic correlate. Decreases in pituitary gland weights were seen in females at 130 mg/kg/day with no microscopic correlate. Decreases in epididymal weights were seen in males at all dose levels with no micropscopic correlate. The changes in epididymidis, thyroid/parathyroid, and pituitary gland weights may be due to exaggerated pharmacologic effects of the test article.
All other organ weight observations were similar to controls and/or incidental.

Test Article-related Organ Weight Changes - Terminal
Male and Female (Percent change relative to vehicle control)

Dose level: mg/kg/day	15		45		130	
Sex	M	F	M	F	M	F
Number Examined	23	22	24	25	25	22
Epididymides (g)	↓3.00	NA	↓7.00	NA	↓10.00[a]	NA
Epididymides/BWt%	↓4.15	NA	↓6.48	NA	↓8.18	NA
Epididymides/BrWt ratio	↓2.72	NA	↓7.34	NA	↓8.79	NA
Liver (g)	↑2.59	↑0.91	↑10.29[b]	↑5.44	↑20.21[b]	↑27.78[b]
Liver/BWt%	↑2.21	↓0.43	↑11.41[b]	↑6.40[b]	↑23.22[b]	↑26.10[b]
Liver/BrWt ratio	↑3.77	↑2.26	↑10.45[b]	↑6.03	↑22.85[b]	↑30.36[b]
Pituitary (g)	↓5.00	↑3.57	↑5.00	↓3.57	NC	↓14.29[b]
Pituitary/BWt%	↓8.75	↑3.03	↑2.50	↓3.03	↓1.25	↓17.42[b]
Pituitary/BrWt ratio	↓6.67	↑6.90	NC	↓1.72	↓2.22	↓13.79[b]
Thyroid/parathyroid gl (g)	NC	NC	NC	↑25.00[b]	↑25.00[b]	↑25.00[b]
Thyroid/parathyroid gl/BWt%	↑2.55	↑4.66	↑8.28	↑11.40[b]	↑18.47[b]	↑11.92[b]
Thyroid/parathyroid gl/BrWt ratio	↑4.60	↑8.14	↑8.05	↑10.47[b]	↑18.39[b]	↑15.12[b]

[a]Significantly different from control; ($p<0.05$)
[b]Significantly different from control; ($p<0.01$)
BWt - Body Weight
BrWt - Brain Weight
↑ - Increased
↓ - Decreased
M - Male
F - Female
NC - No Change
NA - Not Applicable

Histopathology - termination

Peer Review –not indicated in protocol

Neoplastic

PGL4001: There was no evidence of any PGL 4001 or vehicle-induced carcinogenicity seen in this study.
NMU: The following were the most common neoplastic lesions seen in the DMU treated animals:

Tumor	*Males*	*Females*
Malignant Lymphoma	13	14
Skin –		
Keratoacanthoma	2	3
Papilloma	3	5
Stomach –		
Carcinoma (glandular)	2	2
Carcinoma (nonglandular)	2	4
Papilloma	10	15
Uterus		
Adenoma		1
Carcinoma		2
Polyps		8

Non Neoplastic - Minimal panlobular hepatocellular hypertrophy in the liver was seen in males and females at 130 mg/kg/day (12 of 25 and 15 of 25, respectively). All other differences in observation incidence between vehicle or water controls and treated animals were small and not considered significant. There were no significant differences in incidence of hyperplasia or neoplasia in the mammary glands, uterine wall and endometrium, vagina, or ovaries between vehicle or water controls and treated animals. **Other microscopic observations were usual and/or incidental in mice of this strain and age.**

Toxicokinetics – Days 1 and 182

There were no differences in TK parameters for male and female mice for PGL4001 or its major metabolite PGL4002. There was no accumulation and AUC levels were actually lower in 130 mg/kg males and females on day 182.

Summary of TK Parameters – PGL4001						
Day	Dose (mg/kg/day)	Sex	AUC_{0-24} (hr•ng/mL)	C_{max} (ng/mL)	$t_{1/2}$ (hr)	T_{max} (hr)
1	15	Male	11200	2370	2.45	0.500
		Female	12200	2280	1.63	0.500
		Combined	11700	2330	2.04	0.500
	45	Male	36300	5460	3.16	1.00
		Female	37800	4660	2.28	0.500
		Combined	37100	5060	2.72	0.750
	130	Male	96400	9130	10.1	1.00
		Female	93200	8830	13.7	1.00
		Combined	94800	8980	11.9	1.00
182	15	Male	12600	2600	3.68	0.500
		Female	17300	3120	1.93	0.500
		Combined	15000	2860	2.80	0.500
	45	Male	24800	3680	4.12	0.500
		Female	41800	4760	1.95	0.500
		Combined	33300	4220	3.03	0.500
	130	Male	52200	6150	3.51	2.00
		Female	83300	7070	2.15	1.00
		Combined	67700	6610	2.83	1.50

Summary of TK Parameters – PGL 4002						
Day	Dose (mg/kg/day)	Sex	AUC_{0-24} (hr•ng/mL)	C_{max} (ng/mL)	$t_{1/2}$ (hr)	T_{max} (hr)
1	15	Male	4510	910	1.97	0.500
		Female	6080	974	2.23	0.500
		Combined	5290	942	2.10	0.500
	45	Male	14800	2190	2.55	1.00
		Female	18100	2190	1.90	1.00
		Combined	16500	2190	2.22	1.00
	130	Male	35700	3550	6.04	2.00
		Female	38900	4350	6.39	1.00
		Combined	37300	3950	6.22	1.50
182	15	Male	6140	1020	3.19	0.500
		Female	10100	1480	1.97	0.500
		Combined	8120	1250	2.58	0.500
	45	Male	11100	1370	3.67	0.500
		Female	19200	2030	1.94	0.500
		Combined	15200	1700	2.81	0.500
	130	Male	23700	2890	3.10	2.00
		Female	38300	3070	2.05	1.00
		Combined	31000	2980	2.58	1.50

Dosing Solution Analysis

Homogeneity: 99.6-100.6
Stability (Average % Recovery): 98.5 – 100.1
Concentration:

Concentration				
Dose Level (mg/kg/day)	Nominal Concentration (mg/mL)	Average Calculated Concentration[a] (mg/mL)	Average %Recovery[a, b]	%Relative Standard Deviation[a]
0 (vehicle)	0	0	NA	NA
0 (water)	0	0	NA	NA
15	1.5	1.4 – 1.5	95.0 – 101.9	0.1 – 8.0
45	4.5	4.3 – 4.6	94.5 – 102.2	0.1 – 2.4
130	13	12 – 13	90.6 – 100.3	0.0 – 2.4

[a]Results are the range of values determined during Weeks 1 to 26.
[b]Average %recovery was calculated from the nominal concentration.
NA – Not Applicable

12 Appendix/Attachments

APPENDIX A

CARCINOGENICITY ASSESSMENT COMMITTEE (CAC/CAC-EC) REPORT AND FDA-CDER RODENT CARCINOGENICITY DATABASE FACTSHEET

P/T REVIEWER(s): Deepa Rao and Lynnda Reid

DATE: 2/17/15

IND/NDA: NDA 22474 (related INDs: 119, 378 (b) (4))

DRUG CODE#: PGL4001, CDB 2914, VA 2914

CAS#: 126784-99-4

DIVISION(s): DBRUP

DRUG NAME(s): ELLA© (Ulipristal acetate)

SPONSOR: HRA Pharma

THERAPEUTIC CATEGORY: Contraceptives/Oral

PHARMACOLOGICAL/CHEMICAL CLASSIFICATION:

Progesterone agonist/antagonist

INDICATON(S): 1) Emergency Contraception (b) (4)

3) Contraception

MUTAGENIC/GENOTOXIC: Negative

- PGL4001 was not mutagenic in the reverse mutation bacterial system at concentrations up to 5000 µg/plate in the presence or absence of the S9 activation system.

- PGL4001 did not show any mutagenic activity in L5178Y mouse lymphoma cells at concentrations up to 200 µg/mL in the presence or absence of the S9 activation system. PGL4001 was not associated with clastogenicity in peripheral human blood lymphocytes at concentrations up to 120 µg/mL.

- Oral administration of PGL4001 up to 512 mg/kg (HED is approximately 2500 mg/day) did not increase the incidence of micronuclei in the bone marrow of male or female mice.

RAT CARCINOGENICITY STUDY:

RAT STUDY DURATION: Target was 104 weeks. Actual treatment duration was up to Week 99 for females and up to Week 100 for females

LABORATORY: (b) (4)

STUDY STARTING DATE: 24 August, 2009 (Day 1 Dosing)

STUDY ENDING DATE: Males: 22 July 2011 and Females: 14 July 2011

CARCINOGENICITY STUDY REPORT DATE: September, 2012

RAT STRAIN: Sprague-Dawley Rats (b) (4)

ROUTE: Oral gavage

DOSING COMMENTS: Dosing deviations are documented in Appendix 1

NUMBER OF RATS:

- Control-1 (C1): Water 60/sex
- Control-2 (C2): Vehicle 60/sex
- Low Dose (LD): 60/sex
- Middle Dose (MD): 60/sex
- High Dose (HD): 60/sex

RAT DOSE LEVELS:

- Low Dose: 1 mg/kg/day
- Middle Dose: 3 mg/kg/day
- High Dose: 10 mg/kg/day

BASIS FOR DOSES SELECTED: Doses used were ECAC recommended estimates based on > 25-fold AUC ratios of rodent to human exposure

PRIOR FDA DOSE CONCURRENCE: Yes. (b) (4)

RAT CARCINOGENICITY: Negative

RAT TUMOR FINDINGS:

- There are no obvious dose-related increased incidences of tumors in PGL4001 treated animals. Statistically significant findings (based on sponsor-conducted statistical analysis) include an increase in adrenal cortical adenomas and pituitary adenomas/carcinomas in the intermediate dose group females administered 3 mg/kg/day. Both these tumors show a decrease in incidence at the high dose of 10 mg/kg/day, and no statistically significant dose-related trends were noted for either of these tumors.

- The incidence of benign thymoma in females is slightly higher than the historical control incidence (provided by the sponsor) and also higher than historical incidences published for Sprague-Dawley rats (McMartin et al, 1992, and Brix et al, 2005). This was not found to be statistically significant (sponsor conducted analysis).

- Neoplastic incidence of interstitial cell adenoma in the testis is considered to be comparable to the background historical control incidence provided by the sponsor and below the background incidence in control Sprague-Dawley rats (McMartin et al, 1992). Neoplastic incidences of thyroid tumors are considered to be comparable to the background historical control incidence provided by the sponsor and historical control incidences in Sprague-Dawley rats (McMartin et al, 1992; Brix et al, 2005).

- All other tumor incidences are considered to be sporadic or incidental, not dose-related, and comparable with the concurrent controls, and/or historical control incidence (provided by the sponsor), and/or comparable to background control incidences for Sprague-Dawley rats (McMartin et al, 1992; Brix et al, 2005). Based on the above criteria for evaluation, all other tumor incidences were considered to unlikely related to the administration of PGL4001.

RAT STUDY COMMENTS:
For emergency contraception, doses used were based on achieving exposure multiples >25 fold greater than observed at the MRHD. Actual multiples of clinical exposure achieved in this study (based on $AUC_{(0-t)}$) following doses of 1, 3, and 10 mg/kg/day in male and female rats were 0.5, 5, 23 and 0.4, 5, and 31, respectively. Multiples of exposure were based on $AUC_{(0-t)}$ of 548±259 ng.h/mL at a single clinical dose of 30 mg. For uterine myoma (fibroids) and contraception, actual multiples of clinical exposure achieved in this study (based on $AUC_{(0-t)}$) following doses of 1, 3, and 10 mg/kg/day in female rats were 1.4, 17.2, and 98.2 times respectively. Multiples of exposure were based on $AUC_{(0-t)}$ of 171.79±85.59 ng.h/mL at a single clinical dose of 10 mg.

IND 049381 / NDA 022474	Emergency Contraception	HRA Pharma	Single 30 mg dose (oral)	1, 3, and 10 mg/kg/day in male and female rats showed multiples of exposure to be 0.5, 5, 23 and 0.4, 5, and 31 times respectively (based on AUC_{0-t} of 548±259 ng.h/mL at a single clinical dose of 30mg)
IND (b) (4)	(b) (4)	(b) (4)	5 mg/day and 10 mg/day for 12 weeks (oral)	1, 3, and 10 mg/kg/day in female rats showed multiples of exposure to be 1.4, 17.2, and 98.2 times respectively (based on AUC_{0-t} of 171.79±85.59 ng.h/mL at a single clinical dose of 10mg)
IND (b) (4)	Contraception	(b) (4)	5 mg/day and 10 mg/day for 12 weeks	

The study was terminated early due morbidity and mortality across all groups. The incidence of morbidity and mortality in the water control group (Dose Group 1) was higher than all other groups. Termination of study in both sexes was based on ECAC survival/termination criteria being achieved in the water control group (Dose Group 1). Sponsor consulted with the non-clinical reviewer prior to termination of the studies (DAARTS IND (b) (4)). All female groups were terminated commencing Week 99 and all male groups were terminated commencing in Week 100.

Dose-related gender differences in body weight gain were noted. Males showed a dose-related decrease in body weight gain with corresponding reductions in food consumption. Females showed an initial increase in body weight gain with corresponding increases in food consumption, followed by a decrease in body weight after week 28 with no significant corresponding changes in food consumption compared to controls.

Treatment-related non-neoplastic findings were observed in the reproductive system (mammary gland, ovary, uterus, vagina, seminal vesicle, prostate), endocrine system (adrenal, pituitary), thymus, muscle, liver, pancreas and lungs. Findings in endocrine sensitive tissues are most likely related to exaggerated pharmacologic effects of the drug.

MOUSE CARCINOGENICITY STUDY:

MOUSE STUDY DURATION: 26 weeks

LABORATORY: (b) (4)

STUDY STARTING DATE: April 29, 2011

STUDY ENDING DATE: October 19, 2011

CARCINOGENICITY STUDY REPORT DATE: July 2, 2012

MOUSE STRAIN: CByB6F1-Tg(HRAS)2Jic (-/- homozygous c-Ha)

ROUTE: Oral Gavage – PGL4001, vehicle and water controls

IP - NMU

DOSING COMMENTS: There were no significant deviations from protocol

NUMBER OF MICE:

- Control-1 (Vehicle): 25/sex
- Control-2 (Water): 25/sex
- Control-3 (NMU): 25/sex
- Low Dose (LD): 25/sex
- Middle Dose (MD): 25/sex
- High Dose (HD1): 25/sex

MOUSE DOSE LEVELS:

- Low Dose: 15 mg/kg/day
- Middle Dose: 45 mg/kg/day
- High Dose: 130 mg/kg/day

BASIS FOR DOSES SELECTED: MTD, based on deaths in wild type mice at 400 mg/kg/day

PRIOR FDA DOSE CONCURRENCE: Yes (see IND (b) (4)

MOUSE CARCINOGENICITY: Negative

MOUSE TUMOR FINDINGS:

PGL4001: There was no evidence of any PGL 4001 or vehicle-induced carcinogenicity seen in this study.

NMU: The following table lists the most common neoplastic lesions seen in the NMU treated animals.

Tumor	*Males*	*Females*
Malignant Lymphoma	13	14
Skin – Keratoacanthoma	2	3

Papilloma	3	5
Stomach –		
Carcinoma (glandular)	2	2
Carcinoma (nonglandular)	2	4
Papilloma	10	15
Uterus		
Adenoma		1
Carcinoma		2
Polyps		8

MOUSE STUDY COMMENTS: There were no significant differences in survival between the PGL4001 treated animals and the vehicle or water controls. There were significant unscheduled deaths in the NMU animals primarily related to tumorgenicity.

Drug related findings included minimal to mild changes in hematology parameters and increased organ weights at doses of 45 and 130 mg/kg/day. Increased liver weights correlated with increased panlobular hepatocellular hyperthrophy at 130 mg/kg/day.

Exposure multiples following doses of 130 mg/kg were approximately 100 fold greater than AUC levels at the maximum recommended human dose of 30 mg/day.

APPENDIX B

Executive CAC Minutes

Date of Meeting: February 24, 2015
Committee:
Abby Jacobs, Ph.D., OND IO, Acting Chair
Paul Brown, Ph.D., OND IO, Member
Karen Davis Bruno, Ph.D., OND IO, Member
Whitney Helms, Ph.D., DHOT, Alternate Member
Lynnda Reid, Ph.D., DBRUP, Pharm Tox Supervisor - Presenting Reviewer (Mouse)
Deepa Rao, D.V.M., Ph.D., DBRUP, Presenting Reviewer (Rat)

Author of Minutes: Deepa Rao, D.V.M., Ph.D.
The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA # 22-474 (Related INDs (b) (4))
Drug Name: Ella (Ulipristal acetate) or PGL4001
Sponsor: HRA Pharma
Background: *Ulipristal acetate (PGL4001) is an approved emergency contraceptive (NDA 22-474). Ulipristal acetate is a selective progesterone receptor modulator (SPRM) with mixed progesterone agonist/antagonist with antiglucocorticoid activities producing antiprogestational effects on female reproductive system organs.* (b) (4)

The two-year rat and 26-week transgenic mouse studies with PGL4001 (ulipristal acetate) were conducted by (b) (4), respectively. Doses were based on recommendations made by ECAC in response to the carcinogenicity protocol assessment requests (IND (b) (4) respectively).

Rat Carcinogenicity Study:

In a 2-year carcinogenicity study, Sprague-Dawley rats received PGL4001 by oral gavage at doses of 1, 3, and 10 mg/kg/day. Two control groups were used in the study: one with water and one with the vehicle (98.7% water, 0.9% w/v NaCl, 0.9% v/v Benzyl Alcohol, 0.4% v/v polyoxyethylene sorbitan monooleate, 0.5% w/v carboxymethylcellulose). All female groups were terminated commencing week 99 and all male groups were terminated commencing week 100 due to morbidity and mortality in the water control group. No treatment-related neoplastic findings were noted in male rats. In female rats, treatment-related neoplastic findings were limited to adrenal cortical adenomas in the intermediate dose group (3 mg/kg/day).

	Females (dose in mg/kg/day)				
	Group 1	**Group 2**	**Group 3**	**Group 4**	**Group 5**
	Vehicle Control	**Water Control**	**1**	**3**	**10**
ADRENAL GLAND	**60**	**60**	**60**	**60**	**60**
Cortical Adenoma (All)	1 (1.7%)	2 (3.3%)	2 (3.3%)	**10 (16.7%)***	1 (1.7%)
Control Incidence - Cortical Adenoma	***15/718 or 2% (Sponsor); 4.6% (1.5 - 11.4%) McMartin et al, 1992; 2/369 or 0.5% (Brix et al, 2005)***				

* statistically significant at $p < 0.05$ as conducted by the sponsor [uni-directional pairwise test (Peto R et al, 1980)]

There was no incidence of adrenal cortical carcinomas.
Although the incidence of adrenal cortical adenomas was significant only in the intermediate dose group (3 mg/kg/day), and not in the lower (1 mg/kg/day) and higher (10 mg/kg/day) dose groups, this incidence in the intermediate dose group could not be definitively ruled out as a treatment-related lesion based on:

1) a statistically significant higher incidence compared to concurrent controls, study site-specific historical controls, as well as the low historical control incidences reported for Sprague-Dawley rats in published literature (Brix et al, 2005; McMartin et al, 1992).

2) the biological plausibility of variable dose-response effects due to agonist/antagonist activity of endocrine modulators.

Despite the increase, this incidence of adrenal cortical adenomas in females may not be relevant to clinical use based on single dose exposure for emergency contraception, and the multiples of exposure of at least 17 times higher than the predicted clinical exposure of PGL4001 when used for the treatment of uterine fibroids or long term contraception.

Tg.rasH2 Mouse Carcinogenicity Study:

In a 26-week Tg.rasH2 mouse study, mice were orally gavaged with 15, 45, or 130 mg/kg/day of PGL4001. Two control groups were used in the study: one with water and one with the vehicle (98.7% water, 0.9% w/v NaCl, 0.9% v/v Benzyl Alcohol, 0.4% v/v polyoxyethylene sorbitan monooleate, 0.5% w/v carboxymethylcellulose). A positive

control group [(mice treated with N-methyl-N-nitrosourea (NMU)] was included. There were no significant differences in survival between the PGL4001 treated animals and the vehicle or water controls. There were significant unscheduled deaths in the NMU treated animals related to neoplasms. No PGL4001 treatment-related neoplastic effects were noted in either sex.

Executive CAC Recommendations and Conclusions:

Rat:

- The Committee concurred that the study was acceptable, noting prior Exec CAC concurrence with the protocol.
- The Committee concurred that adrenal cortical adenomas in the female intermediate dose group may be drug related because of the statistically significant higher incidence than controls, the incidence being notably above historical control incidences, and the biological plausibility of endocrine modulation, but agreed that the finding may not be relevant to clinical use.

Tg.rasH2 mouse:

- The Committee concurred that the study was acceptable, noting prior Exec CAC concurrence with the protocol.
- The Committee concurred that there were no drug-related neoplasms in the study.

Abby Jacobs, Ph.D.
Acting Chair, Executive CAC

cc:\
/NDA 22-474, Division File, DBRUP
/LSoule, DBRUP
/D Rao and L Reid, DBRUP
/JDao, DBRUP
/ASeifried, OND IO

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DEEPA B RAO
03/06/2015

LYNNDA L REID
03/06/2015