CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207318Orig1s000

PHARMACOLOGY REVIEW(S)

Tertiary Pharmacology/Toxicology Review

By: Paul C. Brown, Ph.D., ODE Associate Director for Pharmacology and Toxicology, OND IO
NDA: 207318
Submission date: original 9/1/2015
Drug: pimavanserin
Applicant: Acadia Pharmaceuticals, Inc.
Indication: Parkinson's disease psychosis
Reviewing Division: Division of Psychiatry Products

Discussion:
The pharmacology/toxicology reviewer and supervisor recommended that pimavanserin could be approved from the pharmacology/toxicology perspective for the indication listed above.

The exact mechanism of pimavanserin in the treatment of psychosis is unknown. Therefore, an acceptable established pharmacologic class is "atypical antipsychotic" as with other members of this class.

One of the predominate findings in the nonclinical studies with pimavanserin was the induction of multi-organ phospholipidosis in multiple species. In the rat, phospholipidosis was associated with inflammation and secondary inflammatory fibrosis. These findings were further assessed by FDA pathologists. The fibrosis was not considered to be a direct drug-induced injury to the lungs. In addition, a margin (5 fold) exists between the human exposure and the exposure considered to be the no observed effect level for the chronic inflammation in the lungs.

Initially, the reviewer and supervisor recommended that a juvenile animal study be conducted as a post-marketing requirement. However, they subsequently decided that this was not necessary for this NDA. The supervisor has recommended a post marketing commitment asking the sponsor to conduct additional histochemical staining and examination for collagen in lung tissues of animals from the chronic toxicity studies.

Conclusions:
The pharmacology/toxicology reviewer and supervisor conducted a thorough evaluation of the nonclinical information submitted in support of this NDA. I agree that this NDA may be approved for the above indication. I also agree that no juvenile animal study is necessary for this NDA. Further assessment of collagen in lungs will probably have minimal impact for the current indication; however, such information may better define a no effect level and may be useful if pimavanserin is used for other chronic indications. Additional comments on labeling have been provided separately.

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/s/

PAUL C BROWN
04/27/2016

Supervisory Memo # 2

Drug:	Pimavanserin
NDA #	207318
Indication:	Parkinson's disease Psychosis
Sponsor:	Acadia Pharmaceuticals, Inc.
Review Date:	April, 8 2016
PDUFA Date:	May 1, 2016
Supervisor:	Aisar Atrakchi, Ph.D.
Division Director:	Mitchell Mathis, M.D.
Center/Division:	CDER / Psychiatry Products

This is the 2nd supervisory memo for pimavanserin to address new information submitted to the Agency in SDNs 24, 25 on March 4 and 18, 2016. In order to further evaluate the lung fibrosis observed in the 6 month rat toxicity study, (b) (4) 616007, the sponsor consulted a Pathology Working Group (PWG). The PWG consisted of (b) (4) representing (b) (4) and Ricardo Ochoa who is the applicant pathologist. The PWG agreed that a stain specific for collagen (in this case Masson's Trichrome (MTC)), is necessary to accurately evaluate the slides where "fibrosis" was identified. Lung sections from all animals in this study were recut, stained with MTC, and re-read independently by each pathologist (see Dr. Avila's amendment review for detail). The PWG conclusion was similar to the one from the original report, that the lung fibrosis is a result of chronic inflammation and is not a direct drug-induced injury to the lungs. However, this new report identified more cases of chronic inflammation that were not seen in the previous report which led to alteration in the safety margins for chronic inflammation. The Division consulted the newly submitted information to our internal experts who were also the consultants on the histopathology results from the original NDA and, they too agreed with the overall PWG conclusion (see Drs. Francke and Mog pathology consult review for detail).

The identification of new cases of inflammation in the PWG report that were not identified previously in the original report that used standard H&E stain, introduces the question whether inflammation could also be present in the other repeat dose toxicity studies in the rat (the 2 year carcinogenicity study), as well as studies in mice and monkeys. Therefore, it would seem prudent and necessary to re-evaluate the lung slides using MTC stain for all chronic studies in order to determine the extent of inflammation and whether it is present at lower doses. Therefore, we recommend conducting this assessment as a post-marketing commitment. Information generated from this assessment will also be necessary if pimavanserin is to be indicated in the future for a chronic administration.

Summary and Recommendation:

I agree with the conclusions of Dr. Avila, our internal expert pathologists Drs. Francke and Mog, and the sponsor's PWG. The results of the re-evaluation of the lung slides from the 6 month rat

study using specialized stain for collagen supported the conclusion made in the original NDA review. The lung fibrosis is secondary inflammatory fibrosis in response to chronic inflammation; it is not a direct drug-induced injury. However, the PWG report identified new cases of inflammation not previously observed with standard staining using H&E. This resulted in different (lower), safety margins for inflammation relative to the clinical exposure at the maximum recommended human dose. Therefore, there is reasonable safety concern to support further investigation of the extent of inflammation and whether it is present at lower doses using specialized collagen stain. Therefore, we recommend conducting this assessment as a post-marketing commitment. Information generated from this assessment will also be necessary if pimavanserin is to be indicated in the future for chronic administration.

Upon further discussions with the primary reviewer, we have concluded that a juvenile animal study is not warranted at this time for this indication.

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/s/

AISAR H ATRAKCHI
04/13/2016

Memorandum

Date: March 25, 2016

From: Sabine Francke, D.V.M., Ph.D., FIATP and Steven Mog, D.V.M., DACVP, Senior Science and Policy Staff, Office of Food Additive Safety, CFSAN (HFS-205)

Subject: Division of Psychiatry Products - NDA 207318 (Pimavanserin): PWG Report (Feb. 23, 2016) review

To: Amy Avila, Ph.D., Pharmacology/Toxicology Reviewer, Division of Psychiatry Products FDA/CDER/OND, HFD-130

References:

1. E-mail from Avila to Francke / Atrakchi dated March 2, 2016 subject: RE: Pimavanserin with the following attachment:
    a. 616007 Pathology Working Group Report dated 2/23/2016
2. CFAN Pathology Memorandum dated January 13, 2016 entitled "Division of Psychiatry Products - NDA 207318 (Pimavanserin): Request for nonclinical histopathology consult"
3. (b) (4) 616007, 6 month Rat study, with 6 month recovery
4. E-mail from Avila to Mog / Francke /Atrakchi dated March 18, 2016 subject: RE: Pimavanserin PWG report review draft 031716 with attachment:
    a. (b) (4)-616007 Amendment 2 - A 6-Month Oral (Gavage) Toxicity Study of ACP-103 in Sprague Dawley Rats followed with a 6-Month Recovery Period dated 03/16/16

Based on your request (reference 1), we both have reviewed the Pathology Working Group (PWG) report on Pimavanserin provided to us (dated 02/23/2016; reference 1a). Resulting from this PWG, we also reviewed the amended pathology report (Amendment 2, reference 4a). We have focused our evaluation on your specific questions (reference 1) which we addressed below in this memorandum.

Background:
Briefly, the PWG consisted of only two pathologists; one newly appointed study pathologist (reference 4a pg. 153), representing the Contract Research Organization (b) (4) and one pathologist, retained by the study sponsor (ACADIA Pharmaceuticals Inc.). The purpose of the PWG was to provide additional evaluations of lung slides from all study animals for the 6 month rat study on Pimavanserin only (reference 3). Specifically, the PWG was conducted to "*further evaluate the lung fibrosis observed in several rats at the end of the recovery period.....in order to clarify the diagnoses presented in the original study report"* (reference 1a pg. 1).

Consistent with our recommendation for better visualizing fibrosis in histopathological sections (reference 2 pg. 13), the PWG pathologists also evaluated recuts of the lung sections from all study animals prepared with a Masson's Trichrome (MTC) collagen stain. A list of *"Diagnostic Terms"* (reference 1a pg. 3) was provided in the PWG report, which included two "*new diagnostic terms used to further define these changes* (fibrosis)":

1. **Fibrosis, pleural/subpleural**, defined as "*denotes collage presence in areas of the pleura and the associated subjacent alveoli (i.e. subpleural) independent of the above-mentioned areas and with little inflammatory infiltrates"*.

2. **Inflammation, (chronic or subacute**).

a. Inflammation, **subacute** defined as "*denotes inflammatory foci that are intermediate in duration between that of an acute inflammation and that of a chronic inflammation, usually persisting longer than 3 or 4 weeks and may contain collagen fibers (i.e. fibrosis), were present as focal or multifocal areas in the lung parenchyma"*.

b. Inflammation, **chronic** defined as "*inflammation that may have a rapid or slow onset but is characterized primarily by its persistence and lack of clear resolution; it occurs when the tissues are unable to overcome the effects of the injuring agent. In this case it is used to denote the presence of collagen in foci of inflammatory infiltrates that were not necessarily connected with the pleura and were either focal or multifocal in the lung parenchyma*".

> **Pathology comment**: We do not agree with the PWG's definition of subacute inflammation; the duration of subacute inflammation usually applies to a timeframe of a few days to a few weeks. More importantly, the definition of subacute inflammation generally **does not** include the presence of collagen fibers (fibrosis) as fibrosis is the defining manifestation of chronicity in chronic inflammation (Slauson and Cooper, Mechanisms of Disease, Textbook of Comparative General Pathology, 2002 3rd Ed. pg. 152). This distinction, is in our opinion crucial for a meaningful understanding of the given fibrosis issue and the interpretation of the applied MTC collagen stain. Furthermore, a separate diagnosis ("fibrosis, pleural/subpleural") unnecessarily confuses the issue, as it reintroduces a diagnosis of "fibrosis" in the lung. We re-advocate the use of just the term "chronic inflammation" (reference 2 pg. 15) for all PLD associated pulmonary changes with secondary inflammatory fibrosis of this rat study.

Results:
The PWG evaluated data from the unscheduled deaths (reference 1a 3.2 pg. 4), the primary necropsy data at week 13 (reference 1a 3.3 pg. 7), the primary necropsy data at week 26 (reference 1a 3.4 pg. 8), and the recovery necropsy data at weeks 39 and 52 (reference 1a 3.5 pg. 9, 3.6 pg. 10).

The PWG pathologists reported that none of the treatment animals that died early, had diagnoses of fibrosis pleural/subpleural, chronic inflammation, or a positive trichrome stain (reference 1a pg. 6) and concluded that "*the presence of fibrosis required a longer time to appear...*" (reference 1a pg. 6).

At the 13 week "early" sacrifice time point of the high dose females at 90 mg/kg, the PWG pathologists identified a 100 % incidence (15/15) of PLD and inflammation in two animals (6514 and 6529, only the latter animal with positive MTC stain for fibrosis, reference 1a pg. 7).

At the 26 week the PWG pathologists identified for the low dose group at 60 mg/kg, 15/20 males with PLD, 3 PLD males with inflammation and fibrosis. For the high dose at 90 mg/kg, the PWG reported 16/16 males with PLD, 2 PLD males with inflammation and 2 PLD males with inflammation and fibrosis. From this, the PWG pathologists concluded, that "*inflammatory changes in most of the*

animals were accompanied by the presence of fibrosis evidenced by positivity of the trichrome stain". The PWG pathologists acknowledged furthermore "*that at this time the lungs evidenced increased presence of focal areas of inflammation*".

At the 39 week sacrifice (female high dose recovery only) the PWG pathologists reported 9/10 females with PLD, 5/10 with fibrosis based on a positive MTC stain. 2 of the five fibrosis positive females were reported with chronic inflammation while the remaining 3 were reported with multifocal pleural/subpleural fibrosis. The PWG pathologists further stated, that "*all the fibrosis observed in the five animals was residual, mature collagen accompanied by chronic inflammatory cells (observed on H&E and MTC)"*.

At the 52 week sacrifice for males, the PWG pathologists reported 1/9 (changed from 2/9, recorded in reference 3) and 8/10 animals with remaining PLD after the 6 month recovery phase for 60 and 90 mg/kg, respectively. The PWG pathologists reported that inflammation or fibrosis was not observed for the 60 mg/kg male dose group. For the 90 mg/kg dose group, 8/10 males were reported to be PLD positive; of these, six (6/10) high dose males were reported to also have fibrosis based on a positive MTC stain. 2 of these six fibrosis positive males were reported with chronic inflammation while the remaining 4 were reported with multifocal pleural/subpleural fibrosis.

At the 52 week sacrifice for the 60 mg/kg females, the PWG pathologists reported 8/9 animals with PLD. Five of these (5/9) low dose females were reported to also have fibrosis based on a positive MTC stain. 4 of these five fibrosis positive females were reported with chronic inflammation while the remaining 1 was reported with multifocal pleural/subpleural fibrosis.

Pathology comment:
In the Table below we summarized the combined PWG report (reference 1a pg. 26-27) and in the resulting amended pathology report data (reference 4a pg. 9, Text Table 3) restricted to PLD (macrophages, vacuolated) and secondary lung changes (inflammation and fibrosis).

PWG and Amended Pathology Study Data						
Dosage (mg/kg/day):	Males			Females		
Lungs	0[a]	60[a]	90[a]	0[a]	60[a]	90[b]
Total # of animals at Primary vs. Recovery Necropsy	17/10	20/9	16/10	19/10	17/9	15/10
Macrophages, Vacuolated (PLD)	0/0	16/1	16/8	0/2	17/8	15/9
Minimal	-/-	14/1	0/5	-/2	3/3	0/9
Mild	-/-	1/0	2/3	-/0	5/4	3/0
Moderate	-/-	1/0	12/0	-/0	9/1	9/0
Severe	-/-	0/0	2/0	-/0	0/0	3/0
Fibrosis, Pleural/Subpleural	1/0	0/0	0/4	0/0	0/1	1/3
Minimal	1/-	-/-	-/4	-/-	-/1	0/3
Mild	0/-	-/-	-/0	-/-	-/0	1/0
Inflammation, Chronic	0/0	2/0	2/2	0/0	0/4	0/2
Minimal	-/-	2/0	1/0	-/-	-/1	-/1
Mild	-/-	0/0	1/2	-/-	-/3	-/1
Trichrome (MTC) positive	1/0	3/0	2/6	0/0	0/5	1/5
Minimal	1/-	3/-	1/4	-/-	-/1	0/4
Mild	0/-	0/-	1/2	-/-	-/4	0/1
Moderate	0/-	0/-	0/0	-/-	-/0	1/0
Inflammation, Subacute	0/1	1/0	2/0	0/0	0/0	1/0
Minimal	-/1	0/-	0/-	-/-	-/-	0/-
Mild	-/0	1/-	2/-	-/-	-/-	1/-
Inflammation, Mixed cell						
Moderate	0/0	0/0	0/0	0/0	0/0	1/0

[a]26 weeks for treatment + 26 weeks recovery = total 52 weeks on study; [b]13 weeks on study for treatment + 26 weeks recovery = total 39 weeks on study

Comparing the recorded data above with those of the original pathology report (Table 3, Amendment 1, reference 3 pg. 63), the original study pathologist tabulated a "fibrosis" observation, unassociated with an inflammatory process. As a result of the PWG evaluation, the PWG pathologists added inflammation as diagnostic criteria. They changed 8 of the original "fibrosis" incidences to represent *inflammation, chronic*. In addition, the PWG pathologists added 4 incidences of *inflammation chronic* and 4 incidences of *inflammation subacute*.

In the Discussion section of the PWG report (reference 1a pg. 13), the PWG pathologists proposed a PLD associated "*predisposition for inflammation to occur and become chronic"*. They continued stating that *"These foci of inflammation, like any chronic inflammatory focus, induce production of collagen"* (fibrosis). The PWG pathologists interpreted the occurrence of the resulting inflammatory fibrosis as "*secondary effects to the lung phospholipidosis*" (reference 1a pg. 14) and substantiated this take by pointing out that the type of fibrosis reported was "*multifocal in nature*" while "*the remaining portions of the lung were devoid of fibrosis*".

Pathology comment:
Overall the PWG results confirmed our previous assessment (reference 2) that the fibrosis findings presented in this and other Pimavanserin studies evaluated are representative of "chronic inflammation" which implies some degree of organizing fibrosis. The PWG affirmed that the PLD process is associated with a low grade ongoing inflammatory cell response which organizes over time (chronicity) resulting in collagen deposits manifesting as "inflammatory fibrosis". The PWG confirmed that the secondary inflammatory fibrosis reported in this 6 month rat study with a 6 month recovery phase (reference 3 and 4a) was generally focal to multifocal in distribution and of minimal to mild severity. The PWG report further supports a continuum underlying the development of the minimal-mild, multifocal inflammatory "fibrosis" reported in this 6 month rat study, consisting of PLD, followed by inflammation (subacute), and chronic inflammation (with fibrosis) over time. The "fibrosis" termed pleural/subpleural in the PWG report is, however, in our opinion, not a separate process from the "inflammation, chronic" but a "point in time" observation which represents the resolution process from minimal-mild, multifocal, subpleural inflammatory foci with fibrosis after the originally associated inflammation has subsided.

Summary: In our opinion, the PWG report supports an overall conclusion that low grade chronic inflammation is the source of fibrosis described in the original 6 month rat Pimavanserin study with a 6 month recovery phase.

However, there were several approaches and / or statements in the PWG report with which we did not agree. In addition, inconsistencies and /or omissions largely confused the PWG pathologists' message. Only a few examples are summarized below.

Reference 1a / Topic	**CFSAN Pathology Comment**
Several of the Figures (1-8) provided in the PWG report pg. 18-25 showed inconsistencies.	**Figure Examples:** **Figure 3**, is introduced as **pleural/subpleural fibrosis** on pg. 10 of the PWG report; the figure legend (pg. 20) is consistent with this text statement of pleural/subpleural fibrosis, however, on pg. 27 (PWG Addendum 1, change to data table) a diagnosis change for this animal is noted as "changed fibrosis to **inflammation, chronic**". Similarly, **Figure 6** – is referenced on pg. 9 and 14 of the PWG report as an example of **subpleural fibrosis**; the photo legend (pg. 23) also identifies the change as subpleural fibrosis; however, on pg. 26 (PWG Addendum 1, change to data table) a change of diagnosis for this animal is noted as "changed fibrosis to **inflammation, chronic**". Based on the cellularity present in Figure 6, this change is in our opinion best described as **inflammation, chronic**. The presentation of Figure 3, we suppose is probably reflective of what the PWG pathologists' envisioned as representative for fibrosis pleural/ subpleural. We, however, find this distinction unnecessary as both lesion manifestations are a consequence of a chronic inflammatory process. These recording inconsistencies are perfect examples of why the distinction between "pleural /subpleural fibrosis" and "inflammation, chronic" only leads to confusion even to the PWG pathologists themselves.

	Figure 7 – The figure legend to this photograph (pg. 24) is the only place in the PWG report, where the presence of cholesterol clefts within inflammatory changes, are described by the PWG pathologists. The original pathology report, however, described multinucleated giant cells as well as cholesterol clefts which both are clearly depicted in this photograph. We are at a loss of why this prominent observation of **multinucleated giant cells with cholesterol clefts** would be omitted in the PWG report as it constitutes an uncommon feature of PLD. The PWG pathologists did not describe the presence of intra and extracellular eosinophilic material (phospholipid secondary to macrophage lysis) either, mentioned in 4 of 7 PLD positive Pimavanserin studies (reference 2 pg. 12) including this 6 month rat study with a 6 month recovery phase. That the PWG pathologists were mindful of the aforementioned multinucleated giant cell observation, becomes clear based on changes made, as result of the PWG report, (reference 1a) in the amended pathology report (reference 4a pg. 5 and 7). These changes resulted in the deletion of any reference to multinucleated giant cells previously reported by 2 prior study pathologists (reference 3 pg. 62) in the pathology report narrative. However, as a result of the PWG, a description of "**multinucleated giant cells formed from vacuolated macrophages**" was added by the PWG study pathologist to a PLD observation of one treated 60 mg/kg male rat in the individual animal tables (reference 4a pg. 313, animal 6370). In addition, one diagnosis of "chronic inflammation …[ ] with "**cholesterol clefts**" was added to one treated 90 mg/kg recovery female in the individual animal tables (reference 4a pg. 452, animal 6478, which is also the source of Figure 7 above). However, following these additional entries into the individual animal data tables, the PWG study pathologist chose to comment only on cholesterol clefts but not on multinucleated giant cells in the amended pathology report, despite the fact that both observations are clearly visible in Figure 7 of the PWG report (reference 1a pg. 24). These inconsistencies do not make sense to us. The PWG / study pathologist(s) did not attempt to explain or justify their decision to omit the observation of multinucleated giant cells, in either the PWG report or the amended pathology report. As this review is conducted on a finalized GLP pathology report, all changes - additions and omissions - should have been noted and justified in the amended pathology report by the study pathologist and, in our opinion, also in the PWG report by the PWG pathologists. **Figure 8** – is introduced on pg. 11 in the PWG report and in the figure legend to this photo (pg. 25), this image is supposed to provide an **example of human pulmonary fibrosis** characterized by "diffuse interstitial deposition of connective tissue" implying a **chronic long standing process**. The PWG pathologists also use the same image to illustrate an **acute pulmonary exudative phase with fibrin formation** (pg. 14). Following the provided internet link in the figure legend, the original description accompanying this image reads "DAD (diffuse alveolar damage) – pulmonary edema, formation of hyaline membrane (arrows, containing fibrin, proteinaceous debris and desquamated cells), organization with fibrosis". This image is, therefore, descriptive of a **highly acute process** that is, in our opinion, not a representative human analogue to the fibrosis issues discussed in this 6 month rat study with an additional 6 month recovery phase.

Maximum Tolerated Dose	On pg. 6 and 13 - the PWG pathologists stated that "*both doses* (60 and 90 mg/kg) *exceeded the maximum tolerated dose in this study"*. It is our opinion, that with this statement the PWG pathologists invalidate this rat study (reference 3) in its entirety. We do not agree with this conclusion, as all male rats as well as most of the females survived. However, we do think that this study had prominent shortcomings pertaining to the fact that it only included 2 test doses, while the pivotal 30 mg/kg dose was not retested. The 30 mg/kg dose was, in our opinion, equivocal in previous studies for the presence of PLD (reference 2 pg. 9).
Other comments	On pg. 1 of the PWG report, it is stated, that the PWG consisted of only 2 pathologists, which is unusual. Usually, a PWG is composed of 3-5 voting members with a non-voting chair-person and often includes the original study pathologist. It was stated on pg. 10 (reference 4a) that a PWG was conducted instead of the originally planned Peer Review (pg. 153, protocol amendment 9), because the sponsor requested a PWG. As there are many defining differences between PWGs and Peer Reviews, overall, this PWG resembled the Peer Review process more so than a PWG process.

Your specific questions:

1. Do the basic methods for revaluating the lung tissues outlined in the report appear reasonable?

Pathology comment: The methods outlined in the PWG report, specifically the reevaluation of all lung slides by both pathologists and the evaluation of recut lung sections stained with MTC stain for collagen, are considered reasonable approaches.

2. Do you agree with the PWG and sponsor's overall conclusions and proposed mechanism for the development of lung fibrosis?

Pathology comment: As outlined above, we concur with the overall conclusion of the PWG report that chronic inflammation is the source of the fibrosis described in the original 6 month rat study with a 6 month recovery phase. However, the PWG pathologists describe 2 different mechanisms, a) **Inflammation secondary to PLD** (reference 1a pg. 13, 15), and b) **pleural irritation through rubbing** (pg. 14, 15) with which they attempt to explain 2 distinct diagnoses: a) **inflammation, chronic or subacute** and b) **fibrosis, pleural/subpleural**. With regard to the first mechanism, we agree that the inflammation is likely a response to PLD but not, as proposed by the PWG pathologists, in response to "environmental" or "unidentified" pathogens (pg. 13, 15). We consider the inflammation a response to phagocytic overload, resulting in eosinophilic extracellular material, described and interpreted by the original study pathologist as phospholipid and a consequence of macrophage lysis (reference 2, pg. 10, 12). Over time, the inflammation becomes chronic which is associated with deposition of collagen fibers (fibrosis). This process, in our opinion, remains the same independent of location within the lung (parenchymal or subpleural). The PWG pathologists, however, propose the second mechanism for changes specifically observed in pleural and subpleural locations. We consider the outline of the second mechanism (rubbing) highly speculative. The separate diagnosis of "fibrosis, pleural/subpleural" unnecessarily confuses the issue, as it reintroduces a diagnosis of "fibrosis" in the lung. We re-advocate the use of just the term "chronic inflammation" (reference 2 pg. 15) for all PLD associated pulmonary

changes with secondary inflammatory fibrosis of this rat study.

3. Do you have any additional questions or comments regarding the findings or the conclusions in the report?

Pathology comment: As mentioned above, we noted several inconsistencies within the PWG report; our main concern pertains to the fact that omissions in the amended pathology report, resulting from the PWG evaluation, were not justified and / or made apparent.

The most obvious example of this is the omission of any mentioning of multinucleated giant cells specifically characterizing the PLD of this rat study. The description by 2 prior study pathologists of "vacuolated macrophages" being….[ ] "**characterized by** collections of large **foamy macrophages and multinucleated giant cells**"… implies that multinucleated giant cells were a consistent feature for the majority of the diagnoses pertaining to "macrophages, vacuolated" reported in lungs of treated animals. This omission in the GLP amended pathology report (reference 4a), obviously requires an explanation, as multinucleated giant cells were clearly depicted in at least one figure of the PWG report (Figure 7, reference 1a).

4. After reviewing the PWG report, would you recommend any additional nonclinical studies or evaluations with pimavanserin?

Pathology comment: Overall, we agree with some conclusions of the PWG report, supporting our previously stated opinion that chronic inflammation is the source of the "fibrosis" recorded by the original study pathologist. However, as mentioned above, there are several statements (rubbing mechanism leading to subpleural fibrosis; inflammation in response to "environmental" or "unidentified" pathogens) presented in the PWG report and omissions (e.g. multinucleated giant cells, cholesterol clefts, eosinophilic material) with which we do not agree. It needs to be noted that optimally CFSAN Pathology would have conducted its own review of the lung slides to make an independent assessment, for a comparison with any reported data presented (PWG report, reference 1a; original study report, reference 3; and amended pathology report data, reference 4a). However, in lieu of an independent slide review, we conclude that based on the information provided in the PWG report and in the amended pathology report (reference 4a), there is no evidence of primary pulmonary fibrosis in the rat Pimavanserin 6 month study with a 6 month recovery phase. Therefore we do not consider further studies necessary.

Please let us know if you have any questions.

Sabine Francke-carroll -S

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Sabine Francke, D.V.M., Ph.D., FIATP and Steven Mog D.V.M., DACVP

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BRENDAN MUOIO
03/25/2016
CFSAN reviewed entered into DARRTS by RPM

Pharmacology/Toxicology NDA Review and Evaluation Amendment

Application number: NDA 207318

Supporting document/s: SDNs 24, 25

Applicant's letter date: March 4, 2016, March 18, 2016

CDER stamp date: March 4, 2016, March 18, 2016

Product: Pimavanserin

Indication: Parkinson's disease psychosis

Applicant: Acadia Pharmaceuticals, Inc.

Review Division: Psychiatry Products

Reviewer: Amy M. Avila, Ph.D.

Supervisor: Aisar Atrakchi, Ph.D.

Division Director: Mitchell Mathis, M.D.

Project Manager: Brendan Muoio, Pharm.D.

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 207318 are owned by Acadia Pharmaceuticals or are data for which Acadia Pharmaceuticals has obtained a written right of reference. Any information or data necessary for approval of NDA 207318 that Acadia Pharmaceuticals does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 207318.

Background:

In order to further evaluate the lung fibrosis observed in rats in a 6-month study with a 6-month recovery period (study [redacted]-616007); the applicant requested a Pathology Working Group (PWG) review. The PWG was done in collaboration with [redacted] (the original testing laboratory). [redacted] represented [redacted] and the applicant retained Dr. Ricardo Ochoa. Both pathologists agreed that collagen stains were needed for the review and therefore all lung sections from all animals in study [redacted]-616007 were recut and stained with Masson's Trichrome (MTC), utilizing the same blocks as those used for the original Hematoxylin and Eosin (H&E) slides. Once the slides were prepared they were reviewed separately by both pathologists. Agreement was reached between the two reviewing pathologists regarding diagnoses. The newly agreed upon diagnoses were entered into the database which produced new study data tables. Quality assurance audited the data and a new amended study report (amended number 2) was submitted to NDA 207318 on March 18, 2016 in SDN 25. The PWG report was submitted to the NDA on March 4th, 2016 in SDN 24. Below is a review of both submissions.

Information Submitted:

The authors of the PWG report provided the following definitions of diagnostic terms.

Phospholipidosis	Corresponds to the term Macrophages, Vacuolated as used in the original study report to denote more specifically the nature of the vacuoles observed. Phospholipidosis was identified by electron microscopy.
Inflammation, Subacute	Denotes inflammatory foci that are intermediate in duration between that of an acute inflammation and that of a chronic inflammation, usually persisting longer than 3 or 4 weeks and may contain collagen fibers (i.e. fibrosis), were present as focal or multifocal areas in the lung parenchyma.
Inflammation Chronic	Inflammation that may have a rapid or slow onset but is characterized primarily by its persistence and lack of clear resolution; it occurs when the tissues are unable to overcome the effects of the injuring agent. In this case it is used to denote the presence of collagen in foci of inflammatory infiltrates that were not necessarily connected with the pleura and were either focal or multifocal in the lung parenchyma.
Fibrosis, Pleural/Subpleural	Denotes collagen presence in areas of the pleura and the associated subjacent alveoli (i.e. subpleural) independent of the above-mentioned areas and with little inflammatory infiltrate.
Inflammation, Granulomatous	Denotes a collection of immune cells known as histiocytes. Granulomas form when the immune system attempts to wall off substances it perceives as foreign but is unable to eliminate. These areas often also contain collagen fibers.
Inflammation, Mixed cell	Denotes and inflammation composed of lymphocytes, macrophages and some neutrophils without evidence of chronicity.
Trichrome +	Indicates that the trichrome stain was positive for increased collagen fibers. These fibers were either immature collagen and very fine, or mature collagen and also visible with H&E stain.

[Table excerpted from PWG report, NDA 207318 SDN 24.]

Review and Evaluation:

Unscheduled deaths:

18 animals died or were sacrificed *in extremis* prior to their scheduled necropsies (table below from applicant). Microscopic findings, after re-examination, and diagnosis in the lungs of these rats are included in table 1 below. No inflammation or fibrosis, pleural/subpleural, was identified in any drug-treated animal that died or was sacrificed prematurely. A female at 60 mg/kg/day died on study day 12, had granulomas with trichrome positive staining within the granulomas (fibrosis). However, there was no evidence of phospholipid-laden macrophages within the lungs of this animal, and the granulomas were determined to be older than the 12 days the animal was in the study, therefore the death was not considered drug-related. Most other drug-treated animals that were found dead or died prematurely had evidence of pulmonary phospholipidosis (PLD) (diffuse vacuolated macrophages), with the exception of a 90 mg/kg/day female

that died on study day 4 that had no evidence of PLD. A 60 mg/kg/day female that was found dead on day 51 had only minimal amounts of PLD, while all others had either mild or moderate amounts of diffuse vacuolated macrophages and died starting on day 86 in group 3 animals (90 mg/kg/day), when several females were sacrificed *in extremis*, and day 178 in group 2 females (60 mg/kg/day). The PWG report noted that *"[a]t the time of death many of the animals had considerable respiratory difficulties due to the decrease of respiratory function caused by the severe accumulation of phospholipids."* These findings indicate that the incidence and severity of accumulated vacuolated macrophages in the lungs of rats treated with pimavanserin increased over time and also correlated with adverse effects of respiratory function, but fibrosis or inflammation in the lungs did not result in death or premature sacrifice.

The following tables (1-7) are excerpted from the PWG report, NDA 207318.

Table 1: Selected diagnoses in unscheduled death animals

Diagnosis	0 mg/kg M	0 mg/kg F	60 mg/kg M	60 mg/kg F	90 mg/kg M	90 mg/kg F
Number of Animals	3	1	1	4	4	5
Granulomas	-	-	-	1	-	-
Trichrome +	-	-	-	1	-	-
Fibrosis, Pleural/Subpleural	1	-	-	-	-	-

Microscopic evaluation of lungs from animals at scheduled sacrifices:

End of dosing phase (week 13 for group 3 females, week 26 for males and group 2 females):

Only one 90 mg/kg/day female that was sacrificed at week 13 had a positive trichrome stain which correlated with the finding of pleural/subpleural fibrosis, subacute inflammation, and severe vacuolated macrophages. There was only one other finding of fibrosis, pelural/subpleural in animals sacrificed at the end of the dosing phase, but it was observed in a control male. There were 5 findings of trichrome positive staining at the end of the dosing phase all in males (3 at 60 mg/kg/day and 2 at 90 mg/kg/day). The trichrome positive staining in these males correlated with the finding of chronic inflammation (2 males each at 60 and 90 mg/kg/day); and a separate male at 60 mg/kg/day with positive trichrome staining had no evidence of inflammation but the staining correlated with focal pigmented vacuolated macrophages in the alveolar septae. Subacute inflammation was also observed in the lungs of 1 male at 60 and 2 at 90 mg/kg/day that were negative for trichrome staining.

Table 4: Selected diagnoses in Week 13 Females (Early termination)

Diagnosis	0 mg/kg M	0 mg/kg F	60 mg/kg M	60 mg/kg F	90 mg/kg M	90 mg/kg F
Number of Animals	0	0	0	0	0	15
Trichrome +	-	-	-	-	-	1
Inflammation, Mixed cell	-	-	-	-	-	1
Fibrosis Pleural/Subpleural	-	-	-	-	-	1
Inflammation, Subacute	-	-	-	-	-	1

Table 5: Selected diagnoses in Week 26 Males and Females

Diagnosis	0 mg/kg M	0 mg/kg F	60 mg/kg M	60 mg/kg F	90 mg/kg M	90 mg/kg F
Number of Animals	17	19	20	17	16	0
Trichrome +	1	-	3	-	2	-
Fibrosis, Pleural/Subpleural	1	-	-	-	-	-
Inflammation, Subacute	-	-	1	-	2	-
Inflammation, Chronic	-	-	2	-	2	-

6-month recovery groups (week 39 for group 3 females, week 52 for males and group 2 females):

A greater incidence of positive trichrome staining occurred in recovery group animals (5 each from 60 and 90 mg/kg/day females and 6 from 90 mg/kg/day males). The positive trichrome staining correlated with fibrosis pleural/subpleural or chronic inflammation.

Table 6: Selected diagnoses in Week 39 Females

Diagnosis	0 mg/kg M	0 mg/kg F	60 mg/kg M	60 mg/kg F	90 mg/kg M	90 mg/kg F
Number of Animals	0	0	0	0	0	10
Trichrome +	-	-	-	-	-	5
Fibrosis Pleural/Subpleural	-	-	-	-	-	3
Inflammation, chronic	-	-	-	-	-	2
Inflammation, subacute	-	-	-	-	-	-

Table 7: Selected diagnoses in Week 52 Males and Females

Diagnosis	0 mg/kg M	0 mg/kg F	60 mg/kg M	60 mg/kg F	90 mg/kg M	90 mg/kg F
Number of Animals	10	10	9	9	10	0
Trichrome +	-	-	-	5	6	-
Fibrosis Pleural/Subpleural	-	-	-	1	4	-
Inflammation, chronic	-	-	-	4	2	-
Inflammation, subacute	1	-	-	-	-	-

Below is the text table of the respiratory system microscopic findings excerpted from the amended study report (SDN 25 of NDA 207318). The underlined information indicates changes made from the original pathology report.

Text Table 3. Incidence and Severity of ACP-103-Related Microscopic Findings in the Respiratory System at Primary and Recovery Necropsies [b]

	Males			Females		
Dosage (mg/kg/day):	**0**	**60**	**90**	**0**	**60**	**90**
Lungs						
PN/RN[a]	**17/10**	**20/9**	**16/10**	**19/10**	**17/9**	**15/10**
Macrophages, Vacuolated	0/ 0	16/1	16/8	0/2	17/8	15/9
Minimal	-/-	14/1	0/5	-/2	3/3	0/9
Mild	-/-	1/0	2/3	-/0	5/4	3/0
Moderate	-/-	1/0	12/0	-/0	9/1	9/0
Severe	-/-	0/0	2/0	-/0	0/0	3/0
Vacuolation, Epithelium	0/0	7/0	13/6	0/0	13/6	15/2
Minimal	-/-	6/-	9/6	-/-	10/5	7/2
Mild	-/-	1/-	4/0	-/-	3/1	7/0
Severe	-/-	0/-	0/0	-/-	0/0	1/0
Fibrosis, pleural/subpleural	1/0	0/0	0/4	0/0	0/1	1/3
Minimal	1/-	-/-	-/4	-/-	-/1	0/3
Mild	0/-	-/-	-/0	-/-	-/0	1/0
Inflammation, chronic, focal/multifocal	0/0	2/0	2/2	0/0	0/4	0/2
Minimal	-/-	2/0	1/0	-/-	-/1	-/1
Mild	-/-	0/0	1/2	-/-	-/3	-/1
Trichrome stain, positive	1/0	3/0	2/6	0/0	0/5	1/5
Minimal	1/-	3/-	1/4	-/-	-/1	0/4
Mild	0/-	0/-	1/2	-/-	-/4	0/1
Moderate	0/-	0/-	0/0	-/-	-/0	1/0
Inflammation, subacute	0/1	1/0	2/0	0/0	0/0	1/0
Minimal	-/1	0/-	0/-	-/-	-/-	0/-
Mild	-/0	1/-	2/-	-/-	-/-	1/-
Inflammation, mixed cell, moderate	0/0	0/0	0/0	0/0	0/0	1/0
Trachea						
PN/RN[a]	**17/10**	**20/9**	**16/10**	**19/9**	**17/9**	**15/10**
Vacuolation, Epithelium	0/0	2/0	13/0	0/0	10/0	10/0
Minimal	-/-	2/-	9/-	-/-	7/-	9/-
Mild	-/-	0/-	4/-	-/-	3/-	1/-

PN/RN = number of tissues examined at primary necropsy/recovery necropsy

[a] = number of tissues examined at week 13 primary necropsy/week 39 recovery necropsy for the 90 mg/kg/day group females

[b] = **changes from the original pathology report are underlined**

[Table excerpted from amended study report (b) (4)-616007, NDA 207318 SDN 25.]

At the primary necropsies, the vacuolated macrophages found in the lungs were characterized by diffuse distribution, filled alveolar spaces of the lungs and were minimal to moderate in the 60 mg/kg/day groups and mild to severe in the 90 mg/kg/day groups. Focal to multifocal chronic inflammation was observed in males at both dose levels (60 and 90 mg/kg/day) at the end of dosing phase. The chronic inflammation was

characterized by lymphocytes and increased collagen matrix (fibrosis) that was also observed on trichrome stained lung slides (positive trichrome). Subacute inflammation (trichrome negative staining) was also observed at the end of the dosing phase in 1 male at 60 mg/kg/day and in 2 males and 1 female at 90 mg/kg/day, respectively. One female at 90 mg/kg/day at the 13 week necropsy had positive trichrome staining that correlated with mild fibrosis, pleural/subpleural, and another 90 mg/kg/day female had moderate mixed cell inflammation (trichrome negative staining).

At the recovery necropsies, the incidence and severity of the vacuolated macrophages was lower, indicating partial recovery of the phospholipidosis (although very slow). Also, after the 6-month recovery period the vacuolated macrophages were characterized by multifocal distribution (no longer diffuse) with aggregates in alveolar spaces in the subpleural alveoli and to a lesser extent, the periacinar alveoli. Chronic inflammation was observed recovery group males at 90 mg/kg/day and in recovery group females at both dose levels and correlated with positive trichrome staining. Pleural/subpleural fibrosis was also observed in recovery group males at 90 mg/kg/day and recovery group females at 60 and 90 mg/kg/day and was characterized by increased collagen matrix that expanded the pleura and alveolar septae of the subpleural alveoli and was observed on trichrome stained lung slides (positive trichrome). The chronic inflammation or fibrosis and macrophages corresponded to white areas observed macroscopically.

It is noted that in the original pathology report, inflammation was not listed as a diagnosis in the lungs from any animals in the study. However, fibrosis, and evidence of minimal to severe phospholipidosis was listed. The re-evaluation of lung tissues as part of the PWG identified new findings of subacute and/or chronic inflammation at both dose levels for males and females. In eight instances, the original diagnosis of fibrosis was changed to “inflammation, chronic, focal/multifocal” (4 females at 60, 2 females at 90, and 2 males at 90 mg/kg/day). In addition, eight new cases of inflammation (subacute or chronic) were identified (1 female at 60, 2 males at 60, 4 males at 90 mg/kg/day and in 1 control male). In all cases where the diagnosis of fibrosis still applied (1 female at 60, 3 females at 90, and 3 males at 90 mg/kg/day) or was newly identified (1 control male and one male and female each at 90 mg/kg/day), the diagnostic term was changed to “fibrosis, pleural/subpleural”.

Changes made to study (b) (4) 616007: (table excerpted from PWG report).

Animal number, group	Changes to data
6507, 3F (EE)	Removed inflammation, subacute
6514, 3F (Week 13)	Changed inflammation to mixed cell from granulomatous
6529, 3F (Week 13)	Changed fibrosis to fibrosis, pleural/subpleural, added subacute inflammation
6423, 3F (Week 39)	Added fibrosis, pleural/subpleural
6441, 3F (Week 39)	Removed fibrosis
6470, 3F (Week 39)	Changed fibrosis to inflammation, chronic, focal/multifocal
6478, 3F (Week 39)	Changed fibrosis to inflammation, chronic, focal/multifocal
6516, 3F (Week 39)	Changed fibrosis to fibrosis, pleural/subpleural
6525, 3F (Week 39)	Changed fibrosis to fibrosis, pleural/subpleural
6413, 2F (Week 52)	Changed fibrosis to inflammation, chronic, focal/multifocal
6439, 2F (Week 52)	Removed fibrosis
6453, 2F (Week 52)	Removed fibrosis
6481, 2F (Week 52)	Changed fibrosis to fibrosis, pleural/subpleural
6486, 2F (Week 52)	Changed fibrosis to inflammation, chronic, focal/multifocal
6500, 2F (Week 52)	Changed fibrosis to inflammation, chronic, focal/multifocal
6518, 2F (Week 52)	Changed fibrosis to inflammation, chronic, focal/multifocal

Animal number, group	Changes to data
6287, 1M (Week 26)	Added fibrosis, pleural/subpleural
6317, 2M (Week 26)	Added inflammation, chronic, focal/multifocal
6336, 2M (Week 26)	Added inflammation, chronic, focal/multifocal
6277, 3M (Week 26)	Added inflammation, subacute
6279, 3M (Week 26)	Added inflammation, chronic, focal/multifocal
6296, 3M (Week 26)	Added inflammation, chronic, focal/multifocal
6340, 3M (Week 26)	Added inflammation, subacute
6381, 1M (Week 52)	Added inflammation, subacute
6308, 3M (Week 52)	Changed fibrosis to inflammation, chronic, focal/multifocal
6313, 3M (Week 52)	Changed fibrosis to inflammation, chronic, focal/multifocal
6314, 3M (Week 52)	Changed fibrosis to fibrosis, pleural/subpleural
6320, 3M (Week 52)	Added fibrosis, pleural/subpleural
6355, 3M (Week 52)	Changed fibrosis to fibrosis, pleural/subpleural
6357, 3M (Week 52)	Changed fibrosis to fibrosis, pleural/subpleural

Conclusions:

The PWG made the following conclusions after re-examination of lung tissues, with the use of the trichrome stain for collagen, from all animals of study (b) (4) 616007. The following text is excerpted directly from the PWG report.

The fibrosis observed in this study differs from the disseminated lung fibrosis observed as a direct effect of compounds in several important ways.

1. The fibrosis as presented in these animals was present in two patterns:

    a. Fibrosis of the pleura and subpleural alveoli was observed occasionally in control animals. As observed in this study, the fibrosis in some pimavanserin (ACP-103) treated animals was consistent with irritation of the pleura and perhaps with interference of the lymph drainage by the severe infiltration of phospholipid-laden macrophages. This infiltration, resulting in lung weights up to three times those of controls, added to the physical effect of rubbing of the parietal and visceral pleuras during the process of respiration. This effect was not observed at doses where there was less accumulation of phospholipid-laden macrophages and therefore was not considered a direct compound effect, but a secondary event.

    b. Connective tissue fibers were also observed where there were focal areas of pneumonia, (chronic inflammation). These foci were characterized by a limited number of accumulations of mixed inflammatory cell infiltrations that varied between animals. These are considered consistent with areas where unidentified pathogens might proliferate in a lung where the macrophage phagocytic defense and alveolar defense mechanisms would be impaired by the presence of large amounts of phospholipid within the alveoli. These areas of chronic inflammation did not specifically involve the alveolar septa. The heterogeneity of these areas is evidenced by the presence of different combinations of inflammatory cells.

2. The fibrosis in this study is a late development. This implies that, unlike other compounds that produce diffuse pulmonary fibrosis, it is a secondary effect likely mediated through secondary inflammatory mechanisms such as physical irritation of the pleura or overlying inflammation.
3. The findings in study 616007 lack the diffuse alveolar cell proliferation and the diffuse initial inflammatory infiltrate and the subsequent diffuse collagen infiltration characteristic of pulmonary fibrosis in humans and of most of the animal models of pulmonary fibrosis reported.
4. The presence of increased foci of superimposed inflammation in the lungs of animals in this study may be caused by the impaired phagocytic ability of the phospholipid-laden macrophages, leading to decreased resistance of the lung to infection.
5. The presence of fibrosis of greater incidence and severity after the recovery period is considered related to a greater time for inflammation to occur and for the initial injury due to mechanical rubbing to develop into fibrotic areas. There is no expectation of reversibility of fibrotic lesions.

The PWG pathologists provide two possible explanations for the occurrence of fibrosis in the lungs of rats treated with pimavanserin. It is important to note that both of these possible events leading to fibrosis are *"secondary effects to the lung phospholipidosis."* This reviewer agrees the lung findings of inflammation and fibrosis are directly caused by phospholipidosis in the lungs.

The following text is excerpted from the PWG.

The pattern of fibrosis in the lungs in this study corresponds to two possible events.

1. The large accumulation of phospholipid-laden macrophages that produced a marked enlargement of the lung mass led to severe respiratory distress in groups 2 and 3 and to mortality or early sacrifice in group 3. This is evidence that the dosing in both of the experimental dose groups in this study clearly exceeded the ability of the organism to metabolize and dispose of the phospholipids generated. Therefore, in this study, the Maximum Tolerated Dose was exceeded. The accumulation of macrophages in the lung was consistent with classic phospholipidosis. The effect of this marked enlargement is dual: the presence of the phospholipids in the macrophages reduces their ability to mount a defense of environmental pathogens, producing a predisposition for inflammation to occur and become chronic. These foci of inflammation, like any chronic inflammatory focus, induce production of collagen.

2. The lung, enlarged with phospholipid-laden macrophages to an extent that interferes with respiration and the ability of the defense mechanism of alveolar macrophages and of the ciliated alveolar cells, only aggravates the problem. This marked influx of cells also interferes with the exchange of gasses, leading to the clinical signs of severe dyspnea observed in this study. The visceral pleura of the enlarged lungs rub against the parietal pleura of the thoracic cavity producing friction and irritation. Furthermore the drainage of lymph from the lung, which uses lymphatic vessels in the subpleural space, may become impaired due to pressure, leading to local edema, which worsens the problem. Therefore, the fibrosis observed (see Figure 6), when not caused by inflammatory foci, was present in the pleura and subjacent alveoli due to this chronic irritation.

This reviewer agrees with the overall conclusions made in the PWG report, that the fibrosis in the lungs of rats is part of a chronic inflammatory response secondary to phospholipidosis and not a direct primary fibrotic process similar to human pulmonary fibrosis. Furthermore, the PWG report and amended study report were also reviewed by Drs. Francke and Mog (CFSAN expert pathologists), who were also consulted to review the histopathology data from the original NDA 207318 submission. Drs. Francke and Mog also agreed with the overall conclusions in the PWG report (see consult review of the PWG report). Explanation number 1 above provided by the PWG pathologists for the possible events leading to fibrosis appears to be the most plausible. This reviewer does not agree with the statement in the PWG report that the doses used in the rat

study (60 and 90 mg/kg/day) were beyond MTD doses. The majority of males and females at 60 mg/kg/day and males at 90 mg/kg/day survived until scheduled necropsies. By saying this, the pathologists and applicant are invalidating the study. Also, multi-nucleated giant cells and cholesterol clefts were noted as being observed in the lungs however, these findings were not entered as a separate line listing in the data tables. Multi-nucleated giant cells and cholesterol clefts are not typically seen with phospholipidosis. This finding should be looked at more closely in any future nonclinical studies with pimavanserin.

Recommendations:

The new submitted data to the NDA, PWG report and amended study report (b) (4)-616007, do not change this reviewer's recommendation for approval of pimavanserin for the indication of Parkinson's disease psychosis (PDP). However, these new data altar the safety margins for chronic inflammation in the lungs of rats. This impact will change this reviewer's recommended language for section 13.2 (Animal Toxicology and/or Pharmacology) of the label.

In addition, it is clear from the PWG report that the use of more sensitive microscopic techniques (including the use of a special stain to detect collagen) identified new adverse findings in the lungs of rats treated with pimanvanserin that were not identified with H&E staining (subacute and chronic inflammation in males and females at both dose levels tested). Therefore, the question remains if the same sensitive microscopic techniques were used to re-evaluate lung tissues from rats in other chronic repeat-dose studies in which lower doses were used (the first 6-month rat study in which 30 mg/kg/day was the highest dose tested) or the 2-year rat carcinogenicity study (high doses of 30 mg/kg/day for males and 50 mg/kg/day for females) or from monkeys in the chronic 12-month repeat-dose toxicity study, would additional diagnoses of inflammation be found. Without the use of special stains to detect collagen and more sensitive microscopic techniques in these studies, the confidence for an accurate no observed effect level (NOEL) for inflammation and/or fibrosis in the lungs of animal is low. This has prompted this reviewer to consider the following postmarketing requirement.

If pimavanserin is approved for the indication of PDP, we are considering a nonclinical postmarketing requirement to further evaluate the effects of phospholipidosis in animals. Additional required data may include microscopic re-evaluation of lung tissue samples using special stains to detect collagen from rats treated with pimavanserin at lower doses to obtain a more accurate NOEL for phospholipidosis-induced inflammation. Microscopic re-evaluation of lung tissue samples using special stains to detect collagen may also be required from the 12-month monkey study in order to determine if inflammation can be detected in the lungs of monkeys using more detailed microscopic techniques.

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/s/

AMY M AVILA
03/25/2016

AISAR H ATRAKCHI
03/25/2016

Supervisory Memo

Drug:	Pimavanserin
NDA #	207318
Indication:	Parkinson's disease Psychosis
Sponsor:	Acadia Pharmaceuticals, Inc.
Review Date:	February 19, 2016
PDUFA Date:	May 1, 2016
Supervisor:	Aisar Atrakchi, Ph.D.
Division Director:	Mitchell Mathis, M.D.
Center/Division:	CDER / Psychiatry Products

This is a 505(b)(1) drug application for pimavanserin a new molecular entity developed by Acadia Pharmaceuticals. The drug indication is for treatment of Parkinson's disease psychosis to be administered orally as an immediate release tablet.

Summary and Recommendation:

The safety of pimavanserin was investigated in standard and adequate animal studies. Pharmacology studies showed pimavanserin binds with high affinity to serotonin $5HT_{2A}$ and $5HT_{2C}$ receptors acting as an antagonist and inverse agonist. This site of action as well as results from in vivo rodent models support the anti-psychotic-like effects of pimavanserin and its potential therapeutic benefit in patients with psychosis associated with Parkinson's disease. Pimavanserin caused a significant prolongation of the QT_c interval in monkey (40 msec), and moderately inhibited the hERG channel with an IC_{50} of 0.21 μM. In the rat and/or rabbit, it decreased respiratory rate, caused rales (noisy breathing), and difficulty breathing. Adverse effects of pimavanserin were investigated in mice, rats, and monkeys following daily administration up to 3, 6, and 12 months respectively. Pimavanserin is a Cationic Amphiphilic Drug (CAD) these are drugs that based on their chemical and physical properties cause phospholipidosis (PLD), an excessive accumulation of phospholipids in cells both in animals and humans. Pimavanserin-induced PLD occurred in all animal species tested, in over 30 tissues/organs, and as early as 2 weeks of daily dosing. The most effected organs in all species are the lungs and kidneys. PLD is a reversible process without functional injury once the causing agent is removed. In general the PLD caused by pimavanserin was either fully or partially reversible and except as noted, did not lead to tissue/organ dysfunction nor impact the

overall well-being of the animal. A dose- and, time/duration- dependent lung inflammation occurred in the rat that led to poor condition and mortality as well as lung fibrosis. The lung fibrosis is *the safety concern* from nonclinical perspective because it is an irreversible pathology and is of clinical relevance. However, the sponsor considered the lung fibrosis to be secondary to persistent chronic inflammation and the inability of the cells to clear the PLD. This conclusion was accepted by the pharmacology reviewer Dr. Avila and by CFSAN Expert pathologists, Drs. Franke and Mog. After a thorough review of the sponsor's data both Drs. Franke and Mog concluded that the fibrosis is not a direct drug insult and therefore, not in line with human pulmonary fibrosis as seen with amiodarone-induced lung fibrosis, for example.

Recommendations:

I agree with Dr. Avila's recommendation to approve pimavanserin to treat patients with Parkinson's disease psychosis based on nonclinical results. However, I would not support any future use of pimavanserin in a younger patient population that would require long term administration unless the finding of lung fibrosis is further investigated due to the uncertainty surrounding the nature and progression to this pathology. This is also in agreement with Dr. Avila's recommendation. Studies should focus on the development of lung fibrosis and its association with the degree and duration of persistent inflammation. Results from such investigation are important since they can demonstrate either the clinical relevance or the lack of such relevance. Additionally, based on off-label use of anti-psychotics in children with autism, I concur with Dr. Avila that a juvenile animal toxicity study is recommended as a postmarketing requirement with special emphasis on the lung and respiratory function.

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/s/

AISAR H ATRAKCHI
02/22/2016
this memo concurs with the reviewer's recommendation

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

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	207318
Supporting document/s:	SDN 1, 7, 8, 12, 20
Applicant's letter date:	September 1, October 14, November 12, and December 9, 2015, February 9, 2016
CDER stamp date:	September 1, October 14, November 12, and December 9, 2015, February 9, 2016
Product:	Pimavanserin
Indication:	Parkinson's disease psychosis
Applicant:	Acadia Pharmaceuticals, Inc.
Review Division:	Psychiatry Products
Reviewer:	Amy M. Avila, Ph.D.
Supervisor/Team Leader:	Aisar Atrakchi, Ph.D.
Division Director:	Mitchell Mathis, M.D.
Project Manager:	Brendan Muoio, Pharm.D.

Template Version: September 1, 2010

Disclaimer

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1 Executive Summary

1.1 Introduction

This application is a 505(b)(1) NDA for pimavanserin (NUPLAZID). The indication is the treatment of Parkinson's disease psychosis. Pimavanserin is a new molecular entity and is being developed as an immediate release tablet formulation for oral administration. This drug is not approved outside the U.S.

1.2 Brief Discussion of Nonclinical Findings

The nonclinical studies conducted with pimavanserin tartrate and submitted with the NDA are adequate to assess the safety of pimavanserin for the treatment of Parkinson's disease psychosis. Pimavanserin binds with high affinity to the serotonin 2A ($5\text{-}HT_{2A}$) and serotonin 2C ($5HT_{2c}$) receptors and acts as an inverse agonist and antagonist. Similar results were found in in vitro functional assays. Pimavanserin demonstrated antipsychotic-like activity in several rodent behavioral models. In safety pharmacology studies, pimavanserin moderately inhibited the hERG channel with an IC_{50} of 0.21 µM and significantly prolonged the QT_c interval in monkeys at a dose which is 57-times the maximum recommended human dose (MRHD) of 34 mg/day based on mg/m^2. Pimavanserin also decreased respiratory rate in rats and produced emesis and nausea in male ferrets.

Toxicity of pimavanserin was studied in three species (mice, rats and monkeys), up to 3-months, 6-months and 12-months in duration, respectively following oral administration. Pimavanserin is characterized as a cationic amphiphilic drug (CAD). CADs are known to cause phospholipidosis (PLD), the excessive accumulation of phospholipids in cells, in animals and humans. Pimavanserin caused widespread, multi-organ, systemic PLD in mice, rats and monkeys after both sub-chronic and chronic administration, as early as 2-weeks of daily dosing in mice and rats. While microscopic findings consistent with PLD (foamy macrophages and/or cytoplasmic vacuolation) were observed in over 30 tissues/organs in rats; the lungs and kidneys were the most severely affected tissues in all species. In mice and monkeys, multi-organ PLD was either fully or partially reversible in all tissues and did not lead to any adverse tissue damage or impact the general well-being of animals. Conversely in rats, high doses of pimavanserin or long-duration of exposure at slightly lower doses resulted in PLD-related adverse tissue damage in the lungs of chronic inflammation with or without secondary fibrosis and PLD-related morbidity/mortality. The sponsor suggested that the severe multi-organ PLD leading to morbidity/mortality and chronic inflammation with fibrosis in the lungs of rats is only dose- *but not* duration- dependent. However, based on the totality of data submitted, this reviewer does not agree with the sponsor and believes multi-organ PLD which leads to toxicity is both *dose- and duration-* dependent. The fibrosis that was observed in the lungs of rats after 3- and 6-months of administration and at the end of a 6-month drug-free period was considered by the sponsor to be the culmination of a chronic inflammatory response due to repeated injury to lung tissue and inability to clear phospholipids. This reviewer agrees with the sponsor's assessment. Moreover, this conclusion is also supported by two internal expert pathologists from CFSAN (Center for

Food Safety and Nutrition), who conducted a thorough histopathology review and evaluation of the data (Appendix 4), and concluded the fibrosis in the lungs is not a direct drug-effect and therefore not consistent with human pulmonary fibrosis. Lung fibrosis was observed only in the rat. Other toxicities observed in monkeys included atrophy of the testes with decreased sperm production at pimavanserin exposures approximately 9-fold the MRHD of 34 mg/day based on AUC and dose-limiting emesis.

There is both a 9-fold safety margin to the no observed effect level (NOEL) for PLD with chronic inflammation and secondary fibrosis in the lungs, and for PLD-related morbidity/mortality compared to the *predicted* human AUC of 1630 ng.hr/ml at the MRHD of 34 mg/day pimavanserin. There is a similar 9-fold safety margin to the NOEL for PLD based on mg/m^2. Although Parkinson's disease psychosis is a chronic indication, the average life expectancy for these patients is not more than a few years. Therefore, the concern for developing multi-organ PLD that may lead to chronic inflammation and possible progression to secondary fibrosis in the lungs is reduced compared to a patient population in which the life expectancy is much longer and taking the drug chronically. For this reason, from a nonclinical standpoint and based on risk to benefit assessment, this reviewer considers the 9-fold safety margin acceptable for the treatment of patients with Parkinson's disease psychosis. However, this safety margin is not acceptable if pimavanserin is to be used off-label to treat other chronic indications in which pimavanserin would be administered chronically to patients expected to live for a longer period of time (e.g. autism).

Pimavanserin was non-genotoxic in the Ames assay, in vitro mouse lymphoma assay, or in the in vivo mouse micronucleus assay. Pimavanserin was not carcinogenic and did not induce tumors in rats (up to approximately 4- and 16-times the MRHD of 34 mg/day based on AUC in males and females, respectively) or in mice (up to approximately 1- and 7-times the MRHD based on AUC in males and females, respectively). Pimavanserin was not teratogenic in rats or rabbits up to 10- and 12-times the MRHD based on AUC, respectively. Pimavanserin adversely affected male reproductive organs and spermatogenesis in rats and decreased pup survival when administered to pregnant rats. Nonclinical data describing the adverse developmental, reproductive and fertility effects of pimavanserin are incorporated into the drug label.
The toxicity assessment for the major, active, human metabolite AC-279 was adequately covered in nonclinical species and impurities present at levels above the qualification threshold have been adequately qualified in nonclinical studies.

1.3 Recommendations

1.3.1 Approvability

Based on the review and evaluation of the results of pimavanserin testing in animals, this application is recommended for approval from a Pharmacology/Toxicology perspective for the indication of Parkinson's disease psychosis.

1.3.2 Additional Non Clinical Recommendations

As stated under section 1.2 above, from a nonclinical perspective this reviewer would not recommend the use of pimavanserin in a patient population with long life expectancy that will be taking the drug chronically. This is because of the concern for development of lung fibrosis as a result of chronic inflammation caused by persistent PLD. Additional nonclinical pharmacology and toxicology studies would be required to address and further investigate the lung fibrosis pathology if such use and/or indication are proposed. For example, such studies could utilize special stains for collagen (Masson's), inflammatory markers, etc. Because of potential off-label use of pimavanserin in children (autism), this reviewer recommends conducting a rat juvenile toxicity study as a postmarketing requirement with special emphasis on lung histopathology and respiratory function as well as neurobehavioral and reproductive assessments.

1.3.3 Labeling

All doses of pimavanserin in labeling are represented as free base; the maximum recommended human dose (MRHD) is 34 mg/day. Therefore all doses of pimavanserin tartrate used in nonclinical studies were converted to free base.

Note: At the time this review was finalized, labeling negotiations with the sponsor are ongoing. The proposed nonclinical labeling that follows is draft labeling recommended by this reviewer for sections 8.1, 12.1, 12.2, 13.1 and 13.2.

8.1 Pregnancy

Risk Summary

(b) (4)

Administration of pimavanserin to pregnant rats during pregnancy and lactation resulted in lower pup survival and body weight at doses 2-times the MRHD of 34 mg/day (b) (4) *[See Data]*.

(b) (4)

Data

Animal Data

Pimavanserin was not teratogenic to pregnant rats when administered during the period of organogenesis at oral doses of 0.9, 8.5, and 51 mg/kg/day which are 0.2 and 10-times the maximum recommended human dose (MRHD) of 34 mg/day based on AUC at mid and high doses respectively. Maternal toxicity included reduction in body weight and food consumption at the highest dose.

Administration of pimavanserin to pregnant rats during pregnancy and lactation at oral doses of 8.5, 26, and 51 mg/kg/day, which are 0.14 to 14-times the MRHD of 34 mg/day based on AUC, caused maternal toxicity including mortality, clinical signs, decreases in body weight and/or food consumption at doses ≥26 mg/kg/day (2- times the MRHD

based on AUC). At these maternally toxic doses there was a decrease in pup survival, reduced litter size, and reduced pup weights and food consumption. Pimavanserin had no effect on sexual maturation, neurobehavioral function including learning and memory, or reproductive function in the first generation pups up to 14-times the MHRD of 34 mg/day based on AUC.

Pimavanserin was not teratogenic to pregnant rabbits during the period of organogenesis at oral doses of 4.3, 43, and 85 mg/kg/day, which are 0.2 to 12-times the MHRD of 34 mg/day based on AUC. Maternal toxicity, included mortality, clinical signs, decreases in body weight and/or food consumption, and abortions occurred at doses ≥85 mg/kg/day (12-times the MRHD of 34 mg/day based on AUC).

12.1 Mechanism of Action

The mechanism of action of pimavanserin in the treatment of [redacted] (b) (4) associated with Parkinson's disease is unknown. However, the efficacy of pimavanserin could be mediated through a combination of inverse agonist and antagonist activity at serotonin 5-HT_{2A} receptors and to a lesser extent at 5-HT_{2C} receptors.

12.2 Pharmacodynamics

In vitro, pimavanserin acts as an inverse agonist and antagonist at serotonin 5-HT_{2A} receptors with high binding affinity (K_i value 0.087 nM) and at serotonin 5-HT_{2C} receptors with [redacted] (b) (4) lower binding affinity (K_i value 0.44 nM). [redacted] (b) (4)

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

There was no increase in the incidence of tumors following daily oral administration of pimavanserin to mice or rats for 2 years. Mice were administered pimavanserin at oral doses of 2.6, 6.0, and 13 (males)/ 8.5, 21, and 43 mg/kg/day (females) which are 0.01 to 1 (males)/0.5 to 7 (females) times the maximum recommended human dose (MRHD) of 34 mg/day based on AUC. Rats were administered pimavanserin at oral doses of 2.6, 8.5, and 26 (males)/4.3, 13, and 43 mg/kg/day (females) which are 0.01 to 4 (males)/0.04 to 16 (females) times the MRHD of 34 mg/day based on AUC.

Mutagenesis

Pimavanserin was not mutagenic in the *in vitro* bacterial Ames reverse mutation test, or in the *in vitro* mouse lymphoma assay, and it was not clastogenic in the *in vivo* mouse bone marrow micronucleus assay.

Impairment of Fertility

Pimavanserin was administered orally to male and female rats before mating, through mating and up to day 7 of gestation at doses of 8.5, 51 and 77 mg/kg/day which are approximately 2, 15 and 22-times the maximum recommended human dose (MRHD) of

34 mg/day based on mg/m^2, respectively. Pimavanserin had no effect on fertility or reproductive performance in male and female rats at doses up to 22-times the MRHD of 34 mg/day based on mg/m^2. Changes in uterine parameters (decreases in the number of corpora lutea number of implants, viable implants, and increases in pre-implantation loss, early resorptions and post-implantation loss) occurred at the highest dose which was also a maternally toxic dose. Changes in sperm parameters (decreased density and motility) and microscopic findings of cytoplasmic vacuolation in the epididymis occurred at doses approximately 15-times the MRHD of 34 mg/day based on mg/m^2.

13.2 Animal Toxicology and/or Pharmacology

(b) (4) phospholipidosis (foamy macrophages and/or cytoplasmic vacuolation) were observed in multiple tissues and organs of mice, rats, and monkeys as early as 14 days following oral daily administration of pimavanserin. The most severely affected organs were the lungs and kidneys. (b) (4)

2 Drug Information

2.1 Drug

CAS Registry Number: 706782-28-7

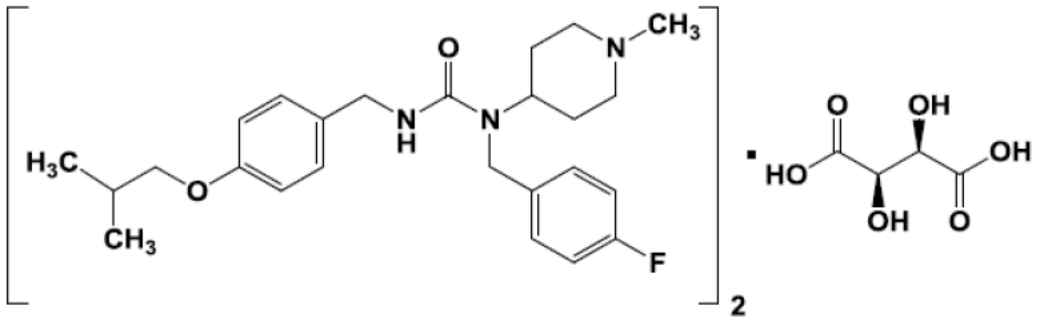
Generic Name: Pimavanserin tartrate

Code Name: ACP-103, (b) (4)

Chemical Name: Urea, *N*-[(4-fluorophenyl) methyl]-*N*-(1-methyl-4-piperidinyl)-*N'*-[[4-(2-methylpropoxy)phenyl]methyl]-,(2*R*,3*R*)-2,3-dihydroxybutanedioate (2:1)

Molecular Formula/Molecular Weight: $(C_{25}H_{34}FN_3O_2)2{\cdot}C_4H_6O_6$ (pimavanserin tartrate): 1000.5 g/mol; $C_{25}H_{34}FN_3O_2$ (pimavanserin): 427.55 g/mol

Structure or Biochemical Description:



Pharmacologic Class: Serotonin receptor 2A (5-HT_{2A}) inverse agonist

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 68,384

2.3 Drug Formulation

Immediate release tablets: 17 mg pimavanserin (20 mg pimavanserin tartrate)

2.4 Comments on Novel Excipients

None

2.5 Comments on Impurities/Degradants of Concern

Two impurities, [redacted] are found above the qualification limits of [redacted]% in drug substance batches. [redacted] The sponsor has proposed limits of NMT [redacted]% and [redacted]% in the drug substance, respectively for impurities [redacted] and NMT [redacted]% for impurity [redacted] in the drug product. The highest amount of impurities [redacted] detected in any drug substance batches to date are [redacted]% and [redacted]%, respectively (see sponsor's table below). The sponsor conducted nonclinical studies to qualify these two impurities including two in vitro genetox assays (Ames and chromosomal aberration) and two separate 4-week general oral toxicology studies in rats (however, typically 90-day repeat-dose toxicity studies are generally required to qualify impurities for chronic indications. During the pre-NDA meeting it was stated that the adequacy of these 4-week studies would be a matter of review). Both impurity [redacted] were found to be non-genotoxic when tested in the Ames and chromosomal aberration assays. In addition, no new or exaggerated toxicities were identified in rats treated orally with ACP-103 spiked with impurity [redacted] at [redacted]% (see special toxicology section 10 below).
All identified potentially genotoxic impurities [redacted] are being held to ≤[redacted] µg/day, which is [redacted] ppm for the MRHD of 34 mg pimavanserin, per ICH M7. The sponsor was notified by e-mail on February 4, 2016 that according to ICH M7 (May 2015), *"[w]hen there are three or more Class 2 or Class 3 impurities specified*

*on the drug substance specification, **total** mutagenic impurities should be limited as described in Table 3 for clinical development and marketed products."* Therefore, these five potentially genotoxic, class 3 impurities, should be held to a total limit of no more than (b) (4) µg/day. The sponsor confirmed in SDN 20, that the total daily intake for multiple impurities is lower than the 5 µg/day threshold referenced in ICH M7.

Table 3: Acceptable Total Daily Intakes for Multiple Impurities

Duration of treatment	≤ 1 month	>1 - 12 months	>1 - 10 years	>10 years to lifetime
Total Daily intake [µg/day]	120	60	30	5

[Table excerpted from ICH M7 (2015) guidance document.]

(b) (4) was the only impurity found to be mutagenic in an Ames assay, however none of these potential impurities have been detected in any drug substance batches up to a LOD (limit of detection), of (b) (4) ppm, and will also be held to ≤ (b) (4) µg/day.

Imp./FoI	Impurity Nomenclature	Structure	Origin	Highest Amount Observed in Drug Substance
				(b) (4)

[Table (portion of full table) excerpted from Drug Substance overall summary section of NDA 207318 submission.]

The proposed limit for impurity (b) (4) in the drug product is (b) (4) %, also based on qualification in nonclinical studies.

Conclusion:
The safety assessments conducted with impurities (b) (4) through genetic toxicity testing and general toxicity up to 28 days in rats seem adequate to qualify these impurities at levels above the ICH limit of (b) (4) % in the drug substance and to (b) (4) % for impurity (b) (4) in the drug product. Values up to (b) (4) mg/kg/day of each impurity showed no unique or exaggerated toxicity compared with those observed with the API up to daily dosing for 28 days. At the proposed limits of (b) (4) % for impurity (b) (4) and (b) (4) % of impurity (b) (4) these impurities could be present in clinical batch up to (b) (4) mg/person/day and

(b) (4) mg/person/day (calculated based on MRHD of 34 mg pimavanserin per day), which is less than those tested in animal studies. However, it should be noted that for chronic indications impurities are to be tested in general toxicity studies up to 90 days to be qualified at higher limits (ICH M3(R2), 2010). Nevertheless, to date neither of these impurities has been detected at levels greater than (b) (4) % and (b) (4) % respectively in the drug substance. Therefore, based on absence of assessment up to 90 days and the manufacturing capability of limiting these impurities to the lower specifications, we encourage and highly recommend that the sponsor limit the highest amounts to (b) (4) % and (b) (4) % respectively.

2.6 Proposed Clinical Population and Dosing Regimen

Patients with Parkinson's disease psychosis. Maximum recommended human dose of 34 mg pimavanserin (free base)/day.

2.7 Regulatory Background

Pre-NDA meeting held on June 2, 2014 with the Agency's meeting minutes sent on July 2, 2014 and the sponsor's meeting minutes received on July 29, 2014.
Breakthrough Therapy designation was granted on August 13, 2014.
A series of nonclinical information requests were submitted to the sponsor during the NDA review on September 30, 2015. The sponsor submitted responses to those requests on October 14, 2015 in SDN 7.

3 Studies Submitted

3.1 Studies Reviewed

All studies submitted by the sponsor were reviewed except as indicated below.

3.2 Studies Not Reviewed

All pharmacology studies were reviewed and evaluated with conclusions provided in this review. However, formal written reviews for each study are not done. No formal written reviews were conducted for the bioanalytical methods studies.

3.3 Previous Reviews Referenced

Dr. Violetta Klimek was the nonclinical reviewer for the IND (68,384). Several reviews are located in DARRTS for studies conducted during the IND phase, including reviews for the mouse and rat Special Protocol Assessments and meetings with the Executive Carcinogenicity Assessment (ECAC) committee to review those protocols. Summaries of these reviews are included in this review.

4 Pharmacology

4.1 Primary Pharmacology

In vitro radioligand binding assays with pimavanserin (tartrate salt) revealed that pimavanserin binds with high affinity to the human recombinant serotonin 2A (5-HT_{2A}) receptor (K_i of 0.087 nM) and binds with moderate affinity to the human recombinant 5-HT_{2C} (K_i of 0.44 nM). Pimavanserin tartrate demonstrates only minimal binding affinity to the human recombinant 5-HT_{2B} receptor with a K_i of 0.33 µM (330 nM). Pimavanserin was also shown to bind with high affinity to 5-HT_{2A} receptors in homogenates from cerebral cortex of several animal species (mouse, rat, rabbit, dog, and monkey) by displacing binding of [^{3}H]-MDL100907, a selective 5-HT_{2A} receptor ligand, (pK_i values ranging from 7.3-8.3). In addition, pimavanserin bound with high affinity to 5-HT_{2A} receptors in human cortex from normal and Parkinson's disease brains.

Table 1: Binding affinity of pimavanserin tartrate to human recombinant 5-HT_{2A}, 5-HT_{2B} and 5-HT receptors

Receptor Type	IC_{50}	K_i	n_H
Serotonin 5-HT_{2A}	0.30 ± 0.038 nM	0.087 ± 0.011 nM	1.14 ± 0.12
Serotonin 5-HT_{2B}	520 ± 160 nM	330 ± 100 nM	0.86 ± 0.027
Serotonin 5-HT_{2C}	0.84 ± 0.056 nM	0.44 ± 0.029 nM	1.05 ± 0.10

Data represent mean ± SEM (duplicate measurements of 2 independent experiments)

[Excerpted from the pharmacology written summary section of NDA 207318.]

Table 2: Binding affinity of pimavanserin tartrate to 5-HT_{2A} receptors in homogenates from cerebral cortex of various animal species

Species	[^{3}H]-MDL100907 (nM)	pK_i Pimavanserin
Mouse	0.38	8 ± 0.1
Rat	0.7	7.3 ± 0.6
Rabbit	0.5	8.1 ± 0
Dog	0.5	8.3 ± 0
Monkey	0.5	8.2 ± 0.1

Data are presented as mean ± SEM

[Excerpted from the nonclinical summary section of NDA 207318. MDL100907 is a selective 5-HT_{2A} receptor ligand.]

The functional activity of pimavanserin at 5-HT_{2A} and 5-HT_{2C} receptors, as well as other receptors, was measured using the following in vitro cell-based assays: 5-HT receptor coupled activation of phosphatidylinositol-hydrolysis using tsA cells (a transformed HEK-293 cell line) transfected with human 5-HT_{2A} or 5-HT_{2C} receptors, receptor selection and amplification technology (R-SAT™), and a cell-based bioluminescence resonance energy transfer (BRET) assay. These assays demonstrated that pimavanserin acts as a potent antagonist at both the 5-HT_{2A} and 5-HT_{2C} receptor, with greater potency at the 5-HT_{2A} receptor (pK_i values of 8.8-9.0 at 5-HT_{2A} compared to pK_i values of 7.6-8.3 at 5-HT_{2C}). In addition, pimavanserin acts as an inverse agonist at 5-HT_{2A} and 5-HT_{2C} receptors, again with greater potency at the 5-HT_{2A} receptor (pEC_{50} of

8.7-9.4 and 7.1-7.2, respectively). Pimavanserin did not demonstrate any functional activity at 5-HT_{2B} receptors in vitro.

Table 3: Functional activity selectivity of pimavanserin in in vitro cell-based assays transfected with human recombinant 5-HT2A or 5-HT2C receptors

Assay	Antagonist Activity ($pK_i \pm SD$)		Inverse Agonist Activity ($pEC_{50} \pm SD$)	
	5-HT_{2A}	5-HT_{2C}	5-HT_{2A}	5-HT_{2C}
5-HT-receptor-coupled activation of phosphatidylinositol-hydrolysis using tsA cells[a]	8.99 ± 0.55	8.29 ± 0.19	ND	ND
Receptor Selection and Amplification Technology (R-SAT™)[b]	8.8 ± 0.3 / 9.0 ± 0.6	7.6 ± 0.4 / 7.8 ± 0.3	8.7 ± 0.6 / 9.4 ± 0.3	7.1 ± 0.3 / 7.2 ± 0.4
G-protein coupled receptors (GPCR)-arrestin BRET assay using transfected HEK293 T cells[c]	9.04	8.01	ND	ND

pK_i: negative logarithm of the inhibition constant
pEC_{50}: negative logarithm of the inverse agonist EC_{50}
ND: not determined
[a] Study 2005-01: ACP-103 (tartrate salt of pimavanserin)
[b] Study 2013-04: (b) (4) (tartrate salt of pimavanserin)/ (b) (4) ((b) (4) salt of pimavanserin)
[c] Study 2006-03: ACP-103 (tartrate salt of pimavanserin)

[Excerpted from the nonclinical summary section of NDA 207318]

Similar to pimavanserin, the pimavanserin metabolites AC-279 (major), AC-423, AC-527 and AC-627 demonstrated potent antagonistic activity at 5-HT_{2A} receptors, moderate antagonistic activity at 5-HT_{2C} receptors and no agonist or antagonist activity at 5-HT_{2B} receptors as measured by the ability to block agonist activity in in vitro assays.

Table 4: Antagonistic activity of pimavanserin compared to its metabolites at 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptors

Compound	5-HT_{2A} Receptor		5-HT_{2B} Receptor		5-HT_{2C} [VGV][b] Receptor	
	Inhibition (%) ± SD	pK_i[a] ± SD	Inhibition (%) ± SD	pK_i[a] ± SD	Inhibition (%) ± SD	pK_i[a] ± SD
AC-527	83 ± 17	7.7 ± 0.2	2 ± 22	-	95 ± 11	6.6 ± 0.3
AC-423	95 ± 5	8.6 ± 0.2	4 ± 4	-	115 ± 13	7.0 ± 0.3
AC-627	98 ± 8	8.9 ± 0.4	9 ± 11	-	99 ± 1	7.0 ± 0.1
AC-279	101 ± 7	8.8 ± 0.4	16 ± 8	-	112 ± 32	7.3 ± 0.8
Pimavanserin	92 ± 11	8.8 ± 0.3	9 ± 20	-	110 ± 19	7.6 ± 0.4

[a] pK_i is the negative logarithm of the inhibition constant calculated from the IC_{50} by the method of Cheng and Prusoff.
[b] VGV: The 'VGV' isoform of 5-HT_{2C} receptors was used in these studies.

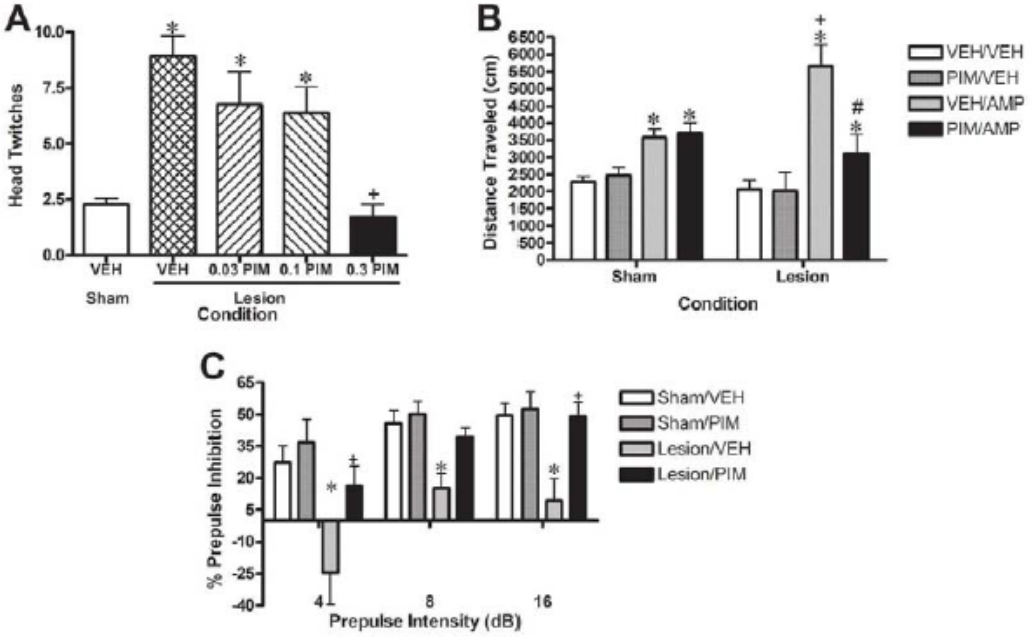
[Excerpted from the pharmacology written summary section of NDA 207318]

Pimavanserin demonstrated in vivo functional activity, efficacy, in several animal models for antipsychotic activity, including the MK-801 induced hyperactivity model, spontaneous locomotor activity, amphetamine-induced hyperactivity, apomorphine-induced rotations, pre-pulse inhibition, and head twitches induced DOI (a serotonin agonist). The activity of pimavanserin compared to the antipsychotics clozapine, quetiapine and haloperidol was also assessed. Add details of models and summarize results. Mice that were administered ACP-103 (10 mg/kg, i.p.) for 2 weeks developed

tolerance to pimavanserin's effect to attenuate MK-801-induced hyperactivity. This indicates that the efficacy of pimavanserin in rodents decreases with repeated administration.

The activity of pimavanserin was assessed in a rodent model of Parkinson's disease which also evaluated psychosis-like behaviors (McFarland, K. et. al, 2011). In this rodent model, rats received bilateral 6-hydroxydopamine (6-OHDA) lesions of the substantia nigra pars compacta (SNc) and then were evaluated in various animal models for antipsychotic activity. Rats with lesions were either pretreated with vehicle or increasing doses of pimavanserin and were compared against sham treated animals. Pimavanserin pretreatment of rats significantly reversed the number of head twitches that were induced with 6-OHDA lesions, significantly reduced the amount of amphetamine-induced hyperactivity, and significantly disrupted prepulse inhibition induced by the 6-OHDA lesions.

Figure 1: Effect of pimavanserin on head twitch, amphetamine-induced hyperactivity and prepulse inhibition behavior in a rodent model of Parkinson`s disease



Effect of pimavanserin (PIM) pretreatment on (A) spontaneous head twitch, (B) amphetamine-induced hyperactivity, and (C) prepulse inhibition. In each case, pretreatment with pimavanserin (0.3 mg/kg, subcutaneous [sc]) normalized behavior disrupted by bilateral substantia nigra pars compacta lesions. Data were analyzed using a one-way analysis of variance (ANOVA) followed by Dunnett's multiple comparison post-hoc analyses (A), or two-way ANOVAs followed by Bonferroni post-hoc analyses (B and C). *Significant difference from vehicle/vehicle (B) or Sham/vehicle (A and C) performance, $p < 0.05$; +significant difference from Sham vehicle/AMP (B) or lesion/vehicle (C), $p < 0.05$; #significant difference from lesion vehicle/amphetamine (B), $p < 0.05$.

[Excerpted from the nonclinical summary section of NDA 207318]

Pimavanserin was also evaluated in rodent models of Alzheimer's disease psychosis (ADP) and sleep maintenance. Pimavanserin did not induce catalepsy in mice or rats

(up to 30 mg/kg, oral) as compared to haloperidol or increase serum prolactin levels in male rats (3 mg/kg, s.c.).

4.2 Secondary Pharmacology

The off-target effects of pimavanserin were evaluated in radioligand binding assays at 65 different receptor targets. Pimavanserin showed a ≥50% inhibition of binding at 10 receptors other than 5-HT_{2A}, including norepinephrine transporters, calcium and sodium channels, dopamine D_3, muscarinic M_1, M_2, and M_3, sigma σ_1 and σ_2 receptors. However, pimavanserin did not demonstrate any significant functional agonist or antagonistic activity at the 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, 5-HT_{1F}, 5-HT_{2B}, and 5-HT_7, serotonin receptors or at any other monoamine G-protein coupled receptor that was tested in the R-SAT™ assay (including α_{1a}, α_{1b}, α_{1d}, α_{2a}, α_{2b}, and α_{2c} adrenergic receptors; D_1, D_2, and D_3 dopamine receptors; H_1 or H_3 histamine receptors; or M_1, M_2, M_3, M_4, or M_5 muscarinic receptor types). Pimavanserin did not show any binding affinity or functional activity at SST2, SST3, SST4 or SST5 somatostatin receptors or any antagonistic activity at histamine H_3 receptors. Pimavanserin also did not show significant inverse agonist activity at the 5-HT_{2B}, 5-HT_6 or 5-HT_7, serotonin receptors. Follow-up full concentration-response curves were generated for the 11 receptors that pimavanserin showed >50% inhibition of binding. Pimavanserin is much more potent at 5-HT_{2A} receptors compared to other receptors tested (338- to 11,837-fold) . Therefore, the potential for any significant off-target effects is lessened.

Table 5: Binding affinities of pimavanserin to off-target receptors

Receptor	K_i (nM)	Fold selectivity[a] for 5-HT_{2A} receptor
D_3	370	1043
M_1	840	2367
M_2	1800	5073
M_3	940	2649
M_4	660	1860
M_5	330	930
Sigma 1	120	338
Sigma 2	370	1043
Norepinephrine Transporter	4200	11837
Dopamine Transporter	4200	11837
5-HT_{2A}	0.35	1

[a] Fold selectivity was calculated as the K_i target / K_i 5-HT_{2A}.

[Table excerpted from Pharmacology Summary section of NDA 207318.]

4.3 Safety Pharmacology

For detailed reviews of safety pharmacology studies refer to reviews in IND 68,384.

CNS

Study no. SPI02-003, GLP

Male Sprague-Dawley rats (6/group) were administered single doses of pimavanserin tartrate by oral gavage at dose levels of 10, 100, and 1000 mg/kg and a control group

received single oral doses of the vehicle, 0.9% sodium chloride, in a volume of 10 ml/kg. Animals were observed 30, 90, 150, 300 minutes, and 24-hrs after dosing using a primary observation test (Irwin test).
Results:
There were no gross behavioral or physiological changes in the 10 or 100 mg/kg groups. In the 1000 mg/kg group, there was a rapid onset of signs, with all rats exhibiting signs by 30 min postdose. Clinical signs included gasping or decreased respiration rate, decreased locomotor activity, apathy, decreased alertness, piloerection, and salivation. Three animals died following treatment and one was sacrificed moribund. The peak effect occurred ~5-8 hr postdose, and was mostly resolved by 24 hrs postdose. Necropsy findings in the animals that died included distended stomachs (gas and/or fluid filled), and indications of slight gastric damage in 4/6 animals.
NOEL = 100 mg/kg
No Toxicokinetics.

Cardiovascular
hERG channel assay, GLP (study no. 7916-100).
Cloned hERG channels expressed in HEK293 cells.
There was a statistically significant and concentration dependent inhibition of the hERG current by 10.6%, 25.1%, 54.0%, 80.3% and 99.3% at pimavanserin tartrate concentrations of 0.03, 0.075, 0.24, 0.83, and 9.35 μM, respectively. IC_{50} = 0.21 μM.

In vivo cardiovascular studies were conducted in beagle dogs administered i.v. doses of pimavanserin (non-GLP, study no. 2002-19) and in cynomolgus monkeys via oral gavage (GLP, study no. DHTI1004). In the dog i.v. study, there was a limited increase in heart rate at 1.8 mg/kg, without effects on any other cardiovascular parameters. In the oral gavage monkey study, 4 animals were dosed with 1, 10, and 100 mg/kg pimavanserin (expressed as free base) in a cross over design. Vomiting was observed in 2 animals following the 100 mg/kg dose. There were no effects on any cardiovascular parameters at 1 and 10 mg/kg at any time point or at 100 mg/kg up to 6 hrs postdose. There was a statistically significant increase in the QT_c interval at 120 and 360 minutes postdose after the 100 mg/kg dose, ~24-40 msec. The sponsor considered the magnitude of the effect to be small and not time related (not occurring around T_{max}) and hence the relationship to pimavanserin is uncertain. This reviewer considers the findings to be drug-related since they only occurred at the high dose and there was a corresponding marked inhibition of the hERG current. It is not unreasonable to consider the potential role of pimavanserin metabolites on these effects as well. There were no significant changes in gross morphology or rhythm. No toxicokinetic analysis performed.

There is a signal for QT prolongation in humans (refer to clinical review for details).

Respiratory
Study no. SPR02-007, GLP
Male Sprague-Dawley rats (8/group) were administered single doses of pimavanserin tartrate by oral gavage at dose levels of 10, 100, and 500 mg/kg (expressed in terms of free base) and a control group received single oral doses of the vehicle, 0.9% sodium

chloride, in a volume of 10 ml/kg. Respiratory rate and tidal volume were recorded predose and at 60 and 240 min postdose.
Results: There were no effects on respiratory rate or tidal volume at 10 or 100 mg/kg. There was a statistically significant decrease in respiratory rate at 500 mg/kg/day at the 60 min postdose time point (73.8 bpm compared to 106.0 bpm for the control group). Respiratory rate at the high dose was still slightly decreased compared to controls at the 240 min time point, but it did not reach statistical significance (94.0 bpm compared to 81.3 bpm for controls). There was no significant effect on tidal volume at any dose level. NOEL = 100 mg/kg

Gastrointestinal
Two non-GLP gastrointestinal safety pharmacology studies were conducted; one in ferret and mice (study no. 2002-18) and the other in Sprague-Dawley rats (study no. 5789). There was no significant effect on GI transit in male CD-1 (n= 8-10) mice administered single oral doses of pimavanserin tartrate of 10, 30 and 100 mg/kg compared to controls. There was also no significant effects on GI peristalsis in male rats administered a single oral dose of 10 mg/kg pimavanserin tartrate compared to controls. In male ferrets administered single oral doses of 3, 6, and 10 mg/kg pimavanserin tartrate, there was a dose-dependent increase in the incidence of emesis and nausea with an ED_{50} for vomiting of 5.8 mg/kg.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Absorption:
Pimavanserin is highly permeable across biological membranes. Its pharmacokinetic properties are similar to those of other highly lipophilic amines (a cationic amphiphilic drug (CAD)) with a high logP (>1), a high pK_a (>7), and [redacted] has a high apparent permeability (P_{app}) across Caco-2 cells (in both A-to-B and B-to-A direction). Its pharmacokinetic properties allow it to passively distribute across lipid bilayers into the CNS. Four separate single dose pharmacokinetic studies were conducted with pimavanserin. Two investigated absorption via different routes (oral, i.v., intraportal, intraduodenal, intracolonic), one studied the absorption of ^{14}C-pimavanserin and one study compared two different solid state forms [redacted] the [redacted] was used in Phase III studies and is the intended commercial product. Oral bioavailability was dose dependent and ranged from 2.84% after a 3 mg/kg single dose of [redacted] (pimavanserin [redacted]) to 42.6% and 61.2% after a single dose of 10 mg/kg pimavanserin [redacted] or pimavanserin tartrate [redacted] respectively. The volume of distribution measured in rats after i.v. dosing of 1 mg/kg pimavanserin [redacted], pimavanserin tartrate [redacted]) or pimavanserin tartrate [redacted] (ACP-103) was 29.91, 25.52 and 43.70 L/kg, respectively, suggesting partitioning into fatty tissues, which is consistent with its highly lipophilic properties. Clearance rates after i.v. dosing were also high, 367.8 to 998 ml/min.kg. Portal vein and duodenal bioavailability was >100%, which indicates a rapid and extensive absorption from the small intestine and possible saturation of the

presystemic clearance mechanism (intestinal and hepatic metabolism) which would limit oral absorption. The time to reach maximal concentration (T_{max}) was about 1-2 hrs after a single oral dose in rats and increased slightly after repeat dosing, up to 8 hrs. T_{max} values ranged between 2 and 5 hrs in monkeys and did not appear to change substantially after repeated dosing.

The elimination half-life ($t_{1/2}$) was about 7.4 and 7.6 hrs after a single oral dose (30 mg/kg) in male and female rats, respectively. $T_{1/2}$ values increased slightly in rats after repeat dosing, up to 16.6 hrs for females after 91 days of consecutive dosing and 38.6 hrs for males after 187 days of consecutive dosing at 30 mg/kg (data from 6-month rat study no. (b) (4).146.02). $T_{1/2}$ values for the major metabolite (AC-279) also increased after repeat dosing in rats from ~6 hrs to 13 hrs after 364 days of consecutive dosing (data from 2-year rat carcinogenicity study no. (b) (4)-6160004). $T_{1/2}$ values were not calculated in any other rat studies or any studies in monkeys. $T_{1/2}$ values ranged from ~2 hrs to 6 hrs in mice after oral dosing for up to 3-months and did not appear to increase much after repeat dosing. There was evidence of drug accumulation after repeat dosing in both rats and monkeys, as exposure levels were up to 2-fold higher after ~3-months of repeat dosing as compared to exposures on day 1. Steady state appeared to be reached after about 3-months of dosing in rats and 45-91 days of dosing for monkeys. There was a gender difference in exposure levels for rats only, as exposure in female rats were ~55-65% higher than in male rats at equivalent doses. There was no clear evidence of any gender differences in exposures for either mice or monkeys. The sex difference in rats is unclear and could not be explained based on ADME data.

Table 6: Pimavanserin Pharmacokinetic Parameters across Species

Species	Day	Dose (mg/kg)	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-24h} (h*ng/mL)	$t_{1/2}$ (h)
Mouse	1	100	387	1	4460	8
Rat	1	100	246	2	3250	11
Rabbit	1	100	515	0.25	4000	16
Monkey	1	100	559	2	7726	9
Human	1	80*	49	9	835	25
	20	80*	214	7	3606	44

* 80 mg pimavanserin tartrate per day

[Table excerpted from pharmacokinetic written summary of NDA 207318.]

PK data in above table is after a single 100 mg/kg dose in animals. Exposure levels significantly higher were reached in animals after repeated dosing (see general toxicology section below). Also, the MRHD is only 40 mg pimavanserin tartrate (34 mg pimavanserin free base). The estimated human AUC at the MRHD of 34 mg pimavanserin free base is **1630 ng.hr/ml**, based on the clinical pharmacologist's review of the sponsor's document: Expert Opinion entitled "Pharmacokinetic modeling of pimavanserin in healthy subjects, subjects with Parkinson's disease, and subjects with Parkinson's disease psychosis" (see clinical pharmacology review).

Distribution:

Pimavanserin is highly bound to plasma protein in animals and humans (93.8% to 96.8% in vitro) (study BA030066). In addition, plasma samples from two clinical trials (ACP-103-001 and ACP-103-002) were analyzed for the extent of protein binding. The plasma protein binding ranged from 91.2% to 96.8% in the samples analyzed. A separate in vitro study was conducted to investigate plasma protein binding of pimavanserin and the major metabolite, AC-279, in human plasma (study CYP0202-R25). Plasma protein binding of metabolite AC-279 was only 79%, however plasma protein binding of pimavanserin was also lower, only 81%, as well as haloperidol, 72%. Since the plasma protein binding of haloperidol was lower than that reported in published literature, >90%, it is possible that the plasma protein binding in this study was underestimated for pimavanserin and metabolite AC-279.

Table 7: Plasma protein binding of pimavanserin

Species	Concentration of Pimavanserin	Protein Binding Range (%)
Mouse	50, 200, 500, 2500 and 10,000 ng/mL	96.1 - 96.9
Rat	50, 200, 500, 2500 and 10,000 ng/mL	93.8 - 94.6
Rabbit	50, 200, 500, 2500 and 10,000 ng/mL	94.6 - 95.5
Monkey	50, 200, 500, 2000 and 5000 ng/mL	94.1 - 94.8
Human	10, 50, 100, 500 and 1000 ng/mL	94.5 - 95.8

[Data from study BA030066 of NDA 207318]

The blood to plasma ratio of ^{14}C-pimavanserin-derived radioactivity was determined in male and female rats after administration of a single oral dose of 30 mg/kg ^{14}C-pimavanserin. Radioactivity was higher in blood compared to plasma, increased over the course of study. The mean blood-to-plasma ratios for rats ranged from 1.21 to 2.48. The blood-to-plasma ratios were also calculated using human blood samples from the human mass balance study with ^{14}C-pimavanserin tartrate (study CYP202-R20) and the mean blood-to-plasma ratio was 1.80, 1.53, and 1.51 at 0.05, 0.2 and 1 µM pimavanserin, respectively. The ratio values were greater than 1 in both rats and humans indicating that pimavanserin distributes slightly higher into blood cells than plasma which the sponsor suggests may be a consequence of partitioning into phospholipid membranes (Expert Opinion report on the human mass balance study, report no. (b) (4)-13-019).

Tissue distribution of radiolabeled pimavanserin was determined in male Long Evans rats using whole body autoradiography. 5 male Long Evans rats were administered a single oral dose of 30 mg/kg ^{14}C-ACP-103 and tissue distribution of radioactivity was determined up to 72 hrs postdose. ^{14}C-ACP-103 was widely distributed to all tissues by 1 hr postdose and most tissues reached maximum concentration of radioactivity by 4 hrs postdose. Tissues with the highest maximum concentrations of radioactivity, excluding the gastrointestinal (GI) tract, were liver, pituitary gland, uveal tract, spleen,

salivary gland, lung, thyroid, and exo-orbital lacrimal gland. Radioactivity was still measurable in some tissues at 72 hrs postdose with the highest concentration of radioactivity in uveal tract suggesting melanin binding. The half-life ($t_{1/2}$) in the eye and uveal tract is 101 and 432 hrs, respectively. Radioactivity was still present at relatively high levels in both tissues at 72 hr after dosing, although levels did decline over time. Since pimavanserin is highly lipophilic and causes widespread phospholipidosis in multiple tissues, it is possible that drug may be sequestered and could accumulate in tissues after repeated dosing. However, no study was conducted to measure tissue distribution and potential accumulation after repeated/chronic dosing. It may be beneficial to conduct a study that would measure concentrations of pimavanserin and its major metabolite (ACP-279) in tissues that were shown to develop severe phospholipidosis with concurrent tissue damage (lung, kidneys, skeletal muscle, testes, epididymides) to determine if drug accumulates in these tissues, especially after sub-chronic and/or chronic treatment and how long after drug cessation the drug stay in tissues.

Table 8: Tissue Distribution of radioactivity after ^{14}C-ACP-103 administration to rats

Concentrations of Radioactivity in Blood and Tissues After Administration of ^{14}C-ACP-103						AUC_{0-t} (ng-eq.h/g)	$t_{1/2}$ (h)
Tissue	ng Equivalents ^{14}C-ACP-103/g						
	0.25 h	1 h	4 h	24 h	72 h		
Adrenal gland	2360	59500	46300	2970	BLQ	674893	5.05
Bile	70300	383000	102000	12600	ND	2052275	6.63
Blood	BLQ	1910	2480	BLQ	ND	7301[a]	NC
Bone	BLQ	1030	1260	BLQ	ND	3821	NC
Bone marrow	952	26000	43800	2370	ND	576626	4.75
Cecum	1140	15000	14600	5570	BLQ	252295	14.4
Cecum contents	BLQ	5370	360000	48800	1340	5841429	9.25
Cerebellum	BLQ	4670	5750	BLQ	ND	17381	NC
Cerebrum	BLQ	6080	8830	BLQ	BLQ	24645	NC
Choroid plexus	2270	24500	19200	5080	1150	468193	17.6
Diaphragm	1260	18900	22500	1040	ND	305218	4.51
Epididymis	BLQ	2240	11300	6420	BLQ	198725	24.5
Esophageal contents	931000	47500	16400	422	ND	747383	3.51

Concentrations of Radioactivity in Blood and Tissues After Administration of ^{14}C-ACP-103						AUC_{0-t} (ng-eq.h/g)	$t_{1/2}$ (h)
Tissue	ng Equivalents ^{14}C-ACP-103/g						
	0.25 h	1 h	4 h	24 h	72 h		
Esophagus	3390	74700	33900	999	BLQ	541598	3.78
Exorbital lacrimal gland	1290	32200	62700	7540	BLQ	857470	6.54
Eye	BLQ	5950	13200	12500	9000	803956	101
Fat (abdominal)	BLQ	BLQ	BLQ	BLQ	BLQ	9443	7.39
Fat (brown)	BLQ	3140	2370	BLQ	BLQ	191161	4.57
Gastric mucosa	736	15500	13500	648	ND	365760	5.74
Harderian gland	5270	41000	23100	2060	BLQ	1352691	8.62
Inguinal lymph node	817	23200	61300	17500	368	-	-
Intra-orbital lacrimal gland	1140	30400	56200	5880	426	914014	12.7
Kidney	4880	44600	40600	1910	BLQ	572065	4.54
Large intestinal contents	NR	17200	166000	126000	1970	6274680	8.00
Large intestine	889	17400	29900	4000	BLQ	416920	6.89
Liver	42800	138000	107000	4550	853	1685822	19.9
Lung	4240	63100	60700	2790	BLQ	846383	4.50
Lymph nodes	963	21200	38300	3030	ND	510982	5.46
Medulla	BLQ	4850	7070	BLQ	ND	19699	NC
Muscle	503	9850	12500	913	BLQ	171600	5.30
Myocardium	2430	23700	22800	1420	ND	322053	4.99
Nasal turbinates	BLQ	6220	8310	1400	BLQ	121228	7.78
Olfactory lobe	BLQ	3910	5580	BLQ	ND	15701	NC
Pancreas	3260	33200	41100	2700	BLQ	563530	5.09
Pituitary gland	1470	47500	123000	17500	4330	2203218	23.8
Prepuital gland	668	11000	22800	27100	16300	1595759	65.4
Prostate	405	13300	20900	20800	BLQ	473490	NC
Renal cortex	5090	42500	39000	1830	BLQ	549033	4.53
Renal medulla	3980	45300	42400	2020	BLQ	594728	4.55
Salivary gland	1430	38200	64000	14300	892	1315948	12.0
Seminal vesicle	BLQ	2180	4530	1400	BLQ	70183	11.8
Skin	BLQ	4220	7690	2000	1210	193388	66.2
Small intestinal contents	653000	563000	1690000	24200	1040	21664885	10.6
Small intestine	1540	22700	38000	2110	BLQ	501433	4.80
Spinal cord	BLQ	3760	4450	619	ND	64415	7.03

Concentrations of Radioactivity in Blood and Tissues After Administration of ^{14}C-ACP-103						AUC_{0-t} (ng-eq.h/g)	$t_{1/2}$ (h)
Tissue	ng Equivalents ^{14}C-ACP-103/g						
	0.25 h	1 h	4 h	24 h	72 h		
Spleen	4270	58600	69400	3360	BLQ	943710	4.58
Stomach	2680	18700	16300	1370	BLQ	237553	5.60
Stomach contents	1770000	1050000	37400	894	BLQ	3292790	3.71
Testis	BLQ	2530	7540	6030	1530	333194	24.3
Thymus	739	15600	33200	3030	ND	441720	5.79
Thyroid	3410	63000	35700	1820	BLQ	548580	4.66
Urinary bladder	419	6150	12500	14400	BLQ	299491	NC
Urine	2980	29900	133000	13100	BLQ	1718053	5.98
Uveal tract	2700	40700	97700	72900	67500	5299813	432

BLQ = Below the limit of quantitation (< 363 ng equivalents ^{14}C-ACP-103/g); ND = Not detectable; NR = Not represented; NC = not calculated
[a] value calculated from whole body autoradiography, the value for blood calculated by liquid scintillation counting is 41191 (ng-eq·hour/g)

[Table excerpted from Pharmacokinetics Tabulated Summary section of NDA 207318]

The brain-to-plasma ratios of pimavanserin were determined in rats after a single oral administration of 10 mg/kg pimavanserin. The brain/plasma ratios were 3.3-4.5, 3.8-5.8 and 7.6-15.8 at 1, 2 and 4 hrs after dosing. The peak brain and plasma concentrations occurred at 2 hrs after dosing. The brain/plasma ratios also increased over time indicating a longer elimination half-life in brain versus plasma.

Metabolism:

In vitro:

In vitro stability of pimavanserin (b) (4) in liver microsomes of mouse, rat, dog, monkey and human, indicated that pimavanserin was very stable in microsomes from all species including human over the 40 min. incubation period, with the exception of dog. In dog liver microsomes, pimavanserin rapidly degraded and less than 50% of drug remained after only 10 min. of incubation. Also, metabolism of pimavanserin in dog liver microsomes resulted in a very different metabolic profile compared to human, monkey and rat liver microsomes; the major metabolite in dog microsomes was AC-423 as opposed to AC-279 for humans and monkeys. Rats also had high levels of metabolite AC-423, however AC-279 was still formed in rats in vitro at measurable amounts compared to very little if any in dogs. Therefore, dog was not chosen to be used as the non-rodent species for the general toxicity studies.
CYP3A4/5 was determined to be the major enzyme in human liver microsomes responsible for metabolizing pimavanserin to metabolites AC-279, AC-527, and AC-285. CYP2J2 was determined to be the enzyme responsible for converting pimavanserin to metabolite AC-423.

In vivo:

Pimavanserin is extensively metabolized in monkey, rabbit, rat, and mouse (39, 45, 52 and 55 metabolites detected, respectively). 37 metabolites were identified in plasma from human subjects dosed with pimavanserin to steady-state levels (20 days at 80 mg/day). No human specific metabolites were identified in human subjects. Metabolite AC-279 (*N*-desmethyl-pimavanserin) is the most abundant metabolite formed in mouse, rabbit, monkey and humans, while metabolite AC-423 is the most abundant metabolite formed in rats. Based on metabolic profiles, the monkey appears to be the most similar species to humans. In humans, metabolite AC-279 is greater than 25% of pimavanserin and ~15% of total drug-related material based on AUC at steady state. Accordingly, AC-279 qualifies as a major circulating human metabolite. Exposure to AC-279 is greater in all animal species used in toxicity studies (mouse, rat, rabbit and monkey) compared to

humans at the maximum recommended human dose (MRHD) of 34 mg/day pimavanserin (based on the predicted human exposure level for AC-279 of 847 ng.hr/ml). Exposure levels of AC-279 were measured in a 6-month repeat dose toxicity study in rats with a 6-month recovery period (study no. (b) (4)-616007) and in the rat and mouse 2-year carcinogenicity studies (study nos. (b) (4)-616004 and (b) (4)-616-006, respectively); in which exposure levels of AC-279 reached in all three studies were higher than those reached in humans. Therefore, major metabolite AC-279 has been adequately qualified in nonclinical studies and no additional nonclinical studies using AC-279 are necessary.

Originally the structure of metabolite M36 was not known and it was thought to be a potential major human metabolite based on the human mass balance study, however the structure of M36 (AC-272035) was later identified as a bicyclic metabolite of pimavanserin (studies (b) (4)14720 and 2014-05). Also, M36 was measured in human plasma samples following dosing with pimavanserin to steady-state and represented only 5.9-6.4% of total drug-related material (study ACP-103-029). Regardless, M36 is present in multiple animal species (monkey, rat, mouse and rabbit) at exposure levels higher than that in humans (see sponsor's table below). Metabolite M1 was also originally considered a significant circulating human metabolite, but it was later identified as radioactive bicarbonate ($H^{14}CO_3^-$), formed from the release of radioactive carbon dioxide from the urea moiety of ^{14}C-pimavanserin and therefore MIST and DDI considerations are not relevant. No other circulating metabolites identified in human plasma were determined to be major metabolites (>10% of total drug-related material at steady state).

Figure 2: Phase I Metabolites of pimavanserin

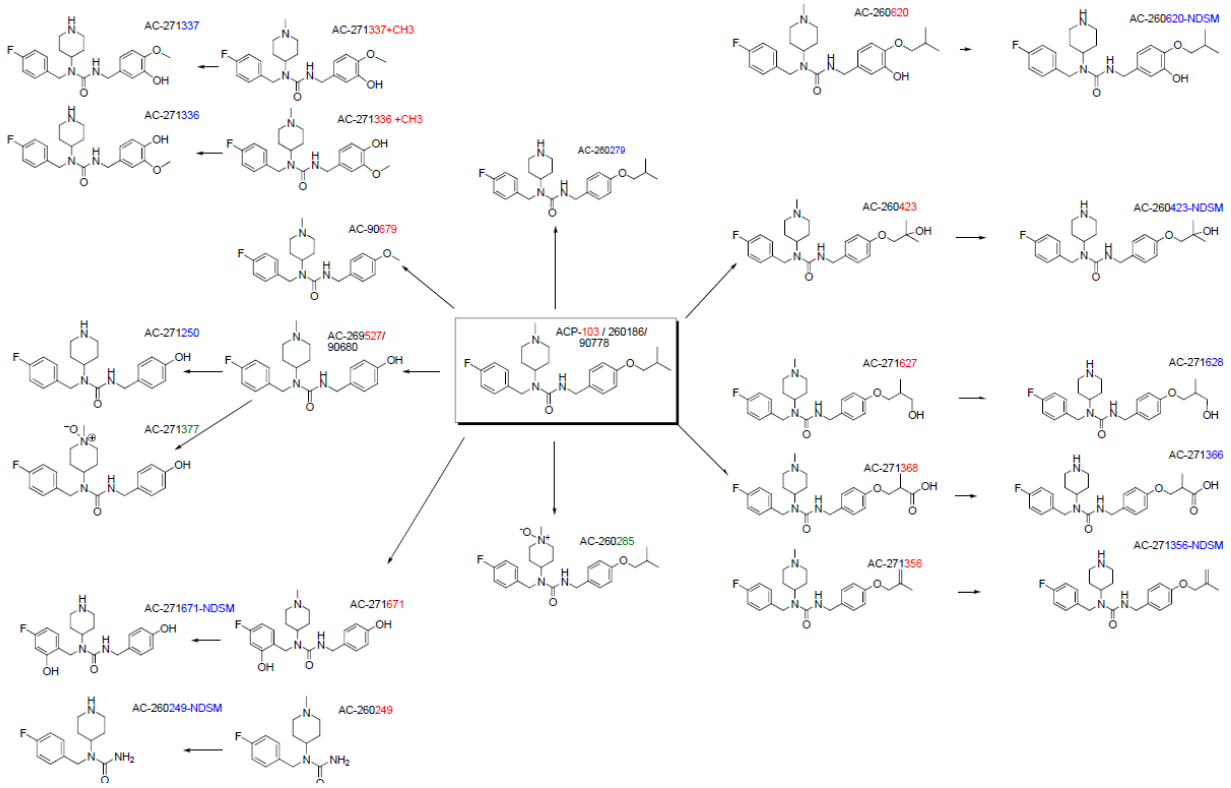


Table 9: AUC0-24h (h*ng/mL) for select metabolites across species on day 1 and for humans at steady-state (80 mg pimavanserin)

Species	Dose (mg/kg)	AC-279	AC-423	AC-527	AC-423 NDSM	AC-368	AC-366
Mouse	100	8210	2730	388	2917	2880	4989
Rat	100	4320	18577	1976	13843	1599	3246
Rabbit	100	13960	2981	880	476	793	722
Monkey	100	4800	2411	1289	1034	1633	1783
Human	80*	527	112	236	40	NP	5
Human	80 *#	1694	550	469	91	74	35

* 80 mg pimavanserin tartrate per day, # Day 20 (steady state), NP: not present

[Excerpted from pharmacokinetics written summary of NDA 207318]

Table 10: Exposure ratios of parent and metabolites AC-279 and M-36 in humans and animals

	Dosing period	AUC (0-24) on Day 1 & 20 (h*ng/mL)				
		Human [1]	Monkey	Rat	Mouse	Rabbit
ACP-103	Day 1	418	7730	3250	4460	4000
	Day 20	1803	ND	ND	ND	ND
AC-279	Day 1	263.5	4800	4320	8210	13960
	Day 20	847	ND	ND	ND	ND
M-36[2]	Day 1	2,893,000	8,549,000	5,818,000	4,895,000	4,191,000
	Day 20	9,349,500	ND	ND	ND	ND
	Dosing period	**Exposure Multiples (plasma AUC_{0-24} ratios) [3]**				
			Monkey	**Rat**	**Mouse**	**Rabbit**
ACP-103	Day 1		19 fold	8 fold	11 fold	10 fold
	Day 20		4 fold	1.8 fold	2.5 fold	2.2 fold
AC-279	Day 1		18 fold	16 fold	31 fold	53 fold
	Day 20		6 fold	5 fold	10 fold	16 fold
M-36[2]	Day 1		3 fold	2 fold	1.7 fold	1.4 fold
	Day 20		0.9 fold	0.6 fold	0.5 fold	0.4 fold

[1] The plasma AUC values following 80 mg dosing were halved because the intended clinical dose of ACP-103 is 40 mg. Exposure in humans is dose linear as seen in ACP-103-002 Clinical Study Report

[2] Plasma AUC values were determined by semi-quantitative LC/MS/MS analysis and are expressed as area rather than h*area.

[3] Exposure multiples are nonclinical plasma AUC (Day 1)/human plasma AUC (from Day 1 or Day 20).

[Table excerpted from study report 2-2009 in NDA 207318.]

In vitro drug-drug interaction studies were conducted to assess the potential for pimavanserin to induce or inhibit CYP450 enzymes. These studies revealed that pimavanserin is a weak to moderate inhibitor of intestinal CYP3A4. A clinical study was conducted to evaluate this further.

Excretion:

The excretion of pimavanserin was evaluated in two separate studies in rats; a mass balance study using a single oral dose of 11 mg/kg (b) (4) pimavanserin (b) (4)) in male Wistar rats (study 2002-17) and a pharmacokinetics, distribution, metabolism, and excretion study using a single oral dose of 30 mg/kg ^{14}C-ACP-103 (^{14}C-pimavanserin tartrate) in male and female Sprague-Dawley rats (study 7916-102). Data from the first study determined that pimavanserin is primarily excreted in feces (64-81% compared to 19-23% in urine of (b) (4) pimavanserin (b) (4)) after a single oral dose to male SPF Wistar rats. Data from the second study showed that pimavanserin is also excreted primarily in the feces and to lesser extent in urine, but values were higher in female rats compared to males (84.4% and 71.9% in feces of female and males, respectively, and 12.0% and 25.4% in urine of females and males, respectively) after a single oral dose. Therefore, female rats excrete more pimavanserin

than male rats. In both studies, the majority of radioactivity was excreted in the feces and urine and elimination was nearly complete 72 hrs postdose.

5.2 Toxicokinetics

Toxicokinetic data are reported in the general toxicology section for each reviewed study.

6 General Toxicology

All pimavanserin dosage information are expressed as free base in the label (MRHD of 34 mg) and not as pimavanserin tartrate (40 mg pimavanserin tartrate). Dosage information was expressed as pimavanserin tartrate in all nonclinical toxicity studies. Therefore, all dose information in the pivotal animal toxicity studies were converted to free base for labeling purposes. The conversion factor for converting the tartrate salt dose to the free base is 0.8507.

6.1 Single-Dose Toxicity

Table 11: Mouse and Rat single-dose toxicity studies

Species/ Strain	Method of Administration (Vehicle/Formulation)	Doses (mg/kg)	Gender and No per Group	Observed Maximum Non-Lethal Dose (mg/kg)	Approximate Lethal Dose (mg/kg)	Noteworthy Findings	Study Number
Mouse/NSA	subcutaneous	100	M: 8	100	-	None	2002-09
Rat/SD	oral gavage	100	M: 8	100	-	None	2002-10
Rat/SD	oral gavage	300	M: 4	300	-	None	2002-14
Rat/SD	oral gavage	1000 (2 doses)	M: 1	1000	-	Increased arousal, decreased locomotor activity, salivation, weight loss, GI tract distention.	2002-15
Rat/SD	oral gavage	Dose-ranging: 500, 1000, 1500, 2000 Main: 1000	M: 2, F: 2 M: 5, F: 5	500	1000	Three rats (M:2, F:1) at 1000 mg/kg, two rats (M:1, F:1) at 1500 mg/kg and one female at 2000 mg/kg were found dead. Nasal/oral soiling, ocular discharge, piloerection, rales, decreased feces, yellow urogenital soiling and chromodacryorrhea at 1000 mg/kg.	TOX02-007
Rat/SD	intravenous	Dose-ranging: 15, 25, 50, 100 Main: 25	M: 1-2, F: 1-2 M: 5, F: 5	25	50	Two rats (M:1, F:1) at 50 mg/kg and two rats (M:1, F:1) at 100 mg/kg were found dead. Ataxia, dyspnea, depression, red-tinged urine, chromodacryorrhea, and tail abnormalities at 25 mg/kg.	TOX02-006

[Table excerpted from Toxicology Tabulated Summary of NDA 207318.]

In study no. TOX02-007, the single dose oral gavage study in rats, the following gross necropsy findings were observed in the 3 rats that were found dead (on days 2, 3 and 5) after a single dose of 1000 mg/kg (excerpted from study report): *"On study Day 15, all surviving Phase II animals were sacrificed by CO2 asphyxiation. The animals were examined externally and internally for any abnormalities. The only abnormalities noted were in three animals that died prior to the scheduled sacrifice, with the cause of the*

deaths undetermined. Abnormalities included: in one male (G051, found dead on Day 3) red/pink mottling of all lung lobes, and red/yellow mottling of the median lobe of the liver; one male (G054, found dead on Day 5) a red color of all lung lobes, and dark red/black foci on the left anterior ventral lung and on the right apical lobe of the lung; and one female (G071 on Day 2) had a diffuse red color of all lobes of the lung, distended stomach with a white focus on the nonglandular portion, and a distended jejunum with an orange color."

6.2 Repeat-Dose Toxicity

6.2.1 Mouse

14-day and 13-week repeat dose toxicity studies were conducted in CD-1 mice with pimavanserin tartrate at doses ranging from 50-300 mg/kg/day and 10-100 mg/kg/day, respectively (study no. (b) (4)-616001 and (b) (4)-616002). The 13-week study was used as the basis for dose selection for the 2-year carcinogenicity study. In the 14-day study, toxicities at doses ≥200 mg/kg/day included drug-related mortality, although no definitive cause of death was determined, along with a decrease in body weight and food consumption and lower white cells counts. Cytoplasmic changes consistent with systemic phospholipidosis (PLD) (cytoplasmic vacuolation and/or vacuolated macrophages) were observed in the lungs, pituitary, kidney and spleen in the 14-day study at doses ≥200 mg/kg/day. The microscopic findings in the lungs correlated with increased lung weights and a couple gross findings of pale or not fully collapsed lungs. There were also decreases in white blood cells, and lymphocytes and increases in neutrophils at ≥200 mg/kg/day. No recovery groups were included in this study; therefore the reversibility of the PLD-findings at doses ≥200 mg/kg/day is unknown. Additional microscopic changes occurred in liver at doses ≥200 mg/kg/day (cytoplasmic alterations and/or necrosis) which correlated with clinical pathology changes of increased ALT and AST, and increased liver weights. However, these liver changes were not consistent with phospholipidosis.

In the 13-week study, drug-related mortality occurred in males at ≥30 mg/kg/day and in females at 100 mg/kg/day, although a definitive cause of death was not determined. Cardio-pulmonary-related clinical signs including pale and/or cool extremities, rales, shallow/labored/decreased respiration, and gasping were observed at doses of 30 and/or 100 mg/kg/day. There was a significant decrease in body weight for males at 100 mg/kg/day. Similar to the 14-day study, higher neutrophil counts and lower lymphocyte counts were observed in males at 100 mg/kg/day. Higher thyroid/parathyroid weights were observed in males at ≥30 mg/kg/day; however there were no correlated microscopic findings. The only microscopic finding observed was cytoplasmic homogeneity in the liver at doses ≥10 mg/kg/day in females and at ≥30 mg/kg/day for males, which was reversible after a 28-day recovery period. The hepatocytes were described as granular, eosinophilic cytoplasm, giving a "ground glass" appearance. The microscopic findings were not associated with alterations in liver weight or clinical chemistry. The changes in the liver were not consistent with phospholipidosis.

Therefore, systemic phospholipidosis was only observed in mice at very high doses (≥200 mg/kg/day).

For detailed reviews of the 14-day and 13-week repeat dose mouse studies, refer to reviews in IND 68,384 in DARRTS.

2.6.7.7.1.1 14-Day Repeat-Dose Study in the Mouse

Report Title: A 14-Day Oral (Gavage) Study of ACP-103 in Mice				**Test Article:**	**Pimavanserin**
Species/Strain:	Mouse/CD-1	**Duration of Dosing:**	14 days	**Study No:**	(b) -616001
Initial Age:	Approx. 40 days	**Duration of Recovery:**	-	**Location in CTD:**	4.2.3.2
Date of First Dose:	28 December 2006	**Method of Administration:**	Oral gavage		
		Vehicle/Formulation:	0.9% saline	**GLP Compliance:**	Yes
Special Features:		Toxicokinetic phase			
No Observed Adverse-Effect Level:		100 mg/kg/day			

Table 2.6.7.7.1-1 14-Day Repeat-Dose Study in the Mouse

Daily Dose (mg/kg/day):		**0 (Control)**		**50**		**100**		**200**		**300**	
No. of Animals in Toxicology Groups		**M: 5**	**F: 5**	**M: 5**	**F: 5**	**M: 5**	**F: 5**	**M: 5**	**F: 5**	**M: 5**	**F: 5**
Toxicokinetics (No. of animals):		M: 12	F: 12	M: 36	F: 36	M: 36	F: 36	M: 36	F: 36	M: 36	F: 36
C_{max} (ng/mL)	Day 0	-	-	1000	1190	2120	1250	2900	2210	2450	2890
	Day 13	-	-	1750	1380	2140	2310	2700	2870	4010	4210
$AUC_{(0\text{-}24h)}$ (ng·h/mL)	Day 0	-	-	7130	6840	13600	11400	21300	25200	39900	31400
	Day 13	-	-	6590	7910	27700	18600	40000	49500	60000	73700
Noteworthy Findings:											
Died or Sacrificed Moribund:		-	-	-	-	-	-	-	2	1	1
Clinical Observations:		0/0	0/0	0/0	0/0	1/1[c]	0/0	0/0	0/0	1/1[d]	1/1[e]
Body Weight Gain (g): Mean ± SD											
Days 0 - 14		1.72 ± 0.50	1.08 ± 0.59	-0.40 ± 1.13	0.02 ± 0.57	2.02 ± 2.27	0.18 ± 0.75	-1.46* ± 1.08	-1.57** ± 1.25	-2.18** ± 2.05	-1.28** ± 1.12

Daily Dose (mg/kg/day):	0 (Control)		50		100		200		300	
No. of Animals in Toxicology Groups	**M: 5**	**F: 5**	**M: 5**	**F: 5**	**M: 5**	**F: 5**	**M: 5**	**F: 5**	**M: 5**	**F: 5**
Hematology[1]:										
WBC ($10^3/\mu L$)	4.15	5.38	4.02	4.95	4.59	5.00	3.15	3.56	3.58	2.93
Neutrophil Absolute ($10^3/\mu L$)	0.59	0.70	1.03	0.84	0.92	0.69	0.86	0.48	1.88	0.76
Lymph Absolute ($10^3/\mu L$)	3.29	4.34	2.83	4.00	3.54	4.05	2.15	2.76	1.56	1.96
Blood chemistry[1]:										
ALP (U/L)	97	149	103	141	99	128	93	111	121	97
ALT (U/L)	50	88	74	38	80	105	50	64	103	174
AST (U/L)	93	182	83	86	143	115	73	133	151	218
Glucose (mg/dL)	180	185	202	190	218	182	170	167	155	130
Blood chemistry[1]:										
Cholesterol	98	73	119	118	120	96	201	118	198	181
Organ Weights, rel. to body weight (% difference):										
Liver	-	-	-3.0	0.3	-0.4	1.9	4.8	21.5	16.4	32.0
Lungs	-	-	-2.5	-8.2	19.2	15.1	2.6	16.5	47.8	26.0
Gross pathology:										
Liver (white areas)	0	0	0	0	0	0	0	0	2	0
Lungs										
Pale	0	0	0	0	1	0	0	0	0	0
Not fully collapsed	0	0	0	0	0	0	0	1	0	0
Histopathology:										
Kidneys										
Alteration, cytoplasmic										
minimal	0	0	0	0	0	0	1	1	1	1
Vacuolation, tubular epithelium										
minimal	0	0	0	0	0	0	0	0	0	1
mild	0	0	0	0	1	0	0	0	0	0

Daily Dose (mg/kg/day):	0 (Control)		50		100		200		300	
No. of Animals in Toxicology Groups	**M: 5**	**F: 5**	**M: 5**	**F: 5**	**M: 5**	**F: 5**	**M: 5**	**F: 5**	**M: 5**	**F: 5**
Liver										
Alteration, cytoplasmic										
minimal	0	0	0	0	0	0	0	2[a]	2	2
mild	0	0	0	0	0	0	0	0	3[a]	2[a]
moderate	0	0	0	0	0	0	0	0	0	1
Inflammation, subacute										
minimal	0	2	2	4	0	2	0	2	2	2
mild	0	0	0	0	0	0	0	1	0	1
Liver										
Necrosis										
minimal	0	0	0	0	0	0	0	0	0	1
mild	0	0	0	0	0	0	0	0	1	0
moderate	0	0	0	0	0	0	0	0	1	0
Lungs										
Macrophages, vacuolated										
minimal	0	0	0	0	0	0	4	5[b]	0	2[a]
mild	0	0	0	0	0	0	0	0	5[a]	3
Histopathology:										
Pituitary gland										
Vacuolation, cytoplasmic										
minimal	0	0	0	0	0	0	4	5[b]	5[a]	4[a]
Spleen										
Macrophages, vacuolated										
minimal	0	0	0	0	0	0	1	4[a]	3	3
mild	0	0	0	0	0	0	0	0	0	1

* Significantly different from the control group at $p \leq 0.05$ using Dunnett's test. ** Significantly different from the control group at $p \leq 0.01$ using Dunnett's test

[a] Includes 1 animal either found dead or euthanized in extremis

[b] Includes 2 animals that were found dead

[c] Cardio-pulmonary gasping

[d] Defecation decreased

[e] CNS changes, body changes (dermal atonia, thin) and cardio-pulmonary gasping were observed in one female that was found dead before the scheduled necropsy

[1] Mean values on Day 14

[Summary table excerpted from Toxicology Tabulated Summary Section of NDA 207318.]

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(b) (4)-616002

Study Title: A 13-Week Oral (Gavage) Toxicity Study of ACP-103 in Mice with a 28-Day Recovery Period

Species/Strain: Crl:CD-1(ICR) mouse
Initial Age: 7-8 weeks
Date of First Dose: 21 February 2007
Special Features: Toxicokinetic phase
No-Observed-Adverse-Effect Level: 10 mg/kg/day

Duration of Dosing: 13 weeks
Duration of Recovery: 28 days
Method of Administration: Oral (gavage)
Vehicle/Formulation: Deionized water

GLP Compliance: Yes

Dosage (mg/kg/day)	0 (Control)		10		30		100	
Sex:Number of Animals	M:15	F:15	M:15	F:15	M:15	F:15	M:15	F:15
Toxicokinetics: AUC_{inf} (ng•hr/mL)								
Study Day 0	NA	NA	385	290	3050	2090	6870	10500
Study Day 89	NA	NA	516	393	3570	3800	21400	21800
Noteworthy Findings								
Found Dead/Euthanized *in extremis*	1	0	0	0	2	0	3	2
Body Weight (%)[a]	37.0 g	29.4 g	-3.2%	1.7%	-3.2%	-3.7%	-9.5%**	0.3%
Food Consumption (%)[a]	5.3 g/day	6.2 g/day	0.0%	1.6%	5.7%	0.0%	0.0%	3.2%
Clinical Observations								
Hypoactivity	-	-	-	-	+	-	+	-
Intermittent tremors	-	-	-	-	+	-	+	-
Impaired equilibrium	-	-	-	-	-	-	+	-
Impaired use of forelimbs	-	-	-	-	-	-	+	-
Partial eye closure	-	-	-	-	+	-	+	-
Dermal atonia	-	-	-	-	+	-	+	+
Thinness	-	-	-	-	+	-	+	+
Pale extremities	-	-	-	-	+	-	-	+
Cool extremities	-	-	-	-	-	-	+	-

NA = Not applicable; M = Male, F = Female; - = No noteworthy findings; + = Noteworthy findings
** = $p<0.01$ when compared to the control values using Dunnett's test.
a = At end of the dosing period. For controls, group means are shown. For test article-treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).

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(b) (4)-616002

Study Title: A 13-Week Oral (Gavage) Toxicity Study of ACP-103 in Mice with a 28-Day Recovery Period

Dosage (mg/kg/day)	0 (Control)		10		30		100	
Sex:Number of Animals	M:15	F:15	M:15	F:15	M:15	F:15	M:15	F:15
Clinical Observations								
Body cool to the touch	-	-	-	-	+	-	+	-
Decreased respiration rate	-	-	-	-	-	-	+	-
Shallow respiration	-	-	-	-	+	-	+	-
Labored respiration	-	-	-	-	-	-	+	-
Rales	-	-	-	-	+	-	+	+
Gasping	-	-	-	-	-	-	+	+
Decreased defecation	-	-	-	-	+	+	+	+
Hematology	-	-	-	-	-	-	-	-
Serum Chemistry	-	-	-	-	-	-	-	-
Gross Pathology	-	-	-	-	-	-	-	-
Organ Weights[a]								
Thyroid/Parathyroid (%)[b]	0.0051 g	0.0051 g	↑2.0%	↓2.0%	↑21.6%	↑3.9%	↑31.4%*	↓3.9%
Histopathology (No. Examined)	10	10	10	10	10	10	10	10
Liver: Cytoplasmic Homogeneity	0	1	1	3	6	9	9	6
Recovery Evaluation								
Number Evaluated	4	5	5	5	3	5	2	3
Body Weight[c] (%)	37.0 g	29.8 g	5.7%	5.7%	-0.5%	0.0%	-0.8%	4.0%
Organ Weights[a]								
Thyroid/Parathyroid (%)[c]	0.0058 g	0.0050 g	↓3.4%	↓4.0%	↓27.6%	↑12.0%	↓10.3%	↓12.0%
Histopathology (No. Examined)	4	5	5	5	3	5	2	3
Liver: Cytoplasmic Homogeneity	0	0	0	0	0	0	0	0

NA = Not applicable; M = Male, F = Female; - = No noteworthy findings; + = Noteworthy findings
* = $p<0.05$ when compared to the control values using Dunnett's test.
a = Both absolute and relative weights differed from controls in the direction indicated. Number indicates percent difference for the absolute organ weights.
b = At end of the dosing period. For controls, group means are shown. For test article-treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).
c = At end of the recovery period. For controls, group means are shown. For test article-treated groups, percent differences from controls are shown.

[Summary table excerpted from study report no. (b) (4)-616002.]

6.2.2.1 Rat Oral dose range-finding and 7-day

Study no. HTI1000

Study Title: Oral dose range-finding and 7-day repeat-dose ranging study in the rat Non-GLP

Conducting laboratory:

(b) (4)

Dose range-finding phase:
Sprague-Dawley rats (4/sex/group) were administered ACP-103 by oral gavage with doses starting at 50 mg/kg/day once daily for 14 days and increased in increments every 2-4 days until toxicity was observed at 400 mg/kg/day. A dose of 400 mg/kg/day was administered for 5 days. Clinical signs started on day 10 with the 400 mg/kg/day dose and included irregular breathing, salivation, piloerection, fur staining, weight loss, hunched posture, partially closed eyes, discharge form nose and distended abdomen. The severity of the signs resulted in 2 females being prematurely sacrificed after 3 and 5 days of dosing at 400 mg/kg/day.
Repeat-dose phase:
Sprague-Dawley rats (5/sex/dose) were administered 250 or 350 mg/kg/day for 7 consecutive days. Body weight loss occurred at both dose levels with corresponding decrease in food consumption. The weight loss was severe in one female at 250 mg/kg/day and resulted in that animal being sacrificed on day 3. Clinical signs were similar to those in the range-finding phase. Necropsy findings included abnormal foci (raised, depressed or pale) on the non-glandular mucosa of the stomach, distended abdomen, pale liver and reddened or darkened pancreas. MTD considered to be between 200 and 250 mg/kg/day.

6.2.2.1 Rat 28-day + 28-day recovery

Study no. HTI1002

Study Title: 28 Day Oral Repeat Dose Toxicity Study in the Rat with Toxicokinetic Sampling and a 28 Day Recovery Period, GLP and QA

Conducting laboratory:

(b) (4)

Study design:
Sprague-Dawley rats 15/sex/group for the control and high dose groups and 10/sex/group for the low and mid dose groups received target dose levels of 0, 16.9, 84.7 and 169 (or 126.8) mg/kg/day ACP-103 (pimavanserin tartrate) by oral gavage for at least 28 days. Dosing in the high dose group was suspended for 2 days during the second week of the study due to the severity of clinical effects noted at this dose level. Dosing resumed at a reduced dose level, of 126.8 mg/kg/day. The last 5 animals/sex

from the control and high dose groups were retained for a further 28 days after completion of dosing to assess the reversibility of any findings. TK satellite groups were included.

Results:
Administration of 84.7 mg/kg/day or 126.8 mg/kg/day ACP-103 orally by gavage for up to 28 days was associated with multi-organ findings indicative of multi-organ phospholipidosis. Primary target tissues affected at both these doses included lungs, liver, spleen, thymus, lymph nodes, cervix, uterus, ovaries, kidneys, jejunum and ileum. In addition, at 169 or 126.8 mg/kg/day, there was a higher incidence of findings within the thyroid glands, prostate and vagina. The no effect level for this finding was 16.9 mg/kg/day. After a 28 day recovery period there was evidence of *some* reversibility. The findings in the lungs persisted at a lower level of severity in all recovery animals. Females were more severely affected than males from both main study and recovery groups. Findings persisted in a wider range of tissues in females after a 28 day recovery period, which correlated with increased exposure in females compared to males at the mid and high doses. Blood samples were only taken out to 8 hrs on day 28 but were taken out to 24 hrs on day 1. Therefore AUC_{0-24} values on day 28 may not be accurate.

Table 12: Toxicokinetics in male rats after 28-days of dosing

Dose Level: (mg/kg/day)	Day 1			Day 28		
	16.9	84.7	169	16.9	84.7	126.9[a]
C_{max} (ng/mL)	193	1070	1030	383	2000	2480
t_{max} (h)	4	8	24	2	4	1
AUC_{0-24} (ng•h/mL)	1070	17000	22100	4580	36600	44800

[a] Dosage was reduced from 169 to 126.9 mg/kg/day on Days 12–28 of the study.

Table 13: Toxicokinetics in female rats after 28-days of dosing

Dose Level: (mg/kg/day)	Day 1			Day 28		
	16.9	84.7	169	16.9	84.7	126.9[a]
C_{max} (ng/mL)	318	748	1410	455	2490	6360
t_{max} (h)	2	2	24	1	1 and 8[b]	2
AUC_{0-24} (ng•h/mL)	1350	14400	28000	4670	54000	115000

[a] Dosage was reduced from 169 to 126.9 mg/kg/day on Days 12–28 of the study.

[b] Mean peak concentrations were the same at 1 and 8 h postdose.

[Tables excerpted from study report. Error in table, high dose should be 126.8.]

6.2.2.2 Rat 3-month + 28-day recovery

Study no. 03-S12-UK

Study Title: A Subchronic Toxicity Study of ACP-103 in the Rat Administered Daily for 3 Months by Oral Gavage with Toxicokinetic sampling (GLP and QA)

Conducting laboratory: (b) (4) (different CRO than both 6-month rat studies)
Study initiation date: January 5, 2004
Drug: ACP-103, lot # 851875/ 98.7 % purity (used during Week 1); Lot # 090/15/99.2 % purity (used for the reminder of the study)

Table 14: Study design of 3-month rat study

Group Number	Dose Level [corrected] (mg/kg)	Frequency	Number of Animals			Dose Volume (ml/kg)	Dose Solution Conc. (mg/ml)
			Toxicology	Recovery	Toxicokinetic		
1	0 [0]	Daily	10M / 10F	5M / 5F	– / –	10	0
2	10 [8.5]	Daily	10M / 10F	5M / 5F	12M / 12F	10	1
3	30 [25.4]	Daily	10M / 10F	5M / 5F	12M / 12F	10	3
4	90 [76.3]	Daily	10M / 10F	5M / 5F	12M / 12F	10	9

[Doses in brackets are of free base. Table excerpted from study report.]

5 rats/sex/group were used in a 28-day recovery period.
*Toxicokinetic samples were taken on days 1 and 28 at predose, 0.5, 1, 2, 4, and 8 hrs postdose only. Therefore, AUC values are for 0-8hr and may not compare directly to AUC values using similar doses from other studies which took samples for TK analysis out to 24 hrs postdose to calculate AUC 0-24hrs.

Results:
Nine deaths occurred during the course of the study across all dose groups for both males and females. However, none were considered drug-related. Many occurred in TK animals during or shortly after bleeding. Clinical signs of fur staining were observed at 30 and 90 mg/kg/day. Reduced body weight compared to controls was observed in males at ≥30 mg/kg/day and in females at 90 mg/kg/day. Changes in clinical chemistry (increased serum aspartate aminotransferase, blood urea nitrogen, and creatinine), coagulation (increased prothrombin time), and hematology (increased WBC counts and morphologic alterations in the mature lymphocytes, described as consisting of cytoplasmic vacuolation) were noted in both males and females at 90 mg/kg. These effects were shown to be reversible in the 28-day recovery period. However, decreased urine pH persisted during the recovery period. Discoloration and/or abnormal consistency of the lungs were noted at high dose. There were weight increases in the following organs: adrenals, kidneys, lungs, spleen, epididymides, and ovaries, which all corresponded to microscopic findings of phospholipidosis. Weight gain in these organs was partially reversed after the 28-day recovery period except in the case of the lungs and kidneys.

Microscopic findings were observed in various organs at 90 mg/kg/day. Histopathology revealed nephrosis (characterized by segmental cortical tubular vacuolation, degeneration, casts, and tubular medullary dilatation) in all males and females at 90 mg/kg/day and myofiber degeneration of skeletal muscle in 3/10 and 7/10 males and females respectively at 90 mg/kg/day. Nephrosis was still observed in 3/5 recovery group males and all recovery group females at the end of the 28-day recovery period, while there was no evidence of skeletal muscle degeneration after the recovery period. Systemic phospholipidosis was present in multiple organs of both sexes at 90 mg/kg/day, most prominently in the lung and kidneys. Foamy macrophages were observed in all (10/10) males and females at 90 mg/kg/day at the end of the dosing period, with a severity level of 2.4 and 3.0, respectively. There was a decrease in the number and severity of affected tissues with evidence of phospholipidosis after the recovery period; however evidence of phospholipidosis (foamy macrophages or cytoplasmic vacuolation) was still present in some tissues (adrenals, epididymides, liver, lung, spleen, ovaries, mesenteric lymph nodes, pituitary gland and skin). It should be noted that foamy macrophages were observed in all (5/5) 90 mg/kg/day recovery group males and females at a severity level of 2.6 and 2.4, respectively, indicating no reversibility after the 28-day recovery period. No other microscopic changes suggestive of phospholipidosis were observed at 10 and 30 mg/kg for both male and female rats. Other findings of interest include cardiomyopathy (degeneration/fibrosis) in 1, 3, 2, and 5 males and 1, 0, 0, and 5 females from the controls, 10, 30, and 90 mg/kg/day groups, respectively. There was no cardiomyopathy in any recovery group animals. The finding was considered to be incidental in the study report (although no background control data were provided); however similar findings were also observed in female rats in the 2-year carcinogenicity study at a dose of 50 mg/kg/day which was above the control background rate. Therefore, the cardiomyopathy observed at the high dose of 90 mg/kg/day in this study may be drug-related and the finding may be dose and duration dependent. "Chronic inflammation" was observed in the lungs of 3/5 males and 4/5 females at 90 mg/kg/day from the recovery groups compared to none in control rats, *but not in any of the rats at the end of the dosing period*. The inflammation was described as an attempt of the body to clear the phospholipids (alveolar luminal material) from the lungs. However, according to the expert histopathology consult review there may have been a compilation error and the summary table data should read "adenomatous hyperplasia" in the lungs of 3/5 high dose recovery males and 1 control recovery male and not chronic inflammation. The female data is correct. Lung fibrosis was observed at similar and lower doses (60 mg/kg/day) in a 6-month repeat dose study in rats with a 6-month recovery period. The chronic inflammation observed in the lungs of rats after 3-months of treatment and 1-month of a recovery period may be a precursor to fibrosis. A second evaluation of the pathology report and a few kidney section slides from control and high dose animals was evaluated (b) (4) and this report was included as an amendment to the original study report. (b) (4) agreed with the contributing pathologist's report that the *"light microscopic morphologic changes compatible with phospholipidosis were present in the kidneys of 90-mg/kg animals from this study."* He also concluded that the lesion is compatible with what was observed in many other tissues.

Plasma samples for TK analysis were taken, but only out to 8 hrs postdose on days 28 and 91. The resultant calculated AUC_{last} values were not similar to those obtained in other rat studies using similar doses. There was also substantial inter-group variability in plasma concentrations. Therefore, the AUC values from this study cannot be directly compared to those in other studies.
NOAEL = 10 mg/kg/day due to decreased body weight at 30 mg/kg/day. No evidence of phospholipidosis at 10 and 30 mg/kg/day.

Table 15: TK parameters in male rats

Days	Parameter	Dose (mg/kg/day)		
		10	30	90
Day 0[a]	t_{max} (h)	2	4	8
	C_{max} (ng/mL)	11.8	145	443
	AUC_{last} (h•ng/mL)	48.7	842	2426
Day 28	t_{max} (h)	1	2	4
	C_{max} (ng/mL)	87.3	239	998
	AUC_{last} (h•ng/mL)	233	1532	6994
Day 91	t_{max} (h)	2	4	4
	C_{max} (ng/mL)	57.7	343	1007
	AUC_{last} (h•ng/mL)	243	2029	7231

[a] Day 0 = experimental start.

Table 16: TK parameters in female rats

Days	Parameter	Dose (mg/kg/day)		
		10	30	90
Day 0[a]	t_{max} (h)	2	4	8
	C_{max} (ng/mL)	17.7	211	438
	AUC_{last} (h•ng/mL)	48.4	1153	2326
Day 28	t_{max} (h)	0.5	8	8
	C_{max} (ng/mL)	44.2	374	1410
	AUC_{last} (h•ng/mL)	146	2277	9922
Day 91	t_{max} (h)	0.5	8	0
	C_{max} (ng/mL)	78.8	509	1707
	AUC_{last} (h•ng/mL)	278	2554	10353

[a] Day 0 = experimental start.

[TK tables excerpted from 03-S12-UK study report.]

6.2.2.3 Rat 6-month + 3-month recovery

Study title: A 6-month oral administration repeat dosing toxicity study of ACP-103 in Sprague-Dawley rats followed by a 3-month recovery period

Study no.:	(b) (4) 146.02
Study report location:	EDR SDN 1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	May 30, 2006
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	ACP-103, lot no. 981756, 100%

Key Study Findings

All drug related findings were observed at the high dose of 30 mg/kg/day. These included a decrease in mean body weight and body weight gain in both sexes, signs of lethargy, sedation, hunched posture and a few incidences of raspy breathing. Microscopic findings were limited to increased incidence and severity of macrophage infiltration in the alveoli of the lungs in females at 30 mg/kg/day, but the finding completely resolved following the 3-month recovery period. None of the effects adversely affected the overall well-being of the animals, therefore the highest dose of 30 mg/kg/day is the NOAEL for both males and females.
However, the NOEL for drug-related phospholipidosis in the lungs (macrophage infiltration) is 30 mg/kg/day for males but **10 mg/kg/day for females**.

Methods

Doses:	0, 3, 10, 30 mg/kg/day pimavanserin tartrate 0, 2.6, 8.5, 25.5 mg/kg/day pimavanserin free base
Frequency of dosing:	Once daily
Route of administration:	Oral gavage
Dose volume:	10 ml/kg
Formulation/Vehicle:	0.9% sodium chloride for injection, USP
Species/Strain:	Rat/Sprague-Dawley (SD) IGS (b) (4)
Number/Sex/Group:	20/sex/group
Age:	~6 weeks upon receipt
Weight:	Males: 126.2-221.0 g, females: 120.3-190.7 g
Satellite groups:	Toxicokinetics: 6/sex/group Recovery: 5/sex/group
Unique study design:	NA
Deviation from study protocol:	None that affected the outcome of the study or data integrity.

Observations and Results

Mortality

6 animals were found dead and one sacrificed moribund during the course of the study. Dosing error was determined as the cause of death for 3 animals; however no cause of death was determined for the remaining animals. There were no clinical signs in any of those animals preceding death, with the exception of slight gasping and fast respiration on the day preceding death (day 19) for male #349.

Table 17: Mortality in 6-month rat study

Unscheduled Deaths

Group	SSAN	Sex	Day	Dead vs. Moribund	Test article related?
1	270	M	D117	Found Dead	No - Dosing Error
1	283	M	D163	Found Dead	No
1	378	F	D112	Moribund	No
2	311	M	D167	Found Dead	No - Dosing Error
4	349	M	D20	Found Dead	No - Dosing Error
4	469	F	D26	Found Dead	Unknown
4	357	M	D127	Found Dead	Unknown

Note: SSAN 475 (Group 4) died on D1 and was not considered in this evaluation as it was a: TK satellite animal.

[The above table was excerpted from the study report.]

Clinical Signs

Drug-related clinical signs were observed mainly in high dose animals and included hunched posture, lethargy and sedation in most all males and females at 30 mg/kg/day. Hunched posture was also observed in 4 males and 1 female at 10 mg/kg/day and 1 male at 3 mg/kg/day. Lethargy was observed in 1 female at 3 mg/kg/day. These findings occurred mainly during the 2nd and 3rd months of dosing and did not worsen with time. *Raspy breathing* was also observed in 5 high dose (30 mg/kg/day) (2 males and 3 females) animals compared to only 1 control animal during the course of the study. Most of the respiratory findings occurred only for a few days and *did not persist or worsen*. However, one male had slight to moderate raspy breathing on days 139-161 and one female was observed *wheezing* on days 179-180. Clinical observations were performed twice daily starting on acclimation day 2; the first in the morning and the second at least 4 hrs after the first observation.

Body Weights

Drug-related effect noted only in high dose groups. A slight drug-related decrease in mean body weight (-6% compared to controls) at the end of the dosing period for both males and females and body weight gain was statistically significantly decreased compared to controls (17-20% compared to controls) for both males and females. These changes did not correspond to a decrease in food intake.
Body weights were recorded on acclimation day 1, prior to the first day of dosing, once weekly throughout the study and on the day of necropsy.

Table 18: Mean body weight on day 179 and body weight gain in rats

Group	Males		Females	
	BW (g) / % of control	BW Gain (g) / % of control	BW (g) / % of control	BW Gain (g) / % of control
1	625.3 / NA	390.8 / NA	352.4 / NA	170.2 / NA
2	622.5 / -0.4%	393.0 / +0.6%	325.2 / -7.7%	148.5 / -12.7%
3	606.2 / -3.1%	364.2 / -6.8%	333.6 / -5.3%	146.6 / -13.9%
4	587.0 / -6.1%	323.7 ** / -17.2%	331.0 / -6.1%	134.8 ** / -20.8%

*: Body Weight Gains (g) = Body Weights on D179 – Body Weights on A7. Data in the table were from terminal and recovery animals.

**: Statistical differences from control.

[Table excerpted from study report.]

Food Consumption

There were no drug-related effects on food consumption. Food consumption was recorded once weekly.

Ophthalmoscopy

There were no drug-related findings.

Eye exams were conducted once during acclimation and once during week 26 and 30.

Hematology

There were no drug-related findings.
Blood samples were collected from all main study and recovery animals once during acclimation and once prior to necropsies. An adequate battery of hematology and coagulation parameters was evaluated.

Clinical Chemistry

There were no drug-related findings.
Blood samples were collected from all main study and recovery animals once during acclimation and once prior to necropsies. An adequate battery of clinical chemistry parameters was evaluated.

Urinalysis

There were no drug-related findings.
Urine was collected from each animal over a 24 hr period using a metabolic cage. An adequate battery of urinalysis parameters was evaluated.

Gross Pathology

There were no drug-related macroscopic findings upon necropsy.

Organ Weights

There were no drug-related effects on organ weights.
The following organs were weighed: adrenals, brain (cerebrum, cerebellum and brain stem), epididymides, heart, kidneys, liver, lungs (including bronchi), ovaries, pituitary, prostate/seminal vesicles, spleen, submandibular/sublingular salivary glands, thyroids (including parathyroids), testes, thymus, uterus (body and cervix).

Histopathology

Adequate Battery: Yes

Peer Review: No

Histological Findings
The only drug-related finding was an increased incidence and severity of macrophage infiltration in the alveoli on the lungs of females at 30 mg/kg/day. The incidence rate was similar to controls in the recovery group animals indicating complete reversibility. The sponsor did not report this finding in the lungs to be attributed to systemic phospholipidosis. However, the study pathologist did report the finding in high dose females to be “treatment related”. According to this reviewer and the expert pathology consult review from Drs. Francke and Mog (see consult review in appendix 4), evidence of phospholipidosis in the lungs was observed in female rats at a dose of 30 mg/kg/day. In high dose female rats the incidence of “macrophage infiltration, alveoli” was above that of the background rate in control animals based on increased incidence, severity and distribution: it was focal in controls compared to diffuse and multifocal in treated animals. Although no transmission electron microscopy was conducted in this study in

order definitively know if this finding is PLD-related, due to similar findings in rats in other repeat-dose studies, this finding is considered to be related to PLD. Therefore, the NOEL for any evidence of PLD in the lungs of rats after 6-months of treatment is 30 mg/kg/day for males, but **10 mg/kg/day** for females.

Table 19: Microscopic findings in the lungs of rats (macrophage infiltration, alveoli)

Lesion Incidence Summary

Controls from group(s): 1	Animal sex:	-- Animals Affected -- Males --				-- Females --			
	Dosage group:	Ctls	2	3	4	Ctls	2	3	4
Tissues With Diagnoses	No. in group:	19	20	20	18	19	20	20	20
Lungs/Bronchi ..... Number examined:		19	20	20	18	19	20	20	20
Mononuclear/polymrophonuclear cell infiltration									
	->	18	20	19	18	19	20	20	20
	1>	1	0	1	0	0	0	0	0
..... Total Incidence of Finding Observed:		1	0	1	0	0	0	0	0
Increase, macrophage infiltration, alveoli									
	->	11	16	16	12	17	18	18	11
	1>	8	4	4	6	2	2	2	3
	2>	0	0	0	0	0	0	0	6
..... Total Incidence of Finding Observed:		8	4	4	6	2	2	2	9

[Table excerpted from (b) (4)-146-02 study pathology report. Grade of 1 = minimal, 2 = mild]

[Table excerpted from study report.]

Toxicokinetics

Blood samples were collected from TK satellite animals on days 1, 91, and 182 at pre-dose, 0.5, 1, 2, 4, 8 and 24 hrs post dose. Exposure levels to ACP-103 (AUC and C_{max}) increased after repeat dosing from day 1 to 91, but values were similar from day 91 to 182 indicating steady state was reached. The increase in both parameters in both sexes was not dose-dependent (greater than linear). Exposure was greater in females than males (~2-fold). The half-life ($t_{1/2}$) increased with increasing dose and after repeated dosing indicating a possible decrease in the rate of metabolism.

Table 20: Toxicokinetic parameters for ACP-103 in plasma of rats (day 1, 91 and 182)

Sex	Day	Dose (mg/kg/day)	T_{max} (hr)	C_{max} (ng/mL)	$AUC_{(0\text{-}24hr)}$ (ng·hr/mL)	$t_{½}$ (hr)	Tlast (hr)
Female	1	3	0.500	2.07	2.90	0.784	2.00
Male	1	3	0.500	1.91	2.44	0.410	2.00
Female	1	10	1.00	58.8	404	3.60	8.00
Male	1	10	1.00	48.7	204	1.32	8.00
Female	1	30	2.00	413	4850	5.67	24.0
Male	1	30	1.00	378	4670	4.71	24.0
Female	91	3	0.500	18.2	50.8	1.25	8.00
Male	91	3	1.00	11.6	33.3	1.09	8.00
Female	91	10	2.00	274	2750	15.3	8.00
Male	91	10	1.00	106	1070	2.77	24.0
Female	91	30	4.00	788	13300	16.6	24.0
Male	91	30	8.00	446	8590	NC	24.0
Female	182	3	1.00	15.7	33.1	1.36	4.00
Male	182	3	2.00	5.45	12.7	NC	4.00
Female	182	10	1.00	118	1570	2.50	24.0
Male	182	10	4.00	118	1030	2.79	24.0
Female	182	30	8.00	853	14400	NC	24.0
Male	182	30	2.00	441	8670	38.6	24.0

Concentration vs. time data were pooled from 3 animals/sex/time point and toxicokinetic calculations were done on the mean plasma profiles.
NC = insufficient data in apparent terminal elimination phase to calculate
Tlast = time of last measurable plasma concentration

Dosing Solution Analysis

All dose formulations were within the acceptable range of (b) (4) % of the nominal concentration. No test article was detected in any control article preparations.

6.2.2.4 Rat 6-month + 6-month recovery

Study title: A 6-month oral (gavage) toxicity study of ACP-103 in Sprague Dawley rats with a 6-month recovery period

Study no.:	(b) (4)-616007
Study report location:	EDR SDN 1
Conducting laboratory and location:	(b) (4) *Note this is a different CRO that other 6-month rat study.
Date of study initiation:	January 26, 2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	ACP-103 (b) (4) batch no. 1046433, 99.7% (different batch and lot from previous 6 month study).

Key Study Findings

Drug-related deaths occurred in males dosed at 90 mg/kg/day and females dosed 60 and 90 mg/kg/day. Cause of death not always determined, but many were attributed to tubular degeneration or vacuolation of the epithelium in the kidneys or in 1 case due to vacuolated macrophages in the lungs. Multi-systemic (multi-organ) phospholipidosis was observed in males and females at 60 and 90 mg/kg/day. Lung fibrosis observed in recovery group males and females at 90 mg/kg/day and in recovery group females at 60 mg/kg/day. 1 female at 90 mg/kg/day had lung fibrosis at the 13-week necropsy. Full reversibility was evident in only some tissues. Only partial reversibility (decrease in severity only) was observed in lungs, liver, lymph nodes, kidneys, adrenals, thyroids, spleen (males only), heart, epididymides, and ovaries.

No NOAEL was determined (<60 mg/kg/day)

Methods

Doses:	0, 60, 90 mg/kg/day pimavanserin tartrate 0, 51.0, 76.6 mg/kg/day pimavanserin free base
Frequency of dosing:	Once daily
Route of administration:	Oral gavage
Dose volume:	10 ml/kg
Formulation/Vehicle:	Deionized water
Species/Strain:	Rat/Sprague Dawley (b) (4)
Number/Sex/Group:	30/sex/group (groups 1-3)
Age:	At dosing initiation: ~ 7 weeks old
Weight:	At dosing initiation: males: 180-224 g, females: 141-186 g
Satellite groups:	Toxicokinetic groups: 6/control groups (1A); 12/sex/drug-treated groups (2A-3A) Recovery groups: 10/sex from each toxicology group (1-3)
Unique study design:	≤ 20 rats from the group 3 females (90 mg/kg/day) were euthanized following 13-weeks of dosing due to poor tolerability and mortality. While ≤ 20 rats from groups 1-3 males and groups 1-2 females were euthanized following 26 weeks of dosing. The remaining ≤10 rats/sex/toxicology groups were euthanized following 26-weeks of nondosing (recovery) period.
Deviation from study protocol:	

Observations and Results

Mortality

Drug-related deaths (found dead or euthanized moribund) occurred in males at 90 mg/kg/day and females at 60 and 90 mg/kg/day and were mostly attributed to tubular degeneration or vacuolation of the epithelium in the kidneys or vacuolated macrophages in the lungs, when a cause of death could be determined. However, the cause of death was undetermined for one male and 3 females at 60 mg/kg/day and 6 females at 90 mg/kg/day. Due to clear drug-related deaths in other animals at the same doses, it is presumed that those undetermined deaths are also drug-related. Due to poor tolerability and mortality in females at 90 mg/kg/day, all remaining females in the 90 mg/kg/day main study dose group were euthanized during study week 13. No females in the 90 mg/kg/day group completed more than 3-months of dosing. 10 females from the 90 mg/kg/day recovery group that were dosed for 13-weeks entered the recovery phase and were euthanized during week 39 week after 26-weeks of a non-dosing period.

Table 21: Early Mortality

Animal No.	Sex	Treatment	Dose (mg/kg/day)	Death Status	Study Day	Cause of Death
6358	Male	Vehicle	0	FD	49	Undetermined
6318	Male	Vehicle	0	EE	58	Femur Fracture
6330	Male	Vehicle	0	FD	136	Undetermined
6377	Male	ACP-103	60	FD	331	Undetermined
6338	Male	ACP-103	90	EE	129	Kidney: Vacuolation, epithelium

EE = Euthanized *in extremis*; FD = Found dead

The sponsor's table is continued below.

Animal No.	Sex	Treatment	Dose (mg/kg/day)	Death Status	Study Day	Cause of Death
6346	Male	ACP-103	90	EE	129	Kidney: Vacuolation, epithelium
6392	Male	ACP-103	90	EE	129	Kidney: Vacuolation, epithelium
6394	Male	ACP-103	90	EE	121	Kidney: Vacuolation, epithelium Degeneration, tubular
6522	Female	Vehicle	0	FD	140	Undetermined
6427	Female	ACP-103	60	FD	178	Undetermined
6471	Female	ACP-103	60	EE	203	Lungs: Macrophages, Vacuolated
6483	Female	ACP-103	60	FD	12	Undetermined
6519	Female	ACP-103	60	FD	51	Undetermined
6488	Female	ACP-103	90	FD	92	Undetermined
6503	Female	ACP-103	90	EE	86	Kidney: Vacuolation, epithelium Degeneration, tubular
6507	Female	ACP-103	90	EE	86	Kidney: Vacuolation, epithelium Degeneration, tubular
6532	Female	ACP-103	90	EE	86	Kidney: Vacuolation, epithelium Degeneration, tubular
6536	Female	ACP-103	90	FD	4	Undetermined

EE = Euthanized *in extremis*; FD = Found dead

[The above table is excerpted from the sponsor's study report]

Clinical Signs

Drug-related clinical signs were observed in males and females at 60 and 90 mg/kg/day, were dose-dependent (increased number of animals and frequency with increasing dose), and females were more sensitive than males. Signs observed at both dose levels included: labored respiration, rales, dried red material around

nose/mouth/forelimbs, wet clear material around nose/ventral neck/forelimbs, wet/yellow material around urogenital area, dried yellow material around urogenital area/anogenital area/ventral trunk. The respiratory-related clinical sign of rales was observed in 0, 23, and 28 males and 0, 25, and 28 females at 0, 60 and 90 mg/kg/day at the 1-2 hr postdose time point respectively. Additional clinical signs observed in males at 90 mg/kg/day and in females at 60 and 90 mg/kg/day included: dermal atonia, thin, extremities pale/blue/cool to touch, body cool to touch, and decreased defecation. The cardio-pulmonary-related clinical signs correlated with macro- and microscopic findings in the lungs. The incidence and frequency of these signs decreased in the recovery group animals, however a few animals continued to show respiratory-related clinical signs indicating incomplete (or slow) reversibility (11 high dose recovery group females with rales). Clinical signs were recorded at the time of dosing and ~1-2 hrs postdose. During the recovery period, animals were observed once daily. Detailed physical exams were conducted prior to randomization, at the time of randomization, and weekly during the study.

Table 22: Clinical signs in male and female rats

Observations [a]	Males			Females		
Dose Group (mg/kg/day):	0	60	90	0	60	90
Dermal Atonia						
Detailed Physicals	-	-	5/2	-	-	-
At Time of Dose	-	-	14/3	-	7/2	1/1
1-2 hours post-dosing	-	-	13/2	-	6/2	-
Recovery [b]	-	-	6/2	-	7/1	2/1
Thin						
Detailed Physicals	-	-	23/9	-	6/4	19/9
At Time of Dose	-	-	76/8	1/1	38/2	57/6
1-2 hours post-dosing	-	-	47/8	-	17/2	26/6
Unscheduled	-	-	1/1	-	-	-
Recovery [b]	-	-	12/3	-	20/1	19/2
Extremities Pale						
Detailed Physicals	-	-	1/1	-	-	-
At Time of Dose	-	-	1/1	-	1/1	1/1
1-2 hours post-dosing	-	-	-	-	1/1	4/2
Recovery [b]	-	-	-	-	2/1	-

Observations [a]	Males			Females		
Dose Group (mg/kg/day):	0	60	90	0	60	90
Extremities Blue						
Detailed Physicals	-	-	-	-	3/1	-
At Time of Dose	-	-	1/1	-	27/1	-
1-2 hours post-dosing	-	-	-	-	28/1	-
Recovery [b]	-	-	-	-	21/2	17/1
Extremities Cool to Touch						
Detailed Physicals	-	-	1/1	-	2/1	1/1
At Time of Dose	-	-	1/1	-	-	5/4
1-2 hours post-dosing	-	-	1/1	-	1/1	1/1
Recovery [b]	-	-	2/1	-	7/1	-
Body Cool to Touch						
Detailed Physicals	-	-	-	-	-	3/3
At Time of Dose	-	-	-	-	-	3/3
1-2 hours post-dosing	-	-	-	-	-	2/2
Recovery [b]	-	-	-	-	1/1	1/1
Respiration Labored						
Detailed Physicals	-	-	1/1	-	2/1	-
At Time of Dose	-	-	2/2	1/1	6/1	-
1-2 hours post-dosing	-	-	3/3	1/1	8/1	-
Recovery [b]	-	-	1/1	-	7/1	-
Rales						
Detailed Physicals	-	14/6	32/14	-	14/10	30/18
At Time of Dose	-	69/18	221/29	-	57/19	160/27
1-2 hours post-dosing	-	104/23	262/28	-	94/25	177/28
Recovery [b]	-	4/2	-	-	2/2	27/11
Dried Red Material Around Nose						
Detailed Physicals	10/8	20/13	72/23	3/3	37/14	82/26
At Time of Dose	56/18	106/26	376/27	16/8	224/24	250/29
1-2 hours post-dosing	61/11	492/29	744/30	14/9	388/27	305/29
Unscheduled	-	-	2/2	-	-	-
Recovery [b]	71/8	38/9	26/10	34/9	19/6	71/23
Defecation Decreased						
Detailed Physicals	-	-	1/1	-	2/1	-
At Time of Dose	-	-	12/2	1/1	10/2	3/2
1-2 hours post-dosing	-	-	7/1	-	5/1	4/2
Recovery [b]	-	-	-	-	7/1	-

Observations [a]	Males			Females		
Dose Group (mg/kg/day):	0	60	90	0	60	90
Wet Clear Material Around Mouth						
Detailed Physicals	-	2/2	5/3	-	5/4	-
At Time of Dose	-	149/19	163/15	-	96/23	72/19
1-2 hours post-dosing	1/1	259/27	433/26	-	56/16	64/18
Wet Clear Material Ventral Neck						
At Time of Dose	-	-	1/1	-	-	-
1-2 hours post-dosing	-	20/14	33/14	-	15/9	28/15
Wet Clear Material Forelimb(s)						
1-2 hours post-dosing	-	26/13	27/15	-	15/8	24/14
Dried Red Material Around Mouth						
Detailed Physicals	-	1/1	6/5	-	2/2	10/5
At Time of Dose	1/1	2/2	20/7	-	10/5	39/11
1-2 hours post-dosing	-	619/29	442/30	-	227/23	128/27
Unscheduled	-	1/1	-	-	-	-
Recovery [b]	2/1	-	1/1	-	-	-
Wet Yellow Material Urogenital Area						
Detailed Physicals	1/1	1/1	22/11	-	1/1	23/11
At Time of Dose	-	4/4	116/19	-	16/7	119/19
1-2 hours post-dosing	-	39/15	258/24	2/1	47/12	193/24
Recovery [b]	-	3/2	4/2	-	6/1	-
Dried Yellow Material Urogenital Area						
Detailed Physicals	-	2/2	69/15	-	8/3	71/20
At Time of Dose	-	8/7	389/18	-	32/5	373/23
1-2 hours post-dosing	-	13/10	387/21	-	49/8	319/24
Unscheduled	-	-	1/1	-	-	-
Recovery [b]	-	-	38/4	-	19/1	23/6
Dried Yellow Material Ventral Trunk						
Detailed Physicals	-	-	12/5	-	2/2	8/5
At Time of Dose	-	-	114/12	-	4/2	50/9
1-2 hours post-dosing	-	2/2	115/15	-	3/2	47/11
Recovery [b]	-	-	10/1	-	-	-
Observations [a]	**Males**			**Females**		
Dose Group (mg/kg/day):	0	60	90	0	60	90
Dried Yellow Material Anogenital Area						
Detailed Physicals	-	-	9/6	-	2/1	38/11
At Time of Dose	-	1/1	47/9	-	3/2	197/17
1-2 hours post-dosing	-	2/2	49/9	-	2/2	161/19
Recovery [b]	-	-	4/1	-	9/1	9/2
Dried Red Material Forelimb(s)						
Detailed Physicals	2/2	4/4	23/12	-	15/9	84/27
At Time of Dose	3/2	30/15	167/20	2/1	107/19	209/28
1-2 hours post-dosing	1/1	204/24	277/29	1/1	207/26	212/28
Recovery [b]	-	4/3	4/3	2/2	4/4	28/9

- = No noteworthy findings
[a] = Total occurrence/no. of animals
[b] = Includes detailed physicals and recovery observations

[Table excerpted from (b) (4)-616007 study report.]

Body Weights

A drug and dose-related decrease in mean body weight compared to controls was observed for both males and females. Body weights for males at 60 and 90 mg/kg/day

were comparable to controls by the end of the recovery period.
Body weight values for females at 90 mg/kg/day increased during the recovery period as compared to the dosing period. Body weights were recorded during acclimation, at pretest, prior randomization, and at least weekly during the treatment and period and weekly during the recovery period.

Table 23: Mean body weight change from controls at the end of the dosing period

	60 mg/kg/day	90 mg/kg/day*
Males	-2.8%	-17.8%
Females	-9.8%	-13.7%

*90 mg/kg/day females: mean body weight recorded at week 13

Figure 3: Body weights (g) Males: Dosing period

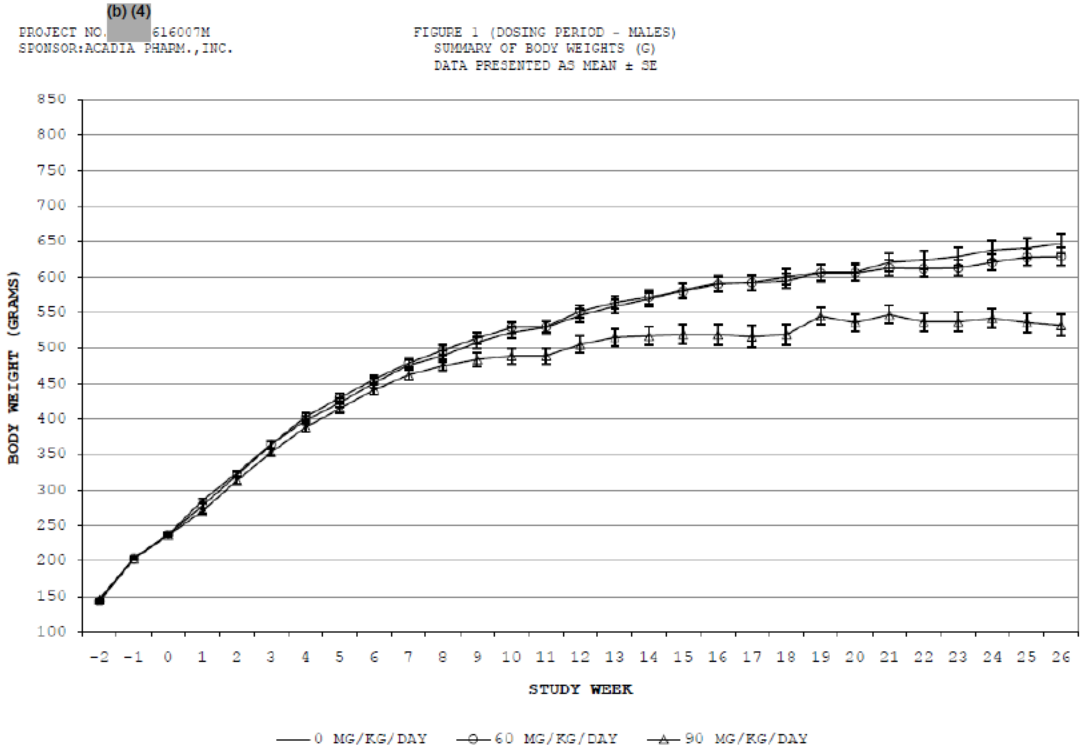


Figure 4: Body weights (g) Females: Dosing period

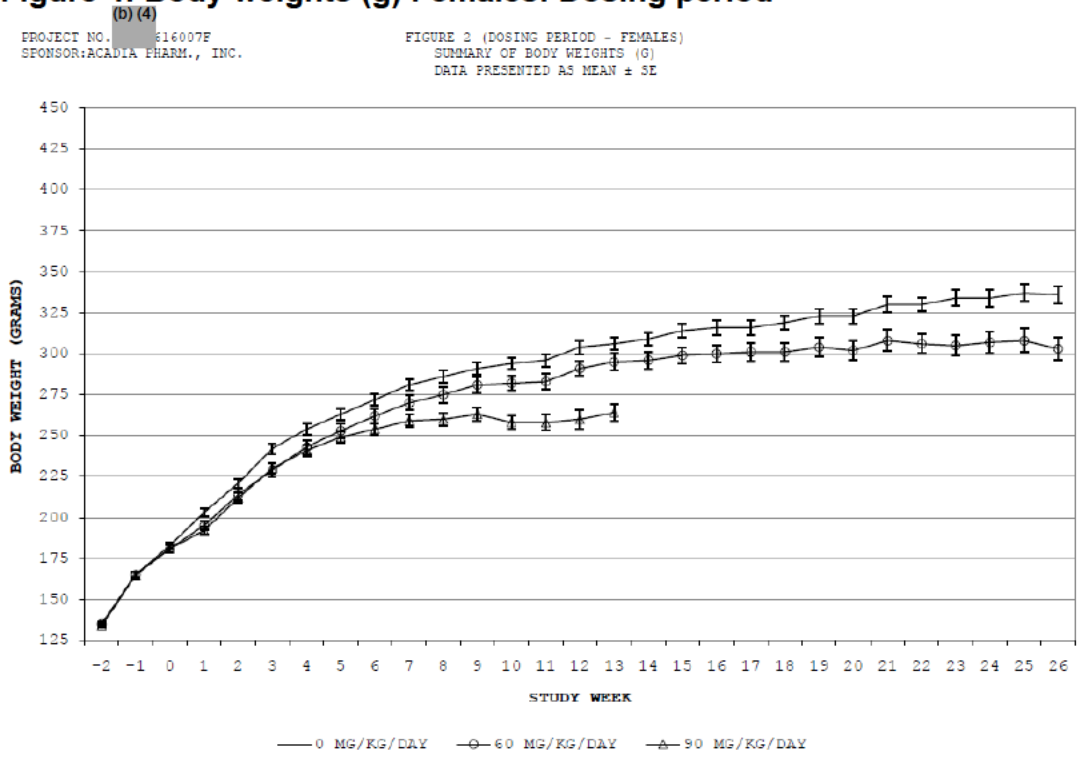


Figure 5: Body weights (g) Males: Recovery Period

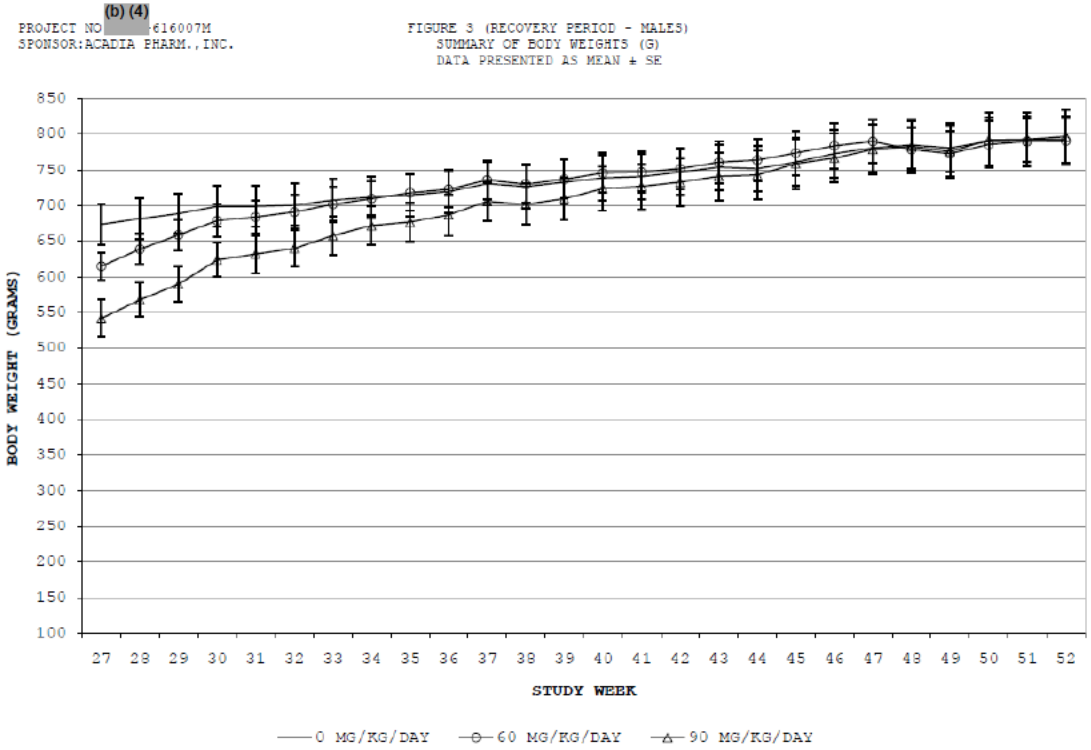
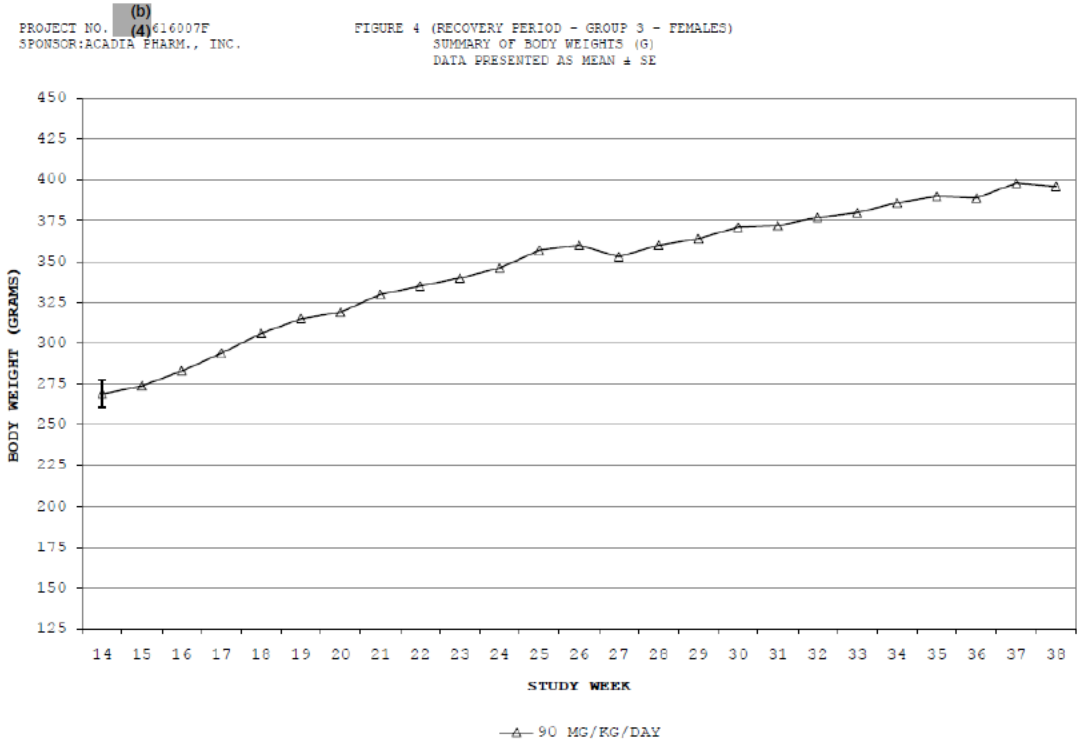


Figure 6: Body weights (g) Females: Recovery Period



[The above 4 figures are excerpted from the sponsor's study report]

Food Consumption

There was a statistically significant decrease in food consumption for males and females at 90 mg/kg/day starting around week 8 to 9 for males (~15% compared to controls) and week 0 to 1 for females (~12% compared to controls) and continued for the duration of the dosing period. Food consumption was comparable to controls, or slightly higher, for males at 90 mg/kg/day starting after the first week of the recovery period. Food consumption for females at 90 mg/kg/day during the recovery period was increased compared to values during the dosing period (weeks 1-13). There was no drug-related effect on food consumption for males or females at 60 mg/kg/day. *Changes in food consumption correlated with effects on body weight.*

Food consumption was recorded weekly beginning at least one week prior to dosing initiation and ending prior to the first day of scheduled necropsy. During week 25 and 38 (group 3 females only), food consumption was recorded twice weekly.

Ophthalmoscopy

There were no drug-related findings. Eye exams were conducted on all animals during week -1, and for all drug-treated animals near the end of treatment (study week 25) and near the end of the recovery period (study week 51). Exams were conducted using an indirect ophthalmoscope and slit lamp biomicroscope.

Hematology

Females at 90 mg/kg/day had higher absolute neutrophil counts and higher absolute monocyte counts as compared to historical control data[1]*. At week 26 necropsy, females at 60 mg/kg/day had higher absolute white blood cell counts, absolute red blood cell counts, hemoglobin concentration, hematocrit, absolute neutrophil counts, absolute lymphocyte counts, and absolute monocyte counts. Males at 60 and 90 mg/kg/day had higher absolute white blood cell counts, lymphocyte counts, absolute monocyte counts, and absolute large unstained counts. Findings only observed at 90 mg/kg/day in males included higher absolute neutrophil counts, lower absolute eosinophil count, higher absolute basophil count, higher red blood cell distribution width, and higher hemoglobin distribution width. The changes in the red blood cell parameters were not considered adverse due to the small change in magnitude and the absence of other alterations. However, the significant increases in white blood cells are consistent with an inflammatory response.
There were no statistically significant drug-related changes in any hematology parameters at the recovery necropsy; therefore all findings are considered reversible.
Blood samples for hematology and coagulation parameter evaluations were collected from all fasted animals at their scheduled necropsies. An adequate battery of hematology and coagulation parameters was evaluated.

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Table 24: Changes in hematology parameters

Daily Dose (mg/kg/day):	0 (Control)		60		90	
Number of Animals:	M: 30	F: 30	M: 30	F: 30	M: 30	F[1]: 30
Hematology:						
WBC (10^3/µL)	9.38	6.78	13.09**	10.05**	15.95**	8.90
Neutrophil absolute (10^3/µL)	1.48	1.08	1.65	2.35**	3.30**	2.18
Lymphocyte absolute (10^3/µL)	7.43	5.31	10.76**	7.14**	11.80**	6.23
Monocyte absolute (10^3/µL)	0.23	0.19	0.38*	0.34**	0.58**	0.33
Eosinophil absolute (10^3/µL)	0.15	0.12	0.15	0.11	0.09**	0.05
Basophil absolute (10^3/µL)	0.04	0.03	0.06	0.04	0.09**	0.02
RDW (%)	12.3	12.2	12.5	12.5	13.7**	13.8
HDW (g/dL)	2.27	2.10	2.31	2.11	2.42*	2.45

[1]*At study week 13, samples from female controls were not collected and therefore females in the 90 mg/kg/day group were compared to the (b) (4) historical control database.
[The above table is excerpted from the sponsor's toxicology tabulated summary section of the NDA]

Clinical Chemistry

The increase in urea nitrogen (BUN), creatinine (up to 2-fold) and phosphorus levels in males at 90 mg/kg/day and females at 60 and 90 mg/kg/day correlated with macro- and microscopic renal findings (tubular degeneration).
Blood samples for clinical chemistry parameter evaluations were collected from all fasted animals at their scheduled necropsies. An adequate battery of clinical chemistry parameters was evaluated.

Table 25: Clinical chemistry parameters

Daily Dose (mg/kg/day):	0 (Control)		60		90	
Number of Animals:	M: 30	F: 30	M: 30	F: 30	M: 30	F[1]: 30
Blood Chemistry:						
Urea nitrogen (mg/dL)	14.2	17.1	14.8	20.1	25.0**	32.0
Creatinine (mg/dL)	0.2	0.3	0.2	0.4*	0.4**	0.4
AST (U/L)	97	203	91	134	120*	156
Glucose (mg/dL)	105	104	109	98*	94**	94
Phosphorus (mg/dL)	6.3	6.5	6.9**	7.1*	7.2**	8.2
Triglycerides (mg/dL)	94	66	80	58	60**	41

[1]*At study week 13, samples from female controls were not collected and therefore females in the 90 mg/kg/day group were compared to the (b) (4) historical control database.

[The above table is excerpted from the sponsor's toxicology tabulated summary section of the NDA]

Urinalysis

There was a significant decrease in urine specific gravity for males at 60 and 90 mg/kg/day and a decrease in urine pH for males at 90 mg/kg/day and females at 60 and 90 mg/kg/day. There was also a dose-related increase in the amount of urine amorphous crystals observed during microscopic evaluation of urine sediment in both males and females at both doses compared to controls. The toxicological relevance of the increase in urine crystals and whether the crystals would form a precipitate is unknown.

There were no drug-related findings at the recovery necropsies, indicating that all findings were reversible.

Urine was collected from all animals using metabolism cages at their scheduled necropsies. An adequate battery of urinalysis parameters, including microscopic evaluation of sediment, was evaluated.

Table 26: Urinalysis parameters

Daily Dose (mg/kg/day):	0 (Control)		60		90	
Number of Animals:	M: 30	F: 30	M: 30	F: 30	M: 30	F[1]: 30
Urinalysis:						
Specific gravity	1.039	1.030	1.022**	1.025	1.023**	1.031
pH	6.6	6.2	6.4	5.7**	5.6**	5.7

[1]*At study week 13, samples from female controls were not collected and therefore females in the 90 mg/kg/day group were compared to the (b) (4) historical control database.

[The above table is excerpted from the sponsor's toxicology tabulated summary section of the NDA]

Gross Pathology

Macroscopic findings were observed in females at 60 and/or in males and females at 90 mg/kg/day they included findings in the adrenal glands, kidneys, liver, lungs, lymph nodes, parathyroids, spleen, thyroids and thymus. Macroscopic findings in rats that died or were sacrificed early included enlarged adrenal glands, kidneys and lymph nodes, discoloration (pale, mottled, white areas or yellow areas) of the kidneys, lungs, liver, thyroid and spleen, adhesions on the liver, and lungs not fully collapsed. Similar findings were also observed in surviving males and females at 60 and 90 mg/kg/day during the scheduled necropsies.

Table 27: Correlation between selected necropsy findings, organ weights and microscopic findings.

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Necropsy	Organ Weight	Histopathology
Adrenals - Enlarged	↑adrenal weights	Vacuolation, Cytoplasmic
Kidneys - Enlarged -Yellow areas -Mottled -Pale -White areas	↑kidney weights	Degeneration, Tubular Vacuolation, Epithelium Macrophages, Vacuolated
Lymph nodes, Bronchial, Mediastinal, and Mesenteric -enlarged	-	Macrophages, Vacuolated
Lungs -Not fully collapsed -Pale -Mottled -Yellow areas -White areas	↑lung weights	Macrophages, Vacuolated Vacuolation, Epithelium
Liver -White areas -Yellow areas -Nodule	↑liver weight relative to final body weight	Vacuolation, Hepatocellular, Centrilobular Macrophages, Vacuolated
Parathyroids -Enlarged	-	Vacuolation, Cytoplasmic
Thyroids -Pale	-	Vacuolation, epithelium
Spleen -Rough -Pale	-	Macrophages, Vacuolated
Thymus -Discoloration, yellow	-	Macrophages, Vacuolated
-	↑pituitary weights	Vacuolation, cytoplasmic

- = No correlate

Organ Weights

There was a significant increase in relative weights of the adrenal glands, brain, kidneys, liver, lungs, pituitary, prostate, and spleen in both males and females in addition to increased testes and epididymides weights in males. Relative lung weights were increased 3- to 4-fold compared to controls. The increased organ weights correlated with multi-organ phospholipidosis observed microscopically.

Daily Dose (mg/kg/day):	0 (Control)		60		90	
Number of Animals:	M: 30	F: 30	M: 30	F: 30	M: 30	F[1]: 30
Organ Weights (rel. body weight):						
Adrenal Glands	0.010	0.022	0.012*	0.033**	0.020**	0.042
Brain	0.358	0.645	0.373	0.699*	0.441**	0.775
Epididymides	0.248	NA	0.255	NA	0.308**	NA
Kidneys	0.693	0.736	0.736	0.898**	0.995**	1.164
Liver	2.598	2.814	2.850**	3.182**	2.995**	3.556
Lungs	0.289	0.456	0.374	1.713**	1.353**	1.850
Pituitary	0.002	0.007	0.003**	0.008	0.003**	0.007
Prostate	0.196	NA	0.194	NA	0.195	NA
Spleen	0.136	0.239	0.169**	0.223	0.196**	0.261
Testes	0.620	NA	0.645	NA	0.760**	NA
Final body weight (g)	604	309	593	287*	485**	249

[1]*At study week 13, no control females were sacrificed therefore there is no direct comparison for the 90 mg/kg/day females that were sacrificed at week 13.

[The above table is excerpted from the sponsor's toxicology tabulated summary section of the NDA]

Histopathology

Adequate Battery: Yes, a standard battery of tissues and organs were examined microscopically. Tissues from all animals, including those that were found dead or euthanized early, were examined. In addition, right lung samples from selected animals (3/sex/control, three 90 mg/kg/day males, three 60 mg/kg/day females) were evaluated via transmission electron microscopy (TEM).

Peer Review: No

Histological Findings
*All histopathology tables included below were excerpted from the sponsor's study report.

Drug-related microscopic findings were observed at both dose levels in males and females and comprised of systemic cytoplasmic vacuolation consistent with findings from previous studies in rats and with multi-organ phospholipidosis. Cytoplasmic vacuolation or accumulation of vacuolated macrophages were found in the *respiratory system (lungs and trachea), urinary system (kidneys, urinary bladder, and ureters), nervous system (brain), cardiovascular system, hepatic system, lymphoid system, exocrine and endocrine systems (adrenals, thyroids, parathyroids, pituitary, lacrimal glands, mammary glands, harderian glands, and mandibular salivary glands), reproductive system (epididymides, prostate, seminal vesicles, ovaries, oviducts, uterus, cervix, and vagina), hematopoietic system (bone marrow of the sternum and femur), gastrointestinal tract, musculoskeletal system, and integumentary system.* Some of the more severe findings that correlated with the multi-organ phospholipidosis included minimal to mild **fibrosis** in the lungs of recovery group males at 90 mg/kg/day and recovery group females at 60 and 90 mg/kg/day and in 1 main toxicity study female at 90 mg/kg/day. Fibrosis is a permanent non-reversible change. It should be noted that the one female rat with lung fibrosis was from the 90 mg/kg/day main study group that was sacrificed at study week 13 due to that entire dosing group being sacrificed due to poor tolerability and mortality. The fibrosis in the lungs is most likely part of the continuum of a chronic inflammatory response in the lungs due to excessive

phospholipidosis. Minimal to moderate tubular degeneration occurred in the kidneys of males and females at both doses which is considered to be secondary to multi-organ phospholipidosis and was also listed as the cause of death of several animals. The original study pathologist concluded that renal (tubular degeneration) changes were the basis for the higher serum urea nitrogen (BUN) and creatinine levels observed at 90 mg/kg/day. This reviewer agrees with that conclusion. Cytoplasmic vacuolation in the brain was also observed in a few animals at 90 mg/kg/day. Hypertrophy (moderate and severe) in the adrenal cortex was observed in some recovery group animals. Degeneration of skeletal muscle was also observed in males and females at the end of the primary necropsy.
Even though complete reversibility of the phospholipidosis findings was observed following a 6-month drug free period for many tissues and organs, only partial or minimal evidence of recovery (with only a slight decrease in the severity level) was observed in the lungs, liver, lymph nodes, kidneys, adrenals, thyroids, spleen (males only), heart, epididymides, and ovaries.

Retinal dysplasia was observed in one 90 mg/kg/day female at the 13 week necropsy, and in one 60 mg/kg/day female at the 26-week necropsy, which was not included in the sponsor's tables below.

Table 28: Microscopic findings in the respiratory system

Text Table 3. Incidence and Severity of ACP-103-Related Microscopic Findings in the Respiratory System at Primary and Recovery Necropsies.

	Males			Females		
Dosage (mg/kg/day):	**0**	**60**	**90**	**0**	**60**	**90**
Lungs	**17/10**	**20/9**	**16/10**	**19/10**	**17/9**	**15/10**
PN/RN[a]						
Macrophages, Vacuolated	1/ 2	15/2	16/8	0/2	17/8	15/9
Minimal	1/ 2	13/2	0/5	-/2	3/3	0/9
Mild	0/0	1/0	2/3	-/0	5/4	3/0
Moderate	0/0	1/0	12/0	-/0	9/1	9/0
Severe	0/0	0/0	2/0	-/0	0/0	3/0
Vacuolation, Epithelium	0/0	7/0	13/6	0/0	13/6	15/2
Minimal	-/-	6/-	9/6	-/-	10/5	8/2
Mild	-/-	1/-	4/0	-/-	3/1	7/0
Fibrosis	0/0	0/0	0/5	0/0	0/7	1/5
Minimal	-/-	-/-	-/4	-/-	-/4	0/5
Mild	-/-	-/-	-/1	-/-	-/3	1/0
Trachea	**17/10**	**20/9**	**16/10**	**19/9**	**17/9**	**15/10**
PN/RN[a]						
Vacuolation, Epithelium	0/0	2/0	13/0	0/0	10/0	10/0
Minimal	-/-	2/-	9/-	-/-	7/-	9/-
Mild	-/-	0/-	4/-	-/-	3/-	1/-

PN/RN = number of tissues examined at primary necropsy/recovery necropsy
[a] = number of tissues examined at week 13 primary necropsy/week 39 recovery necropsy for the 90 mg/kg/day group females

In addition to the findings listed in the sponsor's table above, minimal hemorrhage in the lungs occurred in two 90 mg/kg/day males and two 60 mg/kg/day females at the primary necropsy, in one 90 mg/kg/day male at the 6-month recovery necropsy and in two 90 mg/kg/day females at the 39-week necropsy compared to no findings in any control

animals. Also, mineralization was observed in the lungs of one high dose (90 mg/kg/day) male at the 6-month recovery (#6281).

The following is excerpted from the pathology report:
"In the lungs, minimal to severe vacuolated macrophages were observed in all dose groups at the primary and recovery necropsies and were characterized by collections of large foamy macrophages and multinucleated giant cells with lightly eosinophilic cytoplasm filling the alveoli. Macrophages were accompanied by cholesterol clefts and variable amounts of extracellular eosinophilic proteinaceous material. The extracellular material was similar to the macrophage cytoplasm and likely a result of macrophage lysis and release of contents. The vacuolated macrophages were associated with the gross observations of pale lungs, white areas, and lungs that did not collapse, and the higher absolute and relative lung weights. In addition, in the 60 and 90 mg/kg/day group males and females, pneumocytes lining the alveoli protruded into the lumen and contained numerous cytoplasmic vacuoles as did the respiratory epithelium of the larger airways and the trachea (minimal to mild vacuolated epithelium). At the recovery necropsies, the incidence and severity of vacuolated macrophages and vacuolated epithelium was lower; however, minimal to mild interstitial and pleural fibrosis was observed in the 90 mg/kg/day group males and females and the 60 mg/kg/day group females in addition to vacuolated epithelial cells and macrophages. The fibrosis and macrophages correlated to the white areas observed at the recovery necropsies and the higher absolute and relative lung weights that persisted at the recovery necropsies. Although the incidence and/or severity of vacuolation (epithelial and macrophage) was reduced following the nondosing (recovery) period and would have likely completely resolved with additional time, the fibrosis was considered a permanent change."

Table 29: Microscopic findings in the urinary system

Text Table 4. Incidence and Severity of ACP-103-Related Microscopic Findings in the Urinary System at Primary and Recovery Necropsies.

	Males			Females		
Dosage (mg/kg/day):	**0**	**60**	**90**	**0**	**60**	**90**
Kidneys	**17/10**	**20/9**	**16/10**	**19/10**	**17/9**	**15/10**
PN/RN[a]						
Degeneration, Tubular	0/0	1/0	12/0	0/0	5/0	8/0
Minimal	-/-	0/-	1/-	-/-	3/-	1/-
Mild	-/-	1/-	10/-	-/-	2/-	4/-
Moderate	-/-	0/-	1/-	-/-	0/-	3/-
Infiltrate, Mononuclear	3/2	2/2	10/0	1/1	3/0	2/0
Minimal	3/1	2/1	10/-	1/1	3/-	2/-
Mild	0/1	0/1	0/-	0/0	0/-	0/-
Vacuolation, Epithelium	0/0	9/1	16/1	0/0	10/1	14/2
Minimal	-/-	8/1	0/1	-/-	6/1	1/ 2
Mild	-/-	0/0	3/0	-/-	3/0	6/0
Moderate	-/-	1/0	11/0	-/-	1/0	7/0
Severe	-/-	0/0	2/0	-/-	0/0	0/0
Macrophages, Vacuolated	0/0	0/0	0/5	0/0	0/0	0/3
Minimal	-/-	-/-	-/5	-/-	-/-	-/3
Urinary Bladder	**17/10**	**20/8**	**16/10**	**19/10**	**17/9**	**15/10**
PN/RN[a]						
Vacuolation, Epithelium	0/0	0/0	7/0	0/0	3/0	13/0
Minimal	-/-	-/-	7/-	-/-	2/-	9/-
Mild	-/-	-/-	0/-	-/-	1/-	4/-
Ureters	**0/0**	**1/1**	**1/0**	**0/0**	**0/0**	**15/0**
PN/RN[a]						
Vacuolation, Epithelium	0/0	0/0	0/0	0/0	0/0	2/0
Minimal	-/-	-/-	-/-	-/-	-/-	1/-
Mild	-/-	-/-	-/-	-/-	-/-	1/-

PN/RN = number of tissues examined at primary necropsy/recovery necropsy
[a] = number of tissues examined at week 13 primary necropsy/week 39 recovery necropsy for the 90 mg/kg/day group females

Table 30: Microscopic findings in the nervous system

Text Table 5. Incidence and Severity of ACP-103-Related Microscopic Findings in the Nervous System at Primary and Recovery Necropsies.

	Males			Females		
Dosage (mg/kg/day):	**0**	**60**	**90**	**0**	**60**	**90**
Brain	**17/10**	**20/9**	**16/10**	**19/10**	**17/9**	**15/10**
PN/RN[a]						
Vacuolation, Cytoplasmic, Neurons	0/0	0/0	1/0	0/0	0/0	0/0
Minimal	-/-	-/-	1/-	-/-	-/-	-/-
Vacuolation, Cytoplasmic, Choroid Plexus	0/0	0/0	0/0	0/0	0/0	4/0
Minimal	-/-	-/-	-/-	-/-	-/-	4/-

PN/RN = number of tissues examined at primary necropsy/recovery necropsy
[a] = number of tissues examined at week 13 primary necropsy/week 39 recovery necropsy for the 90 mg/kg/day group females

4 out of 10 high dose females had minimal brain vacuolation in the choroid plexus and 1 out of 10 high dose males had minimal neuronal cytoplasmic vacuolation. Any PDL in the brain is considered adverse. However, the vacuolation is minimal in severity and was completely reversible. Table 31: Microscopic findings in the cardiovascular system

Text Table 6. Incidence and Severity of ACP-103-Related Microscopic Findings in the Cardiovascular System at Primary and Recovery Necropsies.

	Males			Females		
Dosage (mg/kg/day):	**0**	**60**	**90**	**0**	**60**	**90**
Heart	**17/10**	**20/9**	**16/10**	**19/10**	**17/9**	**15/10**
PN/RN[a]						
Vacuolation, Cytoplasmic	0/0	3/3	10/2	0/0	1/0	8/1
Minimal	-/-	2/3	6/2	-/-	1/-	7/1
Mild	-/-	1/0	4/0	-/-	0/-	1/0

PN/RN = number of tissues examined at primary necropsy/recovery necropsy
[a] = number of tissues examined at week 13 primary necropsy/week 39 recovery necropsy for the 90 mg/kg/day group females

Table 32: Microscopic findings in the hepatic system

Text Table 7. Incidence and Severity of ACP-103-Related Microscopic Findings in the Hepatic System at Primary and Recovery Necropsies.

	Males			Females		
Dosage (mg/kg/day):	**0**	**60**	**90**	**0**	**60**	**90**
Liver	**17/10**	**20/9**	**16/10**	**19/10**	**17/9**	**15/10**
PN/RN[a]						
Vacuolation, bile duct	0/0	5/0	15/0	0/0	7/0	13/0
Minimal	-/-	5/-	13/-	-/-	6/-	10/-
Mild	-/-	0/-	2/-	-/-	1/-	3/-
Vacuolation, hepatocellular, centrilobular	0/0	0/1	4/1	0/0	3/0	11/0
Minimal	-/-	-/1	4/1	-/-	3/-	9/-
Mild	-/-	-/0	0/0	-/-	0/-	2/-
Macrophages, Vacuolated	0/0	0/1	0/0	0/0	2/1	3/3
Minimal	-/-	-/1	-/-	-/-	2/1	1/3
Mild	-/-	-/0	-/-	-/-	0/0	2/0

PN/RN = number of tissues examined at primary necropsy/recovery necropsy
[a] = number of tissues examined at week 13 primary necropsy/week 39 recovery necropsy for the 90 mg/kg/day group females

Table 33: Microscopic findings in the lymphoid system

Text Table 8. Incidence and Severity of ACP-103-Related Microscopic Findings in the Lymphoid System at Primary and Recovery Necropsies.

	Males			Females		
Dosage (mg/kg/day):	**0**	**60**	**90**	**0**	**60**	**90**
Lymph Node, Axillary	**17/10**	**20/9**	**16/10**	**19/10**	**17/9**	**15/10**
PN/RN[a]						
Macrophages, Vacuolated	0/0	3/2	8/6	0/1	6/3	15/6
Minimal	-/-	3/2	7/6	-/1	6/3	12/6
Mild	-/-	0/0	1/0	-/0	0/0	3/0
Lymph Node, Bronchial	**0/0**	**0/0**	**0/0**	**0/0**	**0/0**	**3/0**
PN/RN[a]						
Macrophages, Vacuolated	0/0	0/0	0/0	0/0	0/0	3/0
Minimal	-/-	-/-	-/-	-/-	-/-	1/-
Mild	-/-	-/-	-/-	-/-	-/-	2/-
Lymph Node, Mandibular	**17/10**	**20/9**	**16/10**	**19/10**	**17/9**	**15/10**
PN/RN[a]						
Macrophages, Vacuolated	2/0	7/2	10/3	0/0	2/3	10/6
Minimal	2/-	7/2	9/3	-/-	2/3	10/6
Mild	0/-	0/0	1/0	-/-	0/0	0/0
Lymph Node, Mediastinal	**0/0**	**0/0**	**2/0**	**0/0**	**0/0**	**2/0**
PN/RN[a]						
Macrophages, Vacuolated	0/0	0/0	2/0	0/0	0/0	2/0
Minimal	-/-	-/-	1/-	-/-	-/-	0/-
Mild	-/-	-/-	1/-	-/-	-/-	2/-
Lymph Node, Mesenteric	**17/10**	**20/9**	**16/10**	**19/10**	**17/9**	**15/10**
PN/RN[a]						
Macrophages, Vacuolated	5/2	9/8	15/8	0/6	10/8	14/7
Minimal	5/2	9/8	10/8	-/6	9/8	5/7
Mild	0/0	0/0	5/0	-/0	1/0	6/0
Moderate	0/0	0/0	0/0	-/0	0/0	3/0
Thymus	**17/9**	**20/8**	**16/9**	**19/10**	**17/8**	**15/10**
PN/RN[a]						
Macrophages, Vacuolated	0/0	2/0	1/ 2	0/2	2/1	3/1
Minimal	-/-	2/-	1/ 2	-/2	2/1	2/1
Mild	-/-	0/-	0/0	-/0	0/0	1/0

PN/RN = number of tissues examined at primary necropsy/recovery necropsy
[a] = number of tissues examined at week 13 primary necropsy/week 39 recovery necropsy for the 90 mg/kg/day group females

Text Table 8. Incidence and Severity of ACP-103-Related Microscopic Findings in the Lymphoid System at Primary and Recovery Necropsies (Continued).

	Males			Females		
Dosage (mg/kg/day):	**0**	**60**	**90**	**0**	**60**	**90**
Peyer's Patches	**17/10**	**20/8**	**16/10**	**19/10**	**17/9**	**15/10**
PN/RN[a]						
Macrophages, Vacuolated	0/0	0/0	0/0	0/0	0/0	4/0
Minimal	-/-	-/-	-/-	-/-	-/-	2/-
Mild	-/-	-/-	-/-	-/-	-/-	2/-
Spleen	**17/10**	**20/9**	**16/10**	**19/10**	**17/9**	**15/10**
PN/RN[a]						
Macrophages, Vacuolated	0/0	3/2	14/3	0/0	9/0	15/0
Minimal	-/-	3/0	6/3	-/-	7/-	4/-
Mild	-/-	0/2	8/0	-/-	2/-	10/-
Moderate	-/-	0/0	0/0	-/-	0/-	1/-

PN/RN = number of tissues examined at primary necropsy/recovery necropsy
[a] = number of tissues examined at week 13 primary necropsy/week 39 recovery necropsy for the 90 mg/kg/day group females

Table 34: Microscopic findings in the endocrine ad exocrine systems

Text Table 9. Incidence and Severity of ACP-103-Related Microscopic Findings in the Endocrine and Exocrine Systems at Primary and Recovery Necropsies.

	Males			Females		
Dosage (mg/kg/day):	0	60	90	0	60	90
Adrenal Cortex	**17/10**	**20/9**	**16/10**	**19/10**	**17/9**	**15/10**
PN/RN[a]						
Hypertrophy	2/2	3/1	0/4	1/1	1/2	0/2
Minimal	0/2	0/1	-/3	1/1	0/1	-/0
Mild	2/0	3/0	-/1	0/0	1/0	-/0
Moderate	0/0	0/0	-/1	0/0	0/0	-/1
Severe	0/0	0/0	-/0	0/0	0/1	-/1
Vacuolation, Cytoplasmic	0/0	9/0	15/6	0/0	9/0	15/0
Minimal	-/-	5/-	0/6	-/-	0/-	0/-
Mild	-/-	4/-	7/0	-/-	7/-	8/-
Moderate	-/-	0/-	8/0	-/-	2/-	7/-
Thyroids	**17/10**	**20/9**	**16/10**	**19/10**	**17/9**	**15/10**
PN/RN[a]						
Vacuolation, Epithelium	0/0	5/1	14/6	0/0	5/1	11/5
Minimal	-/-	4/1	1/6	-/-	5/1	8/5
Mild	-/-	1/0	11/0	-/-	0/0	3/0
Moderate	-/-	0/0	2/0	-/-	0/0	0/0
Parathyroids	**14/10**	**17/9**	**16/10**	**16/9**	**14/8**	**13/9**
PN/RN[a]						
Vacuolation, Cytoplasmic	0/0	0/0	4/0	0/0	3/0	8/0
Minimal	-/-	-/-	2/-	-/-	3/-	6/-
Mild	-/-	-/-	2/-	-/-	0/-	2/-
Pituitary	**17/10**	**20/9**	**16/10**	**19/10**	**17/9**	**15/10**
PN/RN[a]						
Vacuolation, Cytoplasmic	9/0	12/0	14/0	0/0	2/0	11/0
Minimal	8/-	10/-	3/-	-/-	1/-	8/-
Mild	1/-	2/-	7/-	-/-	1/-	1/-
Moderate	0/-	0/-	4/-	-/-	0/-	2/-
Lacrimal Gland	**17/10**	**20/9**	**16/10**	**19/10**	**17/9**	**15/10**
PN/RN[a]						
Vacuolation, epithelium	0/0	1/0	1/0	0/0	0/0	3/0
Minimal	-/-	1/-	1/-	-/-	-/-	1/-
Mild	-/-	0/-	0/-	-/-	-/-	2/-

PN/RN = number of tissues examined at primary necropsy/recovery necropsy
[a] = number of tissues examined at week 13 primary necropsy/week 39 recovery necropsy for the 90 mg/kg/day group females

Text Table 9. Incidence and Severity of ACP-103-Related Microscopic Findings in the Endocrine and Exocrine Systems at Primary and Recovery Necropsies (Continued).

	Males			Females		
Dosage (mg/kg/day):	0	60	90	0	60	90
Salivary Gland	**17/10**	**20/9**	**16/10**	**19/10**	**17/9**	**15/10**
PN/RN[a]						
Vacuolation, epithelium, ductal	0/0	2/0	5/0	0/0	1/0	8/0
Minimal	-/-	2/-	5/-	-/-	1/-	5/-
Mild	-/-	0/-	0/-	-/-	0/-	3/-
Mammary Glands	**0/0**	**0/0**	**0/0**	**19/9**	**17/9**	**15/10**
PN/RN[a]						
Vacuolation, epithelium	0/0	0/0	0/0	0/0	6/0	10/0
Minimal	-/-	-/-	-/-	-/-	4/-	9/-
Mild	-/-	-/-	-/-	-/-	2/-	1/-
Harderian Glands	**17/10**	**20/9**	**16/10**	**19/10**	**17/9**	**15/10**
PN/RN[a]						
Vacuolation, epithelium	0/0	0/0	0/0	0/0	0/0	1/0
Minimal	-/-	-/-	-/-	-/-	-/-	1/-

PN/RN = number of tissues examined at primary necropsy/recovery necropsy
[a] = number of tissues examined at week 13 primary necropsy/week 39 recovery necropsy for the 90 mg/kg/day group females

Table 35: Microscopic findings in the reproductive system

Text Table 10. Incidence and Severity of ACP-103-Related Microscopic Findings in the Reproductive System at Primary and Recovery Necropsies.

	Males			Females		
Dosage (mg/kg/day):	**0**	**60**	**90**	**0**	**60**	**90**
Epididymides	**17/10**	**20/9**	**16/10**	**NA/NA**	**NA/NA**	**NA/NA**
PN/RN[a]						
Vacuolation, epithelium	0/0	7/6	16/8	0/0	0/0	0/0
Minimal	-/-	5/6	2/7	-/-	-/-	-/-
Mild	-/-	2/0	14/1	-/-	-/-	-/-
Prostate	**17/10**	**20/9**	**16/10**	**NA/NA**	**NA/NA**	**NA/NA**
PN/RN[a]						
Vacuolation, epithelium	0/0	1/0	9/0	0/0	0/0	0/0
Minimal	-/-	1/-	7/-	-/-	-/-	-/-
Mild	-/-	0/-	2/-	-/-	-/-	-/-
Seminal Vesicles	**17/10**	**20/9**	**16/10**	**NA/NA**	**NA/NA**	**NA/NA**
PN/RN[a]						
Vacuolation, epithelium	0/0	3/0	15/0	0/0	0/0	0/0
Minimal	-/-	2/-	5/-	-/-	-/-	-/-
Mild	-/-	1/-	10/-	-/-	-/-	-/-
Cervix	**NA/NA**	**NA/NA**	**NA/NA**	**19/10**	**17/9**	**15/10**
PN/RN[a]						
Vacuolation, epithelium	0/0	0/0	0/0	0/0	9/0	10/0
Minimal	-/-	-/-	-/-	-/-	8/-	7/-
Mild	-/-	-/-	-/-	-/-	1/-	2/-
Moderate	-/-	-/-	-/-	-/-	0/-	1/-
Macrophages, vacuolated	0/0	0/0	0/0	0/0	5/0	12/0
Minimal	-/-	-/-	-/-	-/-	4/-	7/-
Mild	-/-	-/-	-/-	-/-	0/-	4/-
Moderate	-/-	-/-	-/-	-/-	1/-	1/-
Ovaries	**NA/NA**	**NA/NA**	**NA/NA**	**19/10**	**17/9**	**15/10**
PN/RN[a]						
Vacuolation, cytoplasmic	0/0	0/0	0/0	0/4	6/7	12/7
Minimal	-/-	-/-	-/-	-/4	5/6	7/7
Mild	-/-	-/-	-/-	-/0	1/1	5/0
Oviducts	**NA/NA**	**NA/NA**	**NA/NA**	**19/10**	**17/9**	**15/10**
PN/RN[a]						
Vacuolation, epithelium	0/0	0/0	0/0	0/0	7/0	13/0
Minimal	-/-	-/-	-/-	-/-	7/-	5/-
Mild	-/-	-/-	-/-	-/-	0/-	6/-
Moderate	-/-	-/-	-/-	-/-	0/-	2/-

PN/RN = number of tissues examined at primary necropsy/recovery necropsy
[a] = number of tissues examined at week 13 primary necropsy/week 39 recovery necropsy for the 90 mg/kg/day group females
NA = Not applicable

Text Table 10. Incidence and Severity of ACP-103-Related Microscopic Findings in the Reproductive System at Primary and Recovery Necropsies (Continued).

	Males			Females		
Dosage (mg/kg/day):	**0**	**60**	**90**	**0**	**60**	**90**
Uterus	**NA/NA**	**NA/NA**	**NA/NA**	**19/10**	**17/9**	**15/10**
PN/RN[a]						
Vacuolation, epithelium	0/0	0/0	0/0	0/0	10/0	10/0
Minimal	-/-	-/-	-/-	-/-	8/-	5/-
Mild	-/-	-/-	-/-	-/-	2/-	5/-
Macrophages, vacuolated	0/0	0/0	0/0	0/0	11/0	15/0
Minimal	-/-	-/-	-/-	-/-	7/-	4/-
Mild	-/-	-/-	-/-	-/-	3/-	10/-
Moderate	-/-	-/-	-/-	-/-	1/-	1/-
Vagina	**NA/NA**	**NA/NA**	**NA/NA**	**19/10**	**17/9**	**15/10**
PN/RN[a]						
Vacuolation, epithelium	0/0	0/0	0/0	0/0	1/0	5/0
Mild	-/-	-/-	-/-	-/-	1/-	2/-
Moderate	-/-	-/-	-/-	-/-	0/-	3/-

PN/RN = number of tissues examined at primary necropsy/recovery necropsy
[a] = number of tissues examined at week 13 primary necropsy/week 39 recovery necropsy for the 90 mg/kg/day group females
NA = Not applicable

Table 36: Microscopic findings in the hematopoietic system

Text Table 11. Incidence and Severity of ACP-103-Related Microscopic Findings in the Hematopoietic System at Primary and Recovery Necropsies.

	Males			Females		
Dosage (mg/kg/day):	**0**	**60**	**90**	**0**	**60**	**90**
Marrow, Femur	**17/10**	**20/9**	**16/10**	**19/10**	**17/9**	**15/10**
PN/RN[a]						
Macrophages, Vacuolated	0/0	0/0	1/0	0/0	0/0	1/0
Minimal	-/-	-/-	1/-	-/-	-/-	1/-
Marrow, Sternum	**17/10**	**20/9**	**16/10**	**19/10**	**17/9**	**15/10**
PN/RN[a]						
Macrophages, Vacuolated	0/0	0/0	0/0	0/0	0/0	1/0
Minimal	-/-	-/-	-/-	-/-	-/-	1/-

PN/RN = number of tissues examined at primary necropsy/recovery necropsy
[a] = number of tissues examined at week 13 primary necropsy/week 39 recovery necropsy for the 90 mg/kg/day group females

Table 37: Microscopic findings in the gastrointestinal system

Text Table 12. Incidence and Severity of ACP-103-Related Microscopic Findings in the Gastrointestinal System at Primary and Recovery Necropsies.

	Males			Females		
Dosage (mg/kg/day):	**0**	**60**	**90**	**0**	**60**	**90**
Stomach, glandular PN/RN[a]	**17/10**	**20/9**	**16/10**	**19/10**	**17/9**	**15/10**
Dilatation, glandular	0/0	1/0	1/0	2/0	4/0	8/0
Minimal	-/-	1/-	1/-	2/-	4/-	8/-
Duodenum PN/RN[a]	**17/10**	**20/9**	**16/10**	**19/10**	**17/9**	**15/10**
Vacuolation, Epithelium	0/0	0/0	2/0	0/0	0/0	3/0
Minimal	-/-	-/-	2/-	-/-	-/-	3/-
Rectum PN/RN[a]	**17/10**	**20/9**	**16/10**	**19/10**	**17/9**	**15/10**
Vacuolation, Cytoplasmic, Smooth Muscle	0/0	0/0	1/0	0/0	0/0	0/0
Minimal	-/-	-/-	1/-	-/-	-/-	-/-
Esophagus PN/RN[a]	**17/10**	**20/9**	**16/10**	**19/10**	**17/9**	**15/10**
Degeneration	0/0	0/0	0/0	0/0	0/0	4/0
Minimal	-/-	-/-	-/-	-/-	-/-	3/-
Moderate	-/-	-/-	-/-	-/-	-/-	1/-
Vacuolation, Cytoplasmic	0/0	0/0	0/0	0/0	0/0	4/0
Minimal	-/-	-/-	-/-	-/-	-/-	2/-
Mild	-/-	-/-	-/-	-/-	-/-	1/-
Moderate	-/-	-/-	-/-	-/-	-/-	1/-
Infiltrate, Mononuclear	0/0	0/0	0/0	0/0	0/0	1/0
Minimal	-/-	-/-	-/-	-/-	-/-	1/-

PN/RN = number of tissues examined at primary necropsy/recovery necropsy
[a] = number of tissues examined at week 13 primary necropsy/week 39 recovery necropsy for the 90 mg/kg/day group females

Table 38: Microscopic findings in the musculoskeletal system

Text Table 13. Incidence and Severity of ACP-103-Related Microscopic Findings in the Musculoskeletal System at the Primary and Recovery Necropsies

	Males			Females		
Dosage (mg/kg/day):	**0**	**60**	**90**	**0**	**60**	**90**
Skeletal Muscle PN/RN[a]	**17/10**	**20/9**	**16/10**	**19/10**	**17/9**	**15/10**
Degeneration	4/0	5/0	8/0	1/0	2/0	10/0
Minimal	4/-	5/-	7/-	1/-	1/-	6/-
Mild	0/-	0/-	1/-	0/-	1/-	4/-
Vacuolation, Cytoplasmic	0/0	0/0	5/0	0/0	1/0	9/0
Minimal	-/-	-/-	4/-	-/-	0/-	3/-
Mild	-/-	-/-	1/-	-/-	1/-	6/-

PN/RN = number of tissues examined at primary necropsy/recovery necropsy
[a] = number of tissues examined at week 13 primary necropsy/week 39 recovery necropsy for the 90 mg/kg/day group females

Skeletal degeneration was also observed in a shorter (3-month) repeat dose study in rats at a similar dose. The degeneration is considered adverse, but it was completely reversible.

Table 39: Microscopic findings in the integumentary system

Text Table 14. Incidence and Severity of ACP-103-Related Microscopic Findings In the Integumentary System at the Primary and Recovery Necropsies.

	Males			Females		
Dosage (mg/kg/day):	0	60	90	0	60	90
Skin	17/10	20/9	16/10	19/10	17/9	15/10
PN/RN[a]						
Vacuolation, Epithelium, Follicular	0/0	2/0	5/0	0/0	2/0	5/0
Minimal	-/-	2/-	4/-	-/-	2/-	4/-
Mild	-/-	0/-	1/-	-/-	0/-	1/-

PN/RN = number of tissues examined at primary necropsy/recovery necropsy
[a] = number of tissues examined at week 13 primary necropsy/week 39 recovery necropsy for the 90 mg/kg/day group females

Special Evaluation (Transmission Electron Microscopy)

Samples of right lung were submitted necropsy from the following animals:
Group 1 males: 6288, 6289, 6292
Group 3 males: 6277, 6278, 6279
Group 1 females: 6418, 6431, 6440
Group 2 females: 6407, 6424, 6429
The samples were inventoried (b) (4) and transferred to the (b) (4) for processing for TEM and preparation of electron photomicrographic images under the direction of (b) (4)
Results:
"The administration of ACP-103 orally (by gavage) to rats for 26 weeks was associated with the accumulation of concentric lamellar inclusions in lysosomes in the cytoplasm of alveolar macrophages and other cells in the lungs (type 2 pneumocytes, lymphocytes and bronchial submucosal glands). The accumulation of concentric lamellar inclusions in the lung samples of these animals was considered to be consistent with drug-induced phospholipidosis."

Toxicokinetics

Exposure to ACP-103 and metabolite AC-260279 was up to 2-fold higher in females compared to males at the same dose level. While exposure to metabolite AC-269527 was similar in males and females and exposure to metabolite AC-260423 was higher in males as compared to females. Exposure (AUC) to parent and metabolite AC-260279 were not dose-dependent and increased nonlinearly relative to increase in dose for males. Exposure was less than dose-proportional for metabolites AC-269527 and AC-260423 for males. Exposure comparisons could not be made for females due to blood collections for each dose not collected on the same days. Blood samples from TK satellite animals were collected from 3 rats/sex/group at 0.5, 1, 2, 4, 8, and 24 hrs after dosing on study days 0, 92 (90 mg/kg/day females only), and 182 and from 3 rats/sex in the control group on study days 0 and 182 at 2 hrs after dosing.

Table 40: Toxicokinetics for ACP-103

	60 mg/kg/day		90 mg/kg/day	
	Males	Females	Males	Females
$AUC_{24\ hr}$ (ng•h/mL)				
Day 0	6820	7660	9410	9810
Day 92	NA	NA	NA	47,000
Day 182	15,900	30,700	29,800	NA
C_{max} (ng/mL)				
Day 0	466	482	590	480
Day 92	NA	NA	NA	2430
Day 182	872	1850	1530	NA
T_{max} (hr)				
Day 0	8.00	8.00	8.00	2.00
Day 92	NA	NA	NA	8.00
Day 182	8.00	1.00	8.00	NA

NA = Not applicable

Table 41: Toxicokinetics for metabolite AC-260279

	60 mg/kg/day		90 mg/kg/day	
	Males	Females	Males	Females
$AUC_{24\ hr}$ (ng•h/mL)				
Day 0	718	349	1010	470
Day 92	NA	NA	NA	12,300
Day 182	4260	8290	8330	NA
C_{max} (ng/mL)				
Day 0	48.0	19.2	62.3	26.6
Day 92	NA	NA	NA	600
Day 182	257	493	452	NA
T_{max} (hr)				
Day 0	8.00	8.00	8.00	24.0
Day 92	NA	NA	NA	1.00
Day 182	2.00	1.00	2.00	NA

NA = Not applicable

Table 42: Toxicokinetics for metabolite AC-260423

	60 mg/kg/day		90 mg/kg/day	
	Males	Females	Males	Females
$AUC_{24\ hr}$ (ng•h/mL)				
Day 0	19,800	3350	20,400	4050
Day 92	NA	NA	NA	7760
Day 182	20,900	5210	26,800	NA
C_{max} (ng/mL)				
Day 0	1380	193	1330	201
Day 92	NA	NA	NA	380
Day 182	1240	271	1490	NA
T_{max} (hr)				
Day 0	8.00	8.00	8.00	2.00
Day 92	NA	NA	NA	1.00
Day 182	8.00	8.00	2.00	NA

NA = Not applicable

Table 43: Toxicokinetics for metabolite AC-269527

	60 mg/kg/day		90 mg/kg/day	
	Males	**Females**	**Males**	**Females**
$AUC_{24\ hr}$ (ng•h/mL)				
Day 0	239	189	239	211
Day 92	NA	NA	NA	751
Day 182	414	463	702	NA
C_{max} (ng/mL)				
Day 0	16.6	12.3	15.6	10.2
Day 92	NA	NA	NA	34.4
Day 182	25.8	23.0	37.0	NA
T_{max} (hr)				
Day 0	8.00	8.00	8.00	2.00
Day 92	NA	NA	NA	8.00
Day 182	8.00	4.00	8.00	NA

NA = Not applicable

Dosing Solution Analysis

All dose formulations were found to contain (b)(4)% to (b)(4)% of test article which is within the target concentration range. No drug was detected in any vehicle formulation.

6.2.3.1 Monkey MTD + 7-day

Study no. HTI1001

Study Title: Oral (gavage) maximum tolerated dose (MTD) and 7 day repeat dose study in the primate (conducted in a GLP laboratory, but not formally monitored by a Quality Assurance Unit)

Conducting laboratory: (b) (4)

Design:

Phase 1: one male and one female cynomolgus monkey were administered ACP-103 (lot no. 078/81, 96.7%) once by oral gavage at increasing dose levels. ACP-103 was reconstituted as a solution in the vehicle of 0.9% saline. The dose on day 1 was 5 mg/kg which was then increased every 3-4 day up to 180 mg/kg.

Phase 2: One male and one female monkey were dosed once daily for 8 days in total. A dose of 135 mg/kg was administered on day 1, however due to vomiting in both animals this phase was restarted on day 2 at 100 mg/kg for 7 days.
Animals in both phases were observed through day 26.

Phase 1:

Group	Colour code	Animal numbers		Dose level (mg/kg/day) on days						
		Male	Female	1-4	5-7	8-11	12-14	15-18	19-21	22-26
1	Pink	101	100	5	10	30	40	64	90	180

Phase 2:

Group	Colour code	Animal numbers		Dose level (mg/kg/day)
		Male	Female	
2	Blue	103	102	135 (day 1 only)* 100 (days 2 to 8)*

* Phase 2 re-commenced at a reduced dose level of 100 mg/kg/day following vomiting on day 1 at 135 mg/kg/day

Parameters evaluated for both phases: clinical signs, body weights, hematology, clinical chemistry, urinalysis, gross necropsy and tissues were preserved. Blood samples were taken for toxicokinetic analysis on days 1 and 8 from phase 2 animals, but samples were not analyzed.

Results:

There was no mortality. Vomiting was the limiting factor in both phase 1 and phase 2. Vomiting or salivation occurred after dosing on days 22-25 for the male and on days 22-26 for the female (180 mg/kg dose) during phase 1. Vomiting also occurred on day 15 (64 mg/kg) for the female. Vomiting occurred on days 1-3 and 5 for the male and days 1-5 for the female during phase 2. The timing of the vomiting ranged from 20 minutes to 1 hour after dosing during phase 1 and 15 to 70 minutes after dosing in the female and 60 to 80 minutes after dosing in the male during phase 2. There was a general decrease in body weight during both phases, with the male losing 2.5% of original body

weight and the female losing 7.2% during phase 2. There was a slight to moderate increase in white blood cells (mainly neutrophils) in the male during phase 1 starting on day 12 (dosing over 30 to 180 mg/kg) compared to pre-dose levels. Total protein and albumin was reduced in both phase 1 animals compared to pre-dose levels following the 40 mg/kg and greater. There was also a slight decrease in total protein and albumin during phase 2. The only gross findings observed during necropsy was a red focus in the stomach of the phase 1 male and reddening of the stomach of the phase 2 female. These findings were most likely related to vomiting. The MTD was determined to be between 40 and 64 mg/kg based on vomiting at higher doses.

6.2.3.2 Monkey 28-day + 28-day recovery

Study no. HTI1003

Study Title: 28-day oral (gavage) repeat dose toxicity study in the cynomolgus monkey with toxicokinetic sampling and a 28 day recovery, GLP and QA

Conducting laboratory: (b) (4)

Design:

ACP-103, lot no. 090/24 (107587)

Doses: 0, 4.2, 21.2, 50.8 mg/kg/day pimavanserin free base

Vehicle: 0.9% saline

Cynomolgus monkeys (b) (4) 1-2 years old and weighed 1.98-2.51 kg for males and 1.94-2.45 kg for females the day before dosing commenced.

5/sex/control and high dose groups and 3/sex/low and mid dose groups.

2/sex/control and high dose groups were allowed to recover for 28-days after dosing stopped.

Parameters evaluated: clinical observations, body weights, hematology and clinical chemistry (adequate battery), urinalysis, ophthalmoscopy, ECG, gross pathology, organ weights and histopathology (adequate full battery of tissues and organs). Blood samples for toxicokinetic analysis were taken on days 1 and 28 at pre-dose and 0.5, 1, 2, 4, 8 and 24 hrs (only day 1) after dosing.

Results:

There was no mortality. There was an increased incidence of vomiting and salivation in high dose males and females, with a greater incidence in males. There was a decrease in body weight gain for high dose females compared to controls. Macroscopic findings of *spongy lungs* was observed in 1 low and mid dose females each and red focus(i) on the lungs in 1 high dose female. There was an increased incidence of alveolar macrophage infiltration (slight) in high dose males and females compared to controls. The findings were similar to controls after the recovery period (one incidence of focal alveolar macrophages in the lungs of a control male and one high dose female). There were no other drug-related findings.

Repeat-Dose Toxicity Main Study									
Daily Dose (mg/kg/day):		**0 (Control)**		**4.2**		**21.2**		**50.8**	
Number of Animals:		**M: 5**	**F: 5**	**M: 3**	**F: 3**	**M: 3**	**F: 3**	**M: 5**	**F: 5**
Toxicokinetics:									
C_{max} (ng/mL)	Day 1	-	-	64.4	65.9	440	371	550	591
	Day 28	-	-	50.6	57.1	399	357	669	710
AUC_{0-24h} (ng•h/mL)	Day 1	-	-	576	618	4830	3300	7030	8260
	Day 28	-	-	561	729	5120	3820	10200	12300

6.2.3.3 Monkey 3-month + 1-month recovery

Study no. (b) (4) 177.01

Study Title: A 3-month oral repeat-dose toxicity study of ACP-103 with Toxicokinetics and a 1-month recovery period in cynomolgus monkeys, GLP and QA

Conducting laboratory:

(b) (4)

Design:

Cynomolgus monkeys from (b) (4) stock, age 2-6 years old, weight prior to dosing: males: 2.382-2.966 kg, females: 2.223-3.109 kg.

Doses: 0, 5, 25, 60 mg/kg/day ACP-103 (pimavanserin tartrate) [0, 4.3, 21, 51 mg/kg/day pimavanserin free base) dosed once daily by nasogastric intubation for 3-months

Parameters evaluated in all animals: clinical observations (twice daily), food consumption (twice daily), body weight (once weekly), ECG (once each during weeks 6 and 13), ophthalmology (once each during weeks 6 and 13), urinalysis, hematology, coagulation and serum chemistry (once each during weeks 4 and 13, and last week of recovery), gross pathology, organ weight and histopathology (adequate battery). Blood samples for toxicokinetic analysis were taken from all animals on days 1, 45 and 90 at predose, and 0.5, 1, 2, 4, 8, and 24 hrs postdose.

Results:

There were no mortalities.

There was a dose-related increase in relative lung weights for both males and females at all dose levels, up to 59% and 20% compared to controls, respectively. At the end of the recovery period, lung weights were still increased to the same amount in males and females at 25 and 60 mg/kg/day. Epididymides, prostate/seminal vesicles and testes weights were slightly decreased, which corresponded to small organ sizes observed macroscopically, however theses effects were most likely due to immaturity of animals. Microscopic findings of foamy macrophages or cytoplasmic vacuolation, considered to be consistent with phospholipidosis, were observed in multiple tissues at 25 and 60 mg/kg/day. Foamy macrophages, consistent with PLD, were only observed in the lungs in males and females at the high dose of 60 mg/kg/day. There was full reversibility of these findings at 25 mg/kg/day in the recovery group animals, with some suggestion of partial but not complete reversibility at 60 mg/kg/day. The lung findings were not fully reversible.

NOEL = 5 mg/kg/day and sponsor considered 25 mg/kg/day to be the NOAEL

Repeat-Dose Toxicity Main Study								
Daily Dose (mg/kg/day):	**0 (Control)**		**5**		**25**		**60**	
Histopathology incidence (average severity score for animals with lesion: 1 (minimal) to 5 (severe)):								
Adrenal gland								
Vacuolization, Cytoplasm	0	0	0	0	3* (1.3)	1 (2.0)	3* (2.0)	3 (3.3)
Aorta								
Vacuolization, Cytoplasm	0	0	0	0	0	0	0	1 (1.0)
Epididymis								
Physiologic status, immature	3	NA	3	NA	1	NA	2	NA
Larynx								
Foamy macrophage(s)	0	0	0	0	0	0	0	2 (1.0)
Liver								
Focus/Area of cellular alteration	0	0	0	1 (2.0)	1 (1.0)	0	0	1 (2.0)
Vacuolization, cytoplasm	0	0	0	0	1 (1.0)	1 (1.0)	3* (1.7)	2 (2.0)
Lung								
Foamy macrophage(s)	0	0	0	0	0	0	3* (2.0)	3* (2.0)
Daily Dose (mg/kg/day):	**0 (Control)**		**5**		**25**		**60**	
Number of Animals:	**M: 5**	**F: 5**	**M: 5**	**F: 5**	**M: 5**	**F: 5**	**M: 5**	**F: 5**
Lymph nodes, mandibular								
Foamy macrophage(s)	0	0	0	0	0	0	3* (1.0)	3* (1.3)
Lymph node, mesenteric								
Foamy macrophage(s)	0	0	0	0	0	0	2 (1.0)	3* (1.0)
Pituitary gland								
Vacuolization, cytoplasm	0	0	0	0	0	0	1 (1.0)	1 (2.0)
Prostate								
Physiologic status, immature	3	NA	3	NA	2	NA	2	NA
Salivary gland, mandibular								
Vacuolization, cytoplasm	0	0	0	0	0	0	3* (2.3)	3* (2.3)
Seminal vesicle								
Physiologic status, immature	3	NA	3	NA	2	NA	2	NA
Small intestine, duodenum								
Foamy macrophage(s)	0	0	0	0	0	0	2 (1.0)	3* (1.3)
Small intestine, ileum								
Foamy macrophage(s)	0	0	0	0	0	0	2 (1.0)	2 (1.0)
Small intestine, jejunum								
Foamy macrophage(s)	0	0	0	0	0	2 (1.5)	3* (1.7)	3* (2.0)
Spleen								
Foamy macrophage(s)	0	0	0	0	1 (1.0)	0	3 (1.3)	3* (1.0)
Testis(es)								
Physiologic status, immature	3	NA	3	NA	2	NA	2	NA
Daily Dose (mg/kg/day):	**0 (Control)**		**5**		**25**		**60**	
Number of Animals:	**M: 5**	**F: 5**	**M: 5**	**F: 5**	**M: 5**	**F: 5**	**M: 5**	**F: 5**
Thymus								
Foamy macrophage(s)	0	0	0	0	0	0	0	2 (1.0)
Thyroid gland(s)								
Vacuolization, cytoplasm	0	0	0	0	0	1 (1.0)	0	2 (1.0)

ND = not detected
- no treatment-related findings
* Significantly different from control ($p \leq 0.05$)

Recovery group animals:

Repeat-Dose Toxicity Main Study								
Daily Dose (mg/kg/day):	**0 (Control)**		**5**		**25**		**60**	
Histopathology incidence (average severity score for animals with lesion: 1 (minimal) to 5 (severe)):								
Adrenal gland(s)								
Vacuolization, cytoplasm	0	0	0	0	0	0	2 (1.5)	1 (2.0)
Liver								
Focus/area of cellular alteration	0	1 (1.0)	0	0	1 (3.0)	0	0	2 (1.5)
Vacuolization, cytoplasm	0	0	0	0	0	0	0	1 (1.0)
Lung								
Foamy macrophage(s)	0	0	0	0	0	0	2 (2.5)	1 (1.0)
Lymph node, mandibular								
Foamy macrophage(s)	0	0	0	0	0	0	2 (1.0)	0
Lymph node, mesenteric								
Foamy macrophage(s)	0	0	0	0	0	0	0	1 (1.0)
Pituitary gland								
Vacuolization, cytoplasm	0	0	0	0	0	0	0	1 (1.0)
Salivary gland, mandibular								
Vacuolization, cytoplasm	0	0	0	0	0	0	1 (1.0)	1 (1.0)
Thyroid gland(s)								
Foamy macrophage(s)	0	0	0	0	0	0	1 (1.0)	1 (2.0)

NA = not applicable; ND = not detected
- No treatment-related finding
* Significantly different from control ($p \leq 0.05$)

[The above histopathology tables are excerpted from the Toxicology Tabulated Summary section of NDA 207318.]

Toxicokinetics:
There was no clear gender difference in exposure values, with the exception females having higher exposure levels than males on day 1. Exposures increased greater than dose proportional from 5 to 25 mg/kg/day and roughly dose proportional from 25 to 60 mg/kg/day. Tmax values increased slightly with increasing dose.

Dose Level (mg/kg)	Gender	Day 1			Day 45			Day 90		
		Cmax (ng/mL)	AUClast (h•ng/mL)	Tmax (h)	Cmax (ng/mL)	AUClast (h•ng/mL)	Tmax (h)	Cmax (ng/mL)	AUClast (h•ng/mL)	Tmax (h)
5	Male	46	481	3	41	491	4	40	477	4
	Female	55	513	2	48	508	4	48	487	4
25	Male	365	4192	4	434	6318	6	445	6257	6
	Female	350	3771	4	446	6027	5	451	5775	5
60	Male	525	7081	4	810	15580	8	700	13540	7
	Female	988	12857	5	851	16231	6	916	16231	8

6.2.3.4 Monkey 12-month + 4-month recovery

Study title: A 12-month nasogastric gavage toxicity study of ACP-103 in cynomolgus monkeys followed by a 4-months recovery period

Study no.: (b) (4)-146-01
Study report location: EDR SDN 1
Conducting laboratory and location: (b) (4)
Date of study initiation: May 25, 2006
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: ACP-103 (b) (4) lot no. 981756, 100%

Key Study Findings

Pimavanserin tartrate caused a decrease in body weight independent of food intake, emesis, systemic phospholipidosis in multiple organs/tissues. The drug also caused histopathological findings in testes and epididymides with potential clinical relevance.
NOAEL = 5/25 mg/kg/day
AUC at 5/25 mg/kg/day = 6,680 ng.hr/ml in males and 6,230 ng.hr/ml in females

Methods

Doses:	0, 1/5, 5/25, 25/60 mg/kg/day pimavanserin tartrate (0, 0.9/4.3, 4.3/21, 21/51 mg/kg/day pimavanserin free base) Doses were increased from 1, 5 and 25 mg/kg/day on day 43 to 5, 25 and 60 mg/kg/day
Frequency of dosing:	Once daily
Route of administration:	Nasogastric gavage
Dose volume:	2 ml/kg
Formulation/Vehicle:	0.9% sodium chloride for injection, USP
Species/Strain:	Monkey/Cynomolgus from (b) (4) stock animals following study approval.
Number/Sex/Group:	6/sex/group 2/sex/group for 3-month recovery
Age:	At pre-study physical examination: males: 3.4-9.5 years old, females: 4.2-7.3 years old
Weight:	At pre-study physical examination: males: 2.32-6.49 kg, females: 2.09-4.17 kg
Satellite groups:	2/sex/group from main study were held for a 3-month recovery period
Unique study design:	All animals were dosed for 12 months. 4/sex/group were sacrificed after 12-months of dosing (terminal necropsy day 365) and the remaining 2/sex/group were allowed to recover from dosing for 3-months then sacrificed at recovery necropsy (day 477 or recovery day 113)
Deviation from study protocol:	Several deviations were listed, but there were no impacts on the integrity of the data.

Observations and Results

Mortality

Two animals were found dead; one group 4 (25/60 mg/kg/day) male on day 54 and one group 4 female on day 149. The male died shortly after dosing and did not show any abnormal clinical signs on the day of death or any days preceding death. Based on gross pathology and histopathology, the cause of death was determined to be accidental (dosing error). The macroscopic findings included: moderately dark-red lungs with a large amount of light-red foam in the trachea, a small amount of light-red staining on the skin around the mouth and nose and moderately dark-red mucosa of the stomach. Microscopic findings included: moderate edema and congestion in the lungs. The female that died on day 149 had liquid feces on days 147 and 148 and sporadic emesis on days 10, 22, 66 and 122. Macroscopic findings included watery contents in the large intestine. Microscopic findings included: mildly dilated crypts containing cell debris and mild neutrophil infiltration in the lamina propria of the large intestine (colon

and rectum), increased granulopoiesis and relatively decreased erythropoiesis and megakaryopoiesis in the bone marrow, decreased zymogen granules in the pancreas, decreased glycogen in the hepatocytes and decreased lipids in the adrenals, bile in the bile canaliculi of the liver, atrophy of the thymus, decreased lymphocytes in germinal centers of the lymph nodes and spleen. The cause of death was determined to be colitis of an undetermined etiology. The majority of the microscopic findings in this animal were considered to be due to colitis.

Clinical Signs

There was a dose-related increase in emesis, both number of animals affected and overall incidences, for females at all dose levels compared to controls and for males mainly at the high dose. Emesis was also observed in low and mid dose males; however the incidence was similar to the controls. Clinical observations were conducted twice daily, with the second observation taking place 2-4 hrs after dosing, during the dosing period and once daily during acclimation and recovery periods.

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Table 44: Incidence of emesis in monkeys

Incidence of emesis

Sex	Parameter	Group 1			Groups 2/6			Groups 3/5			Group 4		
		A	D	R	A	D	R	A	D	R	A	D	R
Male	No. of Animals [1]	1	2	0	2	4	0	1	2	0	2	4	0
	Incidence [2]	1	3	0	2	5	0	1	3*	0	2	19	0
Female	No. of Animals [1]	0	1	0	4	4	0	2	5	0	2	6	1
	Incidence [2]	0	1	0	4	8	0	2	15	0	3	39	2

A/D/R = Acclimation/Dosing/Recovery periods
[1]: Number of animals that showed emesis.
[2]: Number of days emesis was observed.
*: Including one retching

[The above table was excerpted from the sponsor's study report.]

Body Weights

Absolute body weight was slightly decreased for high dose males and females compared to controls during the entire dosing period, with the greatest decrease observed during the first 3 months of dosing, however did not reach statistical significance. There was a statistically significant decrease in body weight gain for high dose males, 75% compared to controls, during the first 91 days of dosing and a body weight loss of -2.208 kg for high dose females. Body weight gain was comparable to controls for high dose males and females from day 91 onwards and during the recovery period. Body weights were recorded once weekly throughout the study and on the day of scheduled necropsy.

Food Consumption

There were no drug-related effects on food consumption. Estimated food consumption (fed biscuits) was calculated twice per day.

Ophthalmoscopy

There were no drug-related findings. Eye exams were performed once during the acclimation period and once during weeks 12, 25 (groups 5 and 6) or 26 (groups 1-4) or 41 (groups 5 and 6) and 52 of the dosing period. Since no abnormalities were detected during the dosing period, exams were not conducted during the recovery period.

ECG

There were no drug-related findings. All ECGs were qualitatively and quantitatively within normal limits. ECGs were recorded once during the acclimation period and once during weeks 12, 25 (groups 5 and 6) or 26 (groups 1-4), 38 and 51 of dosing and once during week 16 of the recovery period. QT_c values were calculated using Bazett's formula.

Hematology

There were no clear drug-related, or statistically significant, changes in any hematology or coagulation parameters. Blood was collected from the cephalic saphenous or femoral veins of restrained, conscious animals. Samples were collected once during acclimation, once during weeks 26, 39 and 52 of the dosing period and once during week 16 of the recovery period. An adequate battery of hematology and coagulation parameters was evaluated.

Clinical Chemistry

There were no clear drug-related, or statistically significant, changes in any clinical chemistry parameters. Blood was collected from the cephalic saphenous or femoral veins of restrained, conscious animals. Samples were collected once during acclimation, once during weeks 26, 39 and 52 of the dosing period and once during week 16 of the recovery period. An adequate battery of hematology and coagulation parameters was evaluated.

Urinalysis

There were no drug-related findings. Urine was collected from overnight fasted animals once during acclimation, once during weeks 26, 39 and 52 of the dosing period and once during week 16 of the recovery period. An adequate battery of urinalysis parameters was evaluated.

Gross Pathology

There were no drug-related macroscopic findings in any animals at the terminal necropsies. The macroscopic findings observed in the two animals that were found dead are described in the mortality section.

Organ Weights

Relative testes weights were decreased (not statistically significant) in all dose groups (19-29% compared to controls), but not in a dose-related manner, therefore the toxicological significance is unknown. Relative lung weights were increased 22% and 21% compared to controls for high dose males and females, respectively (not statistically significant).

The following organs were weighed: adrenals, epididymides, kidneys, lungs (including bronchi), pituitary, spleen, thyroids (including parathyroids), thymus, brain (cerebrum, cerebellum and brain stem), heart, liver, ovaries, prostate/seminal vesicles, submandibular salivary glands, testes, uterus (body and cervix).

Histopathology

Adequate Battery: Yes

Peer Review: Yes

Histological Findings

Drug-related microscopic findings were observed in the lungs, stomach, small intestines (duodenum, jejunum or ileum), adrenal and submandibular glands of high dose (25/60 mg/kg/day) males and females at the end of the 12-month dosing period (main study animals). The findings were consistent with multi-organ phospholipidosis (foamy macrophages or foamy cytoplasm). Minimal to mild atrophy of the testes (bilateral, multifocal atrophy of seminiferous tubules) was also observed in 2/3 high dose males at the end of the dosing period. It is unclear if the findings in the testes are related to PLD. None of the above findings were observed in any of the high dose animals at the end of the 4-month recovery period, indicating complete reversibility.

Repeat-Dose Toxicity Main Study								
Daily Dose (mg/kg/day):	0		1/5[a]		5/25[a]		25/60[a]	
Number of Animals:	M: 6	F: 6	M: 6	F: 6	M:6	F: 6	M: 6	F: 6
Adrenal gland								
Foamy cytoplasm, zona reticulate cell	0/4	0/4	0/4	0/4	0/4	0/4	2/3	2/3
minimal	0/4	0/4	0/4	0/4	0/4	0/4	1/3	2/3
mild	0/4	0/4	0/4	0/4	0/4	0/4	1/3	0/3
Duodenum								
Foamy macrophage, lamina propria	0/4	0/4	0/4	0/4	0/4	0/4	2/3	1/3
minimal	0/4	0/4	0/4	0/4	0/4	0/4	2/3	1/3
Ileum								
Foamy macrophage, lamina propria	0/4	0/4	0/4	0/4	0/4	0/4	3/3	0/3
minimal	0/4	0/4	0/4	0/4	0/4	0/4	3/3	0/3

Repeat-Dose Toxicity Main Study								
Daily Dose (mg/kg/day):	**0**		**1/5[a]**		**5/25[a]**		**25/60[a]**	
Number of Animals:	**M: 6**	**F: 6**	**M: 6**	**F: 6**	**M:6**	**F: 6**	**M: 6**	**F: 6**
Jejunum								
Foamy macrophage, lamina propria	0/4	0/4	0/4	0/4	0/4	0/4	3/3	1/3
minimal	0/4	0/4	0/4	0/4	0/4	0/4	2/3	1/3
mild	0/4	0/4	0/4	0/4	0/4	0/4	1/3	0/3
Lung								
Foamy macrophage, perivascular and alveolar	0/4	0/4	0/4	0/4	0/4	0/4	2/3	2/3
mild	0/4	0/4	0/4	0/4	0/4	0/4	2/3	2/3
Stomach								
Fundus-Foamy macrophage, lamina propria	0/4	0/4	0/4	0/4	0/4	0/4	0/3	1/3
mild	0/4	0/4	0/4	0/4	0/4	0/4	0/3	1/3
Pylorus-Foamy macrophage, lamina propria	0/4	0/4	0/4	0/4	0/4	0/4	0/3	1/3
minimal	0/4	0/4	0/4	0/4	0/4	0/4	0/3	1/3
Submandibular gland								
Foamy cytoplasm, epithelial cell, duct	0/4	0/4	0/4	0/4	0/4	0/4	3/3	3/3
minimal	0/4	0/4	0/4	0/4	0/4	0/4	3/3	3/3
Testes								
Multifocal atrophy, seminiferous tubule, bilateral	0/4	NA	0/4	NA	0/4	NA	2/3	NA
minimal	0/4	NA	0/4	NA	0/4	NA	1/3	NA
mild	0/4	NA	0/4	NA	0/4	NA	1/3	NA

[a] Dose levels 1, 5 and 25 mg/kg/day from Day 1 to Day 42 and 5, 25 and 60 mg/kg/day from Day 43 to Day 364. NA=Not applicable; - No noteworthy finding.
* Significantly different from control ($p \leq 0.05$)
§ Death was unrelated to test article.

[The above tables were excerpted from the Toxicology Tabulated Summary of NDA 207318.]

Mild "fibrous thickening" was observed in the lungs of one low dose and one high dose male at the end of the dosing phase (primary necropsy). Similar findings were not observed in any control animals or in any of the recovery group animals. The sponsor did not comment on this finding in the study report. Since fibrosis was observed in the lungs of rats after 6-months of a drug-free period in a 6-month chronic repeat-dose toxicity study (study no. (b) (4) 616007) this finding in monkeys may possibly be drug-related and represent permanent tissue damage as a result of severe phospholipidosis. An information request was sent to the sponsor regarding the "fibrous thickening" in these 2 animals, specifically asking about the clinical relevance and similarity to the rat findings and historical control data. The sponsor responded to the information request (SDN 7) on October 14, 2015. They provided "preliminary" control background data for fibrosis and fibrous thickening in cynomolgus monkeys from this particular laboratory and indicated that it is approximately 10.3% in males and 6.4% in females (or 8.4% in males and females combined; n=~125/sex). The incidence of fibrous thickening in this study was 6.25% (2 out of 32 terminal/found dead animals) and was therefore considered to be comparable to the background rate. The final background data is being processed and will not be available until near the end of the first half of 2016. The sponsor also stated that the study pathologist (b) (4) confirmed that the fibrous thickening in monkeys is not analogous to lung fibrosis and was mild in severity and without any clinical correlates. Based on this information, this reviewer acknowledges that the fibrous thickening observed in monkeys is likely to be incidental and represents a background finding. Nevertheless, since it was only observed in drug-treated animals it is possible that it is drug-related. The only way to know for certain is if more studies were to be conducted.

It is noted that multi-organ phospholipidosis (foamy macrophages, or vacuolation) was observed in the adrenal glands, small intestines, spleen and thyroid at a dose of 25 mg/kg/day in monkeys administered ACP-103 for 3-months (study no. (b) (4) 177-01). It is unclear why evidence of phospholipidosis was not present in this study at the same dose (5/25 mg/kg/day) after 12-months of dosing. A possibility could be the difference in age of the monkeys (slightly older in the 12-month study, and/or different source of monkeys).

The sponsor requested an outside expert review of the testes and epididymides from the two high dose males with testicular findings and expert opinion on the likely functional impact of the findings. Expert consultant pathologist in reproduction, (b) (4) examined the testes and epididymides slides from the two high dose males (animal numbers 36 and 44) and from the four dosing phase control males. Organ weights of testes, epididymides, prostate plus seminal vesicles along with terminal body weights and age of the animals at study start were also provided for the above listed 6 animals. In brief, the conclusion was that the effects in epididymides and prostate appear to be drug related.

The following is an excerpt from (b) (4) evaluation:

> In comparison with controls, the testes of the two Group 4 males were noticeably smaller when viewed subgrossly on the microscope slide. Microscopic changes in the testes of these two animals showed hypospermatogenesis, characterized by reduced numbers of developing germ cells, particularly elongating and maturation phase spermatids and reduced diameter of seminiferous tubules. The testes of animal 44 were more depleted of germ cells than animal 36. The cauda epididymides of both animals contained very few sperm and the ducts were contracted. The luminal contents of animal 44 also contained sloughed germ cells and cell debris from the testes. The findings in the testes and epididymides correlated with decreased absolute organ weights of testes and epididymides in these two animals compared with all the control males and the severity of the changes was also reflected by the degree of lower organ weight in the two affected animals. The findings were not associated with any obvious decreases in prostate and seminal vesicle weight.
>
> In the absence of evidence that these two Group 4 animals were less mature than the other animals on study, it must be assumed that the findings in the testes and epididymides are related to administration of ACP-103. Based on the profile of changes in the testes of decreased sperm production, and the evidence of decreased sperm content in the cauda epididymides, the functional impact is very likely to be reduced fertility. However, the fact that spermatogenesis appeared to be proceeding relatively normally, albeit at a much reduced efficiency, in a high proportion of tubules suggests this change may be readily reversible (but this would need to be confirmed).

Toxicokinetics

Blood samples for toxicokinetic analysis of ACP-103 were collected from animals on days 1, 182, 273 and 364 at pre-dose and 0.5, 1, 2, 4, 8, and 24 hrs postdose. Exposure values increased greater than dose-proportional from the low to mid dose and roughly dose-proportional from the mid to high dose for both males and females. There was no significant gender difference in exposure values. Accumulation ratios could not

be calculated since the doses were changed during the course of the study, however there did not appear to be much evidence of any drug accumulation over time.

Table 45: Toxicokinetic profile for ACP-103 in plasma of male monkeys

Study Days	Parameters	Dose (mg/kg/day) [a]		
		1	5	25
D1	T_{max} (h)	3.33	4.33	5.00
	C_{max} (ng/mL)	9.78	51.8	329
	$AUC_{(0-24h)}$ (ng·h/mL)	93.4	615	3620
		5	**25**	**60**
D182	T_{max} (h)	2.67	4.67	4.90
	C_{max} (ng/mL)	78.7	535	874
	$AUC_{(0-24h)}$ (ng·h/mL)	838	7790	17200
D273	T_{max} (h)	3.00	4.00	5.70
	C_{max} (ng/mL)	74.3	497	906
	$AUC_{(0-24h)}$ (ng·h/mL)	816	6770	17600
D364	T_{max} (h)	4.67	4.00	3.60
	C_{max} (ng/mL)	69.1	493	811
	$AUC_{(0-24h)}$ (ng·h/mL)	863	6680	15000

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[a]: Dose levels 1, 5 and 25 mg/kg/day from D1 to D42 and 5, 25 and 60 mg/kg/day from D43 to D364.
T_{max}: Time to reach peak or maximum concentration
C_{max}: Maximum plasma concentration
$AUC_{(0-24h)}$: Area under the concentration-time curve over the period of 0-24 hours

Table 46: Toxicokinetic profile for ACP-103 in plasma of female monkeys

Study Days	Parameters	Dose (mg/kg/day) [a]		
		1	5	25
D1	T_{max} (h)	2.67	3.33	5.00
	C_{max} (ng/mL)	6.72	51.8	339
	$AUC_{(0-24h)}$ (ng·h/mL)	67.7	526	3840
		5	**25**	**60**
D182	T_{max} (h)	3.00	5.67	3.20
	C_{max} (ng/mL)	65.2	407	930
	$AUC_{(0-24h)}$ (ng·h/mL)	669	5890	16300
D273	T_{max} (h)	3.33	3.67	4.80
	C_{max} (ng/mL)	65.8	546	1030
	$AUC_{(0-24h)}$ (ng·h/mL)	729	6120	18200
D364	T_{max} (h)	3.33	4.00	4.80
	C_{max} (ng/mL)	53.9	451	900
	$AUC_{(0-24h)}$ (ng·h/mL)	585	6230	15200

[a]: Dose levels 1, 5 and 25 mg/kg/day from D1 to D42 and 5, 25 and 60 mg/kg/day from D43 to D364.
T_{max}: Time to reach peak or maximum concentration
C_{max}: Maximum plasma concentration,
$AUC_{(0-24h)}$: Area under the concentration-time curve over the period of 0-24 hours

Dosing Solution Analysis

All formulation concentrations were within the acceptable range of (b) (4)% of nominal except for two samples intended to be 12.5 mg/ml only on two days, which were (b) (4)% and (b) (4)%. Concentrations in those groups were within the specification for all other time points, and it was not considered to have affected the study. No test article was detected in any control samples.

7 Genetic Toxicology

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

Study title: Bacterial Reverse Mutation Test

Study no.:	NTO0001
Study report location:	EDR SDN 1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	May 17, 2002
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	APC-103, batch no. 090/15, 99.7%

Key Study Findings

The assay was adequately conducted and negative. APC-103 was found to be non-mutagenic under the conditions of this assay.

Methods

Strains:	*Salmonella typhimurium* strains TA1535, TA1537, TA98, TA100 and *E. coli* strain WP2 *uvrA*
Concentrations in definitive study:	Plate incorporation method –S9: 0, 0.32, 1.6, 8, 40, 120, 200 µg/plate Plate incorporation method +S9: 0, 1.6, 8, 40, 200, 500, 600, 1000 µg/plate Pre-incubation method –S9: 0, 1.6, 8, 40, 120, 200 µg/plate Pre-incubation method +S9: 0, 1.6, 8, 40, 200, 500 µg/plate
Basis of concentration selection:	A range-finding assay was conducted using concentrations of 8, 40, 200, 1000, and 5000 µg/plate in strains TA98 and WP2 *uvrA*. In strain TA98 in the absence of S9, a slight reduction in the background lawn was observed at 40 µg/plate and a complete absence of growth in the background lawn at 200 and 1000 µg/plate, indicating cytotoxicity. Cytotoxicity, as indicated by no growth in the background lawn, was also observed at concentrations of 1000 µg/plate and higher in strains TA98 and WP2 *uvrA* +S9, and at a concentration of 5000 µg/plate in WP2 *uvrA* –S9.
Negative control:	0.9% w/v saline
Positive control:	Without metabolic activation (S9): TA1535, TA100: Sodium azide 1 µg/plate TA1537: 9-aminoacridine 50 µg/plate TA98: 2-nitrofluorene 0.5 µg/plate WP2 *uvrA*: 4-nitroquinoline-N-oxide 1 µg/plate With metabolic activation (S9): All strains used 1-aminoanthracene at 2 µg/plate, WP2 *uvrA* at 10 µg/plate
Formulation/Vehicle:	0.9% w/v saline up to 50 mg/ml
Incubation & sampling time:	Both the plate incorporation method and pre-incubation method were used. For both methods, plates were incubated at 37 °C for ~65 hours.

Study Validity

All doses were tested in duplicate for the range-finding assay and in triplicate for the definitive assay. All negative and positive control values were within the historical control range for this laboratory, and all positive controls produced an increase in

revertant colonies within the expected range. Two independent definitive assays were performed, one using the plate incorporation method and the other using the pre-incubation method both with and without metabolite activation (rat liver S9). The liver microsomal fraction (S9) was prepared immediately before use according to the method of Ames *et al.* from male Fischer 344 rats induced with a single dose of Aroclor 1254. The concentrations tested in the definitive assays were acceptable based on cytotoxicity (marked reduction in the background lawn growth) at higher concentrations observed in the dose range-finding assay.

Results

Slightly reduced background lawns were observed at concentration levels of 500 or 600 µg/plate and higher. There was no statistically significant increase in the number of revertant colonies at any concentration of APC-103 in any experiment either in the presence or absence of metabolic activation. Therefore, under the conditions of this assay, APC-103 is considered non-mutagenic.

7.2 *In Vitro* Assays in Mammalian Cells

Study title: In vitro mammalian cell gene mutation tests: point mutation in mouse lymphoma (L5178Y) cells

Study no.:	NTO0002
Study report location:	EDR SDN 1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	May 17, 2002
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	APC-103, batch no. 090/15, 99.7%

Key Study Findings

The study was adequately conducted and negative. APC-103 was considered non-mutagenic under the conditions of this assay.

Methods

Cell line:	L5178Y TK± Mouse lymphoma cells originally obtained from (b) (4) the supplier was not listed.
Concentrations in definitive study:	Experiment 1: +S9: 2.8, 5.6, 11.2, 22.3, 25.1 µg/ml -S9: 2.8, 5.6, 11.2, 13.9, 16.7 µg/ml Experiment 2: +S9: 0.5, 2.5, 5, 10, 15 µg/ml -S9: 0.5, 1, 2, 4, 6 µg/ml
Basis of concentration selection:	The first range-finding assay was conducted using concentrations of 50, 250, 500, 1000, 5000 µg/ml +/- S9. A second assay used concentrations of 5, 10, 25, 50,

	100 µg/ml +/- S9. A third assay used concentrations of 5, 10, 15, 20, 25 µg/ml +S9; 3, 6, 8, 10, 15 -S9 for a 3 hr incubation or 2, 4, 6, 8, 10 µg/ml -S9 for a 24 hr incubation.
Negative control:	1% (v/v) of 0.9% (w/v) saline.
Positive control:	-S9: Ethyl methanesulphonate (EMS): 250, 500 and 750 µg/ml +S9: methylcholanthracene (MCA): 5 µg/ml and benzo (a) pyrene (BP): 15 µg/ml
Formulation/Vehicle:	Solution in 0.9% (w/v) saline
Incubation & sampling time:	In the first experiment, drug treatment was for 3 hours both with and without metabolic activation (S9). In the second experiment, drug treatment was for 3 hours with S9 and for 24 hours without S9.

Study Validity

Two independent experiments were conducted. The negative and positive control values were within the range of the historical control values for this laboratory. The drug solutions did not cause any significant changes in pH or osmolality that could result in artificial aberrations.

Results

Cytotoxicity (severe toxicity/precipitation that prevented cells from being plated) was observed at concentrations ≥25.1 µg/ml in the presence of metabolic activation (S9) and at ≥16.7 µg/ml in the absence of S9. The concentrations selected for mutation frequency assessment in experiment 1 ranged from 2.8-22.3 µg/ml in the presence of S9 and produced relative total growth (RTG) values between 1-82%; and ranged from 2.8-13.9 µg/ml in the absence of S9 producing RTG values between 1-55%. RTG values in experiment 2 at concentrations used for mutation frequency assessment ranged from 3-116% and 22-112% in the presence and absence of S9, respectively. There was no statistically significant increase in mutation frequency or small colony frequency at any dose level of ACP-103 either in the presence or absence of metabolic activation in both experiments. ACP-103 is considered to be non-mutagenic under the conditions of this assay.

Assay 1					
Metabolic Activation	**Test Article**	**Dose Level (µg/mL)**	**Relative Total Growth (%)**	**Mutation Frequencies**	**Small Colony Frequencies**
Without Activation (-S9):	ACP-103	0	-	1.56E-04	1.07E-05
		2.8	55	1.76E-04	2.15E-05
		5.6	42	1.56E-04	1.71E-05
		11.2	20	2.25E-04	2.90E-05
		13.9	1	1.53E-04	9.43E-06
	EMS	750	27	1.82E-03	1.78E-04
With Activation (+S9):	ACP-103	0	-	1.74E-04	1.33E-05
		2.8	82	1.64E-04	6.04E-06
		5.6	72	1.87E-04	1.64E-05
		11.2	45	1.97E-04	1.66E-05
		22.3	1	1.41E-04	1.83E-05
	BP	15	2	9.46E-04	3.73E-04
	MCA	5	34	7.61E-04	1.82E-04

Assay 2					
Metabolic Activation	Test Article	Dose Level (µg/mL)	Relative Total Growth (%)	Mutation Frequencies	Small Colony Frequencies
Without Activation (-S9):	ACP-103	0	-	1.75E-04	3.31E-05
		0.5	112	1.20E-04	1.41E-05
		1	109	1.13E-04	1.48E-05
		2	90	1.43E-04	1.37E-05
		4	20	1.72E-04	3.25E-05
	EMS	250	22	1.23E-03	1.80E-04
	EMS	500	0	2.56E-03	1.00E-03
With Activation (+S9):	ACP-103	0	-	1.41E-04	2.87E-05
		0.5	116	1.44E-04	2.96E-05
		2.5	91	1.31E-04	1.48E-05
		5	74	1.47E-04	3.34E-05
		10	52	1.70E-04	3.97E-05
		15	38	1.80E-04	3.78E-05
	BP	15	3	1.01E-03	5.24E-04
	MCA	5	35	8.00E-04	2.27E-04

[Tables excerpted from Toxicology Tabulated Summary section of NDA 207318.]

7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title: Mouse micronucleus test

Study no: NTO0003
Study report location: EDR SDN 1
Conducting laboratory and location: (b) (4)
Date of study initiation: May 17, 2002
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: APC-103, batch no. 090/15, 99.7%

Key Study Findings

The study was adequately conducted. ACP-103 was considered to be non-clastogenic under the conditions of this assay (at doses up to 500 mg/kg/day to male mice).

Methods

Doses in definitive study:	0, 200, 320, 500 mg/kg/day pimavanserin tartrate (0, 170, 272, 425 mg/kg/day pimavanserin free base)
Frequency of dosing:	Once a day for two consecutive days~24 hrs apart. Animals were sacrificed 24 hrs following the second dose.
Route of administration:	Oral gavage
Dose volume:	10 ml/kg
Formulation/Vehicle:	0.9% (w/v) saline
Species/Strain:	Mouse/CD1 (b) (4)
Number/Sex/Group:	7/group (males only for definitive study)
Satellite groups:	3 controls and 3 males dosed at 500 mg/kg for 2 days. Blood samples were taken at 2 and 4 hrs after dosing. *Plasma samples were not analyzed.
Basis of dose selection:	A range-finding study was conducted using 5 male and 5 female mice dosed by oral gavage with 500 and 800 mg/kg ACP-103 for 2 consecutive days and followed up for 48 hrs. All animals at 800 mg/kg had to be euthanized following the second dose. The MTD was determined to be 500 mg/kg.
Negative control:	0.9% (w/v) saline
Positive control:	Mitomycin C: 0.4 mg/ml, single i.p. injection and sacrificed 24 hrs following the single dose.

Study Validity

There were no adverse clinical signs observed in any control animals or 200 and 320 mg/kg/day drug-treated animals. Clinical signs observed in animals dosed at 500 mg/kg/day included rough coat in all animals and vocalizing in one animal. One animal was found dead following the second dose. An MTD was used in the definitive study, as 800 mg/kg was determined to be a lethal dose in the range-finding study. All negative and positive control values were within the acceptable historical control range for this laboratory.

Results

There was a statistically significant increase in the proportion of micronucleated PCEs at the low dose of 200 mg/kg/day. Since no increase was observed at any of the higher doses and the minimum mean value of micronuclei per 2000 PCE per animal was less than 5, this increase was not considered to be toxicologically relevant.
There was a statistically significant decrease in the PCE/NCE ratio at 500 mg/kg/day. The sponsor attributed this as an indication of drug-related toxicity to the erythrocyte. No other doses were affected. Since this was evidence of drug exposure, the plasma samples from the satellite animals were not analyzed for the presence of drug.

This reviewer agrees with the sponsor's conclusion that there is no overall evidence of clastogenicity following oral gavage administration of ACP-103 to male mice at doses up the MTD of 500 mg/kg.

Table 47: Mean Percentage Micronucleated-PCE's

Geometric Means for Percentage MN-PCE's with Corresponding 95 % Confidence Intervals

Time	Sex	Group				
		1 (Control)	2 (200 mg/kg)	3 (320mg/kg)	4 (500 mg/kg)	5 (MMC4)
24 hrs	Males	0.05 (0.027, 0.089)	0.15* (0.088, 0.248)	0.07 (0.039, 0.119)	0.10 (0.052, 0.169)	4.03*** (2.810, 5.770)

Key: * = p<0.05, *** = p<0.001
(Non-significant findings not marked)

Table 48: Mean Percentage of PCE/NCE

Mean Percentage PCE/NCE with Corresponding 95 % Confidence Intervals

Time	Sex	Group				
		1 (Control)	2 (200 mg/kg)	3 (320 mg/kg)	4 (500 mg/kg)	5 (MMC4)
24 hrs	Males	124.55 (110.1 139.0)	132.40 (117.9, 146.9)	117.62 (103.2, 132.1)	76.42*** (60.8, 92.0)	47.42*** (37.2,57.7)

Key: *** = p<0.001
(Non-significant findings not marked)

[The above tables were excerpted from the sponsor's study report]

7.4 Other Genetic Toxicity Studies

Impurities [redacted]

GLP Ames assays and GLP in vitro mammalian chromosome aberration tests were conducted with impurities [redacted] in order to qualify these two impurities above ICH limits for impurities in both drug substance and drug product. All assays were negative for potential genotoxicity.

All studies were GLP and QA and conducted at the following laboratory:

[redacted]

Impurity [redacted] (lot no. O251AS1, 99.69%) was tested in an Ames assay (study no. [redacted] 9600668) at concentrations up to [redacted] µg/plate in the presence and absence of microsomal activation (S9) in *Salmonella Typhimurium* strains TA1535, TA1537, TA98, and TA100 and *Escherichia Coli* strain WP2 *uvrA* using the plate incorporation method.

Standard positive controls were used at appropriate concentrations and the negative control and vehicle was DMSO. Three independent assays were conducted due to invalid results in a few strains in the initial two assays. The invalid results were due to either five consecutive non-toxic concentrations not being obtained and/or the mean revertant colony counts of the vehicle control being below the historical control range. Each assay was conducted using triplicate plates. The assays were adequately conducted. Precipitation was not observed at any dose level in any assay in the presence or absence of S9. Overall from all three assays, there was no significant increase in revertant colonies either in the presence or absence of S9 in any tester strain. Therefore, impurity (b) (4) is considered non-mutagenic under the conditions of this assay.

Impurity (b) (4) (lot no. KMA 1423, 99.4%) was tested in an Ames assay (study no. (b) (4) 9600721) at concentrations up to (b) (4) µg/plate in the presence and absence of microsomal activation (S9) in *Salmonella Typhimurium* strains TA1535, TA1537, TA98, and TA100 and *Escherichia Coli* strain WP2 *uvrA* using the plate incorporation method. A single assay was conducted using triplicate plates and was adequately conducted. Standard positive controls were used at appropriate concentrations and the negative control and vehicle was sterile water. Cytotoxicity (incomplete, or absent, background lawns of non-revertant colonies, or a reduction in the revertant colony counts) was observed at concentrations ≥ (b) (4) µg/plate in the absence of S9 in all strains and at concentrations ≥ (b) (4) µg/plate with strains TA1537 and TA100 in the presence of S9 and at concentrations ≥ (b) (4) µg/plate with strains TA1535, TA98, and WP2 *uvrA* in the presence of S9. No precipitation was observed. There was no significant increase in revertant colonies either in the presence or absence of S9 in any tester strain at any concentration tested. Therefore, impurity (b) (4) is considered non-mutagenic under the conditions of this assay.

Impurity (b) (4) (lot no. O251AS1, 99.69%) was tested in an in vitro mammalian chromosomal aberration test (study no. (b) (4) 9600802) using human peripheral blood lymphocytes at concentrations of impurity (b) (4) up to (b) (4) µg/ml ((b) (4) mM, the recommended limit dose according to ICH S2(R1)). The negative control and vehicle was DMSO. The positive control used in the absence of metabolic activation (S9) was mitomycin C and in the presence of S9 was cyclophosphamide. Cells were incubated either in the presence or absence of S9 for 4 hrs and in the absence of S9 for 21 hrs. The relative mitotic index was ≥75% at all concentrations analyzed for the 4 hr incubation tests and reached only 56% for the 21-hr incubation. However, since the highest concentration of test article used was the limit dose of (b) (4) mM; the lack of a 50% reduction in mitotic index is acceptable. The assay was adequately conducted. Cultures treated with impurity (b) (4) did not show any statistically significant increases in aberrant cells. There was no toxicity or test article precipitation. Impurity (b) (4) was considered non-genotoxic (not clastogenic) under the conditions of this assay.

Impurity (b) (4) (lot no. KMA 1423, 99.4%) was tested in an in vitro mammalian chromosomal aberration test (study no. (b) (4) 9600803) using human peripheral blood lymphocytes at concentrations of impurity (b) (4) up to (b) (4) µg/ml ((b) (4) mg/ml). The top

concentration is acceptable according to ICH S2(R1), as "the maximum top concentration recommended is (b) (4) millimolar (mM) or (b) (4) milligram (mg)/milliliter (mL), whichever is lower, when not limited by solubility in solvent or culture medium or by cytotoxicity". The negative control and vehicle was sterile water. The positive control used in the absence of metabolic activation (S9) was mitomycin C and in the presence of S9 was cyclophosphamide. Cells were incubated either in the presence or absence of S9 for 4 hrs and in the absence of S9 for 21 hrs. The assay was adequately conducted. Toxicity was observed at concentrations ≥ (b) (4) µg/ml in the 4 hr treatment in the absence of S9, and at concentrations ≥ (b) (4) µg/ml in the 21 hr treatment. Test article precipitation was observed at the end of the 4 hr treatment in the absence of S9 at a concentration of (b) (4) µg/ml and in the 4 hr treatment in the presence of S9 at concentrations ≥ (b) (4) µg/ml. Cultures treated with impurity (b) (4) did not show any statistically significant increases in aberrant cells. Impurity (b) (4) was considered non-genotoxic (not clastogenic) under the conditions of this assay.

Potential Genotoxic Impurities

Ames assays were conducted on four *potential* genotoxic impurities that were identified as genotoxic by *in silico* screening (Derek and Leadscope results). All Ames assays were GLP and adequately conducted up to current standards. The potential genotoxic impurities tested in Ames assays include: (b) (4) Potential impurities (b) (4) were all negative in their representative Ames assay and are therefore considered non-mutagenic. No further nonclinical testing is required for these 3 potential impurities, and they will be controlled according to ICH Q3C(R5).

Potential impurity (b) (4) was found to be mutagenic in an Ames assay, as it produced a significant increase in revertant colonies compared to controls in tester strains TA98, TA100 and WP2*uvrA* in the absence of metabolic activation (S9) and in strains TA98 and TA100 with S9 (study no. (b) (4) 9600580) (see sponsor's data table below). The sponsor has stated they will control impurity (b) (4) according to ICHM7 at ≤ (b) (4) µg/day, which is (b) (4) ppm for the MRHD of 34 mg pimavanserin (see section 2.5 above).

Metabolic Activation	Test Article	Concentration or Dose Level (µg/plate)	Revertant Colony Counts (Mean of 3 plates ± SD)
(b) (4)			

Metabolic Activation	Test Article	Concentration or Dose Level (µg/plate)	Revertant Colony Counts (Mean of 3 plates ± SD)
[redacted]			(b) (4)

Plate or background lawn: IL = incomplete lawn, NL = no lawn, nd = not determined, NA = not applicable
[a] N = 2, incomplete lawn in one plate.

[Tables excerpted from study report.]

8 Carcinogenicity

8.1 24-month rat

Study title: A 24-month oral (gavage) carcinogenicity study of ACP-103 in rats

Study no.:	(b) (4)-6160004
Study report location:	EDR SDN 1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	October 12, 2007
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	ACP-103 (pimavanserin tartrate), lot no. 1046433, 98.8%-100.3%
CAC concurrence:	Yes (meeting minutes faxed on October 17, 2007). See appendix for copy of meeting minutes.

Key Study Findings

- ACP-103 was not carcinogenic in males up to 30 mg/kg/day and in females up to 50 mg/kg/day pimavanserin tartrate. There were no drug-related neoplasms identified. The highest dose tested for males and females is approximately 7- and 12-fold respectively, the maximum recommend human dose (MRHD) of 34 mg pimavanserin free base based on mg/m^2.
- AUC values at 30 mg/kg/day for males and 50 mg/kg/day for females are 6,340 ng.hr/ml and 25,900 ng.hr/ml, respectively, which are 4-fold and 16-fold the MRHD based on AUC. The predicted AUC in humans at 34 mg pimavanserin is 1630 ng.hr/ml.
- AUC values for the major human metabolite, ACP-260279 (ACP-279), at the highest dose in males and females are 1,540 and 3,970 ng.hr/ml, respectively.

These are approximately 2 and 5 fold the predicted AUC for ACP-279 in humans at the MRHD of 34 mg pimavanserin of 847 ng.hr/ml.

- Systemic phospholipidosis (widespread in multiple organs) occurred in high dose males and females. Phospholipidosis-related mortality (excessive vacuolated macrophages in the lungs and adverse respiratory-related clinical signs) occurred in females at 50 mg/kg/day.
- Increased incidence of cardiomyopathy, secondary to the pulmonary phospholipidosis, occurred in females at 50 mg/kg/day.
- Females at 50 mg/kg/day also had open sores on the feet and nodules on the tails that corresponded to microscopic findings of ulcerative pododermatitis and cystic dilation of hair follicles, respectively.
- Adverse (>10%) decrease in body weight for males at 30 mg/kg/day and females at 50 mg/kg/day, compared to controls.
- The NOEL for systemic phospholipidosis in males is 10 mg/kg/day, which corresponds to an AUC of 1,140 ng.hr/ml and is 0.7-fold the MRHD of 34 mg pimavanserin (free base). The NOEL for systemic phospholipidosis and phospholipidosis-related morbidity/mortality in females is 15 mg/kg/day, which corresponds to an AUC of 3,200 ng.hr/ml and is 2-fold the MRHD of 34 mg pimavanserin (free base).

Adequacy of Carcinogenicity Study

The carcinogenicity study was adequately conducted according to the protocol and protocol amendments. No deviations impacted study integrity.

Appropriateness of Test Models

The species and strain used in the study (Sprague Dawley rat) is appropriate for long-term study and there is significant historical control data.

Evaluation of Tumor Findings

A separate statistical review was conducted by Dr. Hepei Chen from the Division of Biometrics.

Methods

Doses:	Males: 0, 0, 3, 10, 30 mg/kg/day pimavanserin tartrate (0, 0, 2.6, 8.5, 26 mg/kg/day pimavanserin free base) Females: 0, 0, 5, 15, 50 mg/kg/day pimavanserin tartrate (0, 0, 4.3, 13, 43 mg/kg/day pimavanserin free base)
Frequency of dosing:	Once daily
Dose volume:	10 ml/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	Deionized water
Basis of dose selection:	The 3- and 6-month repeat-dose toxicity studies were used for the basis of dose selection. The high doses were based on an MTD of body weight decrease for males and mortality for females. The doses used in the study were the doses recommended by the ECAC on (see ECAC meeting minutes in the appendix).
Species/Strain:	Rat/Sprague Dawley
Number/Sex/Group:	60/sex/group
Age:	6 weeks at dosing initiation
Animal housing:	Individually housed
Paradigm for dietary restriction:	NA
Dual control employed:	Yes (both controls were the same: deionized water)
Satellite groups:	Toxicokinetic: 15/sex/drug-treated groups, 6/sex/control groups. TK animals were dosed once daily for 365 consecutive days and blood collected for TK analysis on days 89, 182, and 364.
Deviation from study protocol:	None that affected the integrity of the study.

*All tables and figures excerpted from sponsor's study report, unless stated otherwise.

Observations and Results

Mortality

Due to the group size reaching 20 animals, dosing was stopped for group 5 males (30 mg/kg/day) on day 674 (week 96). On study day 708 (week 101), the surviving number of animals for this group reached 15, and the group 5 males were sacrificed. Dosing was discontinued for group 3 males (3 mg/kg/day) on study day 723 due to surviving animal numbers reaching 20. The sponsor received agreement from the division and the ECAC prior to the early termination and cessation of dosing for these groups. Percent survival for males at study week 101 were 33.3%, 30.0%, 43.1%, 41.7%, and 25.0% at 0, 0, 3, 10, and 30 mg/kg/day, respectively. Percent survival for females at study week 104 were 31.7%, 33.3%, 35.0%, 39.0%, and 42.4% at 0, 0, 5, 15, and 50 mg/kg/day, respectively. Although, there are no statistically significant effects on

survival rates at any dose level for males and females, there appears to be a trend for a decrease in survival for high dose males compared to controls (see figure 6 below). The statistical reviewer (Dr. Hepei Chen) confirmed that there is no statistically significant effect on survival for either males or females. However, it should be noted that a high incidence of clear drug-related deaths occurred in high dose females that were the result of severe phospholipidosis in the lungs with corresponding macroscopic findings and cardio-pulmonary-related clinical observations (see below).
Three of the most common causes of death were: undetermined, pituitary adenomas, and hibernomas and none of these were considered to be drug-related since a similar incidence was also observed in control animals. However, a high incidence of lung-related deaths was observed in females at 50 mg/kg/day and these were clearly drug–related (10 females or 28.6% of all early deaths). The cause of death/euthanasia in 10 high dose females was due to severe, excessive accumulation of vacuolated macrophages in the lungs. These females also had cardiopulmonary-related clinical signs (rales, blue exterminates and/or bodies, and few were gasping), and macroscopic findings in the lungs (pale, not fully collapsed, white areas and a few were mottled and/or firm). These deaths are clearly directly related to severe phospholipidosis in the lungs, which in turn impacted the animals general well-being and lead to mortality/morbidity.

Table 49: Incidence of Common Causes of death in rats from 24-month study

	Males					Females				
Group (mg/kg/day):	**0**	**0**	**3**	**10**	**30**	**0**	**0**	**5**	**15**	**50**
Animals [a]	**42**	**45**	**42**	**39**	**45**	**41**	**40**	**39**	**37**	**35**
Undetermined (number)	17	23	16	14	22	7	4	9	6	3
(% of all early deaths)	40.5	51.1	38.1	35.9	48.9	17.1	10.0	23.1	16.2	8.6
Adenoma, pars distalis	10	6	6	8	4	18	16	13	16	11
(% of all early deaths)	23.8	13.3	14.3	20.5	8.9	43.9	40.0	33.3	43.2	31.4
Hibernoma (all sites)	5	5	5	7	7	7	2	7	2	5
(% of all early deaths)	11.9	11.1	11.9	17.9	15.6	17.1	5.0	17.9	5.4	14.3
Lung, presence of vacuolated macrophages	0	0	0	0	0	0	0	0	0	10
(% of all early deaths)	0	0	0	0	0	0	0	0	0	28.6

[a] = Number of animals not surviving to the scheduled necropsy from each group.

Table 50: Survival at study weeks 25, 50, 80 and 104 (number and percent surviving)

	Males					Females				
Group (mg/kg/day)	0	0	3	10	30	0	0	5	15	50
Study Week										
25	59/60 98%	59/60 98%	58/58 100%	59/60 98%	59/60 98%	59/60 98%	60/60 100%	60/60 100%	60/60 100%	60/60 100%
50	56/60 93%	54/60 90%	54/58 93%	54/60 90%	49/60 82%	59/60 98%	59/60 98%	58/60 97%	59/60 98%	56/59 95%
80	49/60 82%	41/60 68%	41/58 71%	40/60 67%	36/60 60%	40/60 67%	48/60 80%	43/60 72%	43/59 73%	40/59 68%
101	20/60 33%	18/60 30%	25/58 43%	25/60 42%	15/60 25%	19/60 32%	23/60 38%	23/60 38%	24/59 41%	29/59 48%
104	18/60 30%	15/60 25%	18/58 31%	21/60 35%	NA	19/60 32%	20/60 33%	21/60 35%	23/59 39%	25/59 42%

NA = Not applicable

Text Table 1. Kaplan-Meier Estimates of Survival

	Males						Females					
Group (mg/kg/day)	0	0	3	10	30	(O)verall/ (T)rend	0	0	5	15	50	(O)verall/ (T)rend
Study Week												
52	90	90	93	88	82		95	98	95	98	95	
78	82	68	72	67	65		70	80	73	76	73	
92	52	48	48	53	38		52	48	57	54	59	
End of Study	30	25	29	35	25		32	33	35	39	42	
p-value (p)			NT	NT	NT	0.2576 (O) 0.3421 (T)			NT	NT	NT	0.8135 (O) 0.2147 (T)
p-value (1)		0.2496	NT	NT	NT	0.1795 (O) 0.1341 (T)		0.4911	NT	NT	NT	0.7346 (O) 0.2032 (T)
p-value (2)			NT	NT	NT	0.3147 (O) 0.5121 (T)			NT	NT	NT	0.9130 (O) 0.3731 (T)

p-values:
(p): Comparisons using pooled control
(1): Comparisons using control group 1
(2): Comparisons using control group 2
NT = Not tested per statistical methodology.
There were no significant findings

Figure 7: Percent Survival: Males

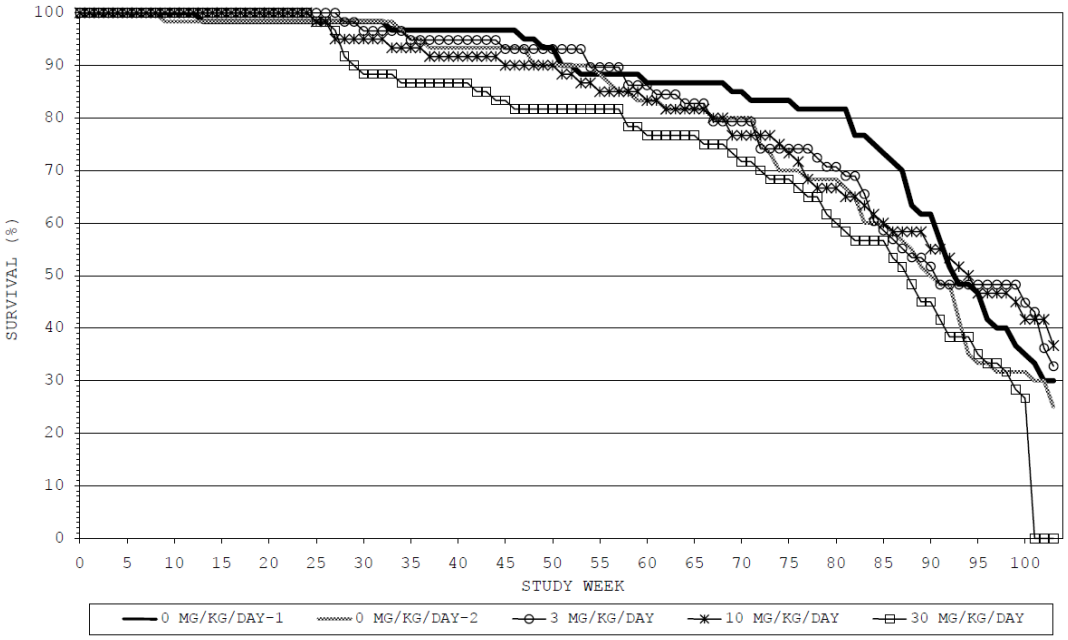
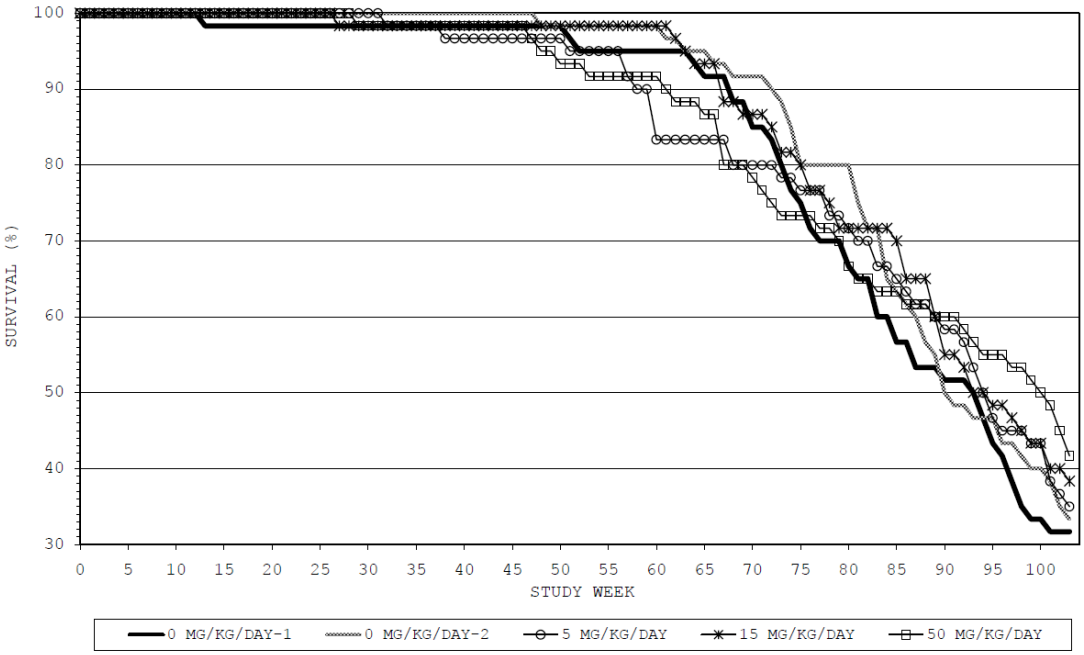


Figure 8: Percent Survival: Females



Clinical Signs

The observation of rales (noisy breathing) was observed in most all high dose males and females throughout the study at the time of detailed physical exams and during the daily observations at 1-2 hrs postdose. The incidence rate was slightly higher in females as compared to males. Gasping was also observed in a few drug treated males and females compared to none in control animals. Wet clear material and/or dried red

material around the mouth were also observed in most high dose males and female compared to only a few control animals. Several (7-10) high dose females were observed with blue extremities and/or blue bodies. Cage sores on the limbs and scabbing of the hindlimbs and tail were observed in many high dose females and correlated with macro- and microscopic findings. The respiratory-related clinical signs correlated with macro- and microscopic findings in the lungs of high dose males and females and were most likely related to an increase in phospholipids in the lungs due to drug-induced phospholipidosis.

Body Weights

There was a statistically significant decrease in absolute body weight for both males and females compared to controls. For males, mean body weights at study week 100 were 2.4%, 2.3%, and 14% lower compared to the combined control groups at 3, 10, and 30 mg/kg/day, respectively. The effect was more pronounced for low and mid dose males early in the study, up to week 64. For females, mean body weights at study week 104 were 6.3%, 9.1%, and 24% lower compared to the combined control groups at 5, 15, and 50 mg/kg/day, respectively. The decreases in weight correlated with a slight decrease in food consumption for males only.

Figure 9: Body weights: Males

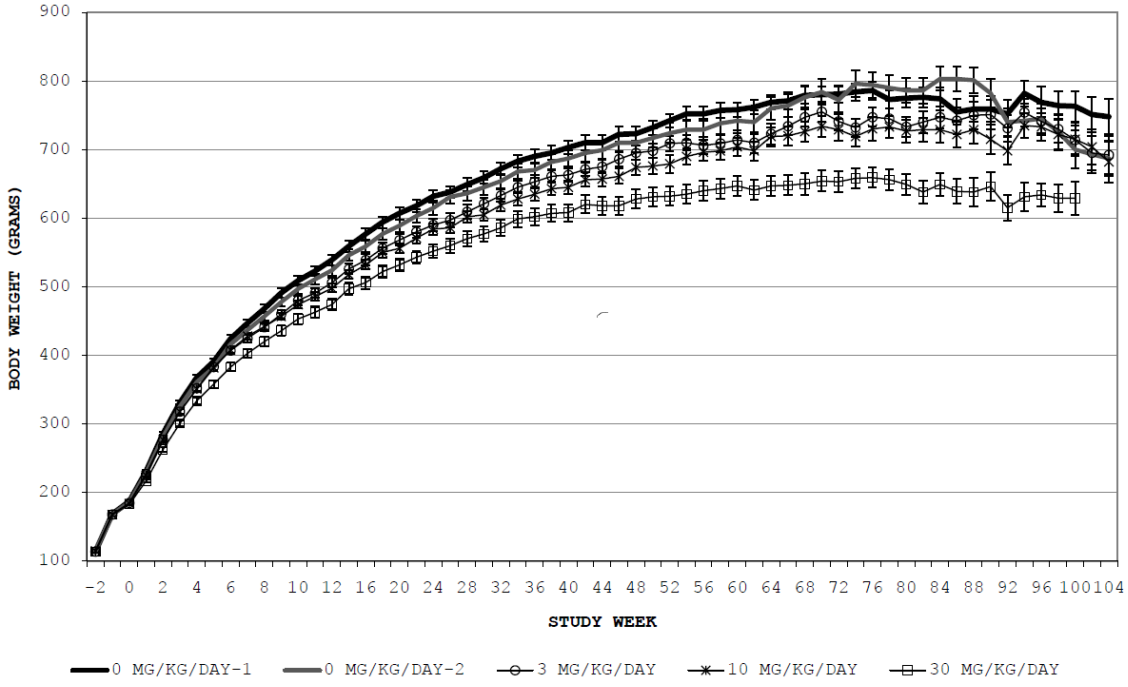
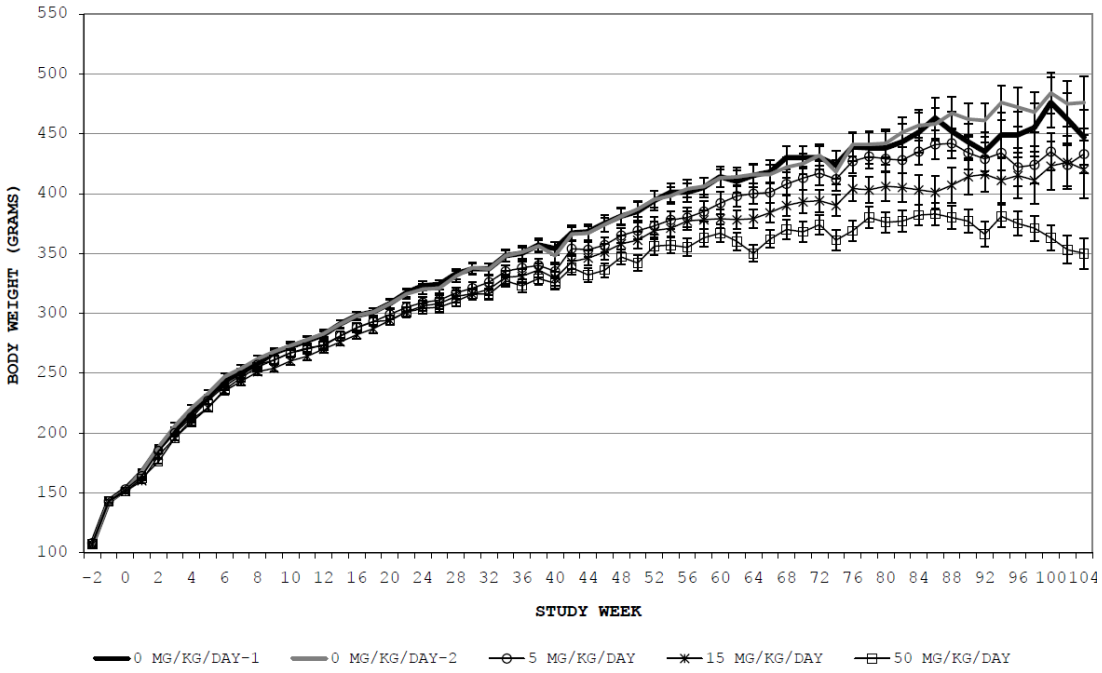


Figure 10: Body weights: Females



Food Consumption

Food consumption was lower for males at 30 mg/kg/day compared to both control groups starting the first week of dosing. At week 26, food consumption was significantly decreased for males at all dose levels 7% compared to group mean controls. Starting around study week 65-66, food consumption for males at 30 mg/kg/day was comparable to controls however; mean body weight continued to decrease. There was no drug-related effect on food consumption for males at 3 or 10 mg/kg/day or for females from any dose group.

Gross Pathology

Drug-related macroscopic findings were observed in the lungs of high dose males and females included lungs not fully collapsed and pale, and observations of mottled lungs, white areas and firm lungs were observed in high dose females only. High dose females also had an increased incidence of open sores on paws and nodules on the tail. The macroscopic findings in the lungs correlated with respiratory-related clinical signs and microscopic findings. The findings on the paws and tail also correlated with microscopic findings in high dose females.
There was no drug-relate effect on the number of animals with palpable masses compared to controls.

Table 51: Macroscopic findings in all rats from 24-month study

	Males					Females				
Group (mg/kg/day):	**0**	**0**	**3**	**10**	**30**	**0**	**0**	**5**	**15**	**50**
Animals [a]	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**
Lungs - Not fully collapsed	4	4	3	6	10	1	3	2	2	19
Lungs - Pale	1	1	0	0	2	0	1	2	1	14
Lungs - Mottled	1	0	0	0	1	0	0	0	0	4
Lungs - White area(s)	6	2	1	1	4	1	1	1	2	17
Lungs - Firm	0	0	0	0	0	0	0	0	0	3
Paws - Open sore(s)	29	26	21	26	35	6	9	5	8	21
Tail - Nodule(s)	27	20	18	19	21	10	10	2	14	27

[a] = Number of animals on study.

Histopathology

Peer Review: Yes. Peer review statement concludes that the pathology data and report reflect the consensus opinions of the study pathologist and the peer review pathologist.

Neoplastic:
No drug-related neoplastic findings were found in males or females from any dose group. A separate statistical review was conducted by Dr. Hepei Chen from the Division of Biometrics. Pituitary adenomas and hibernomas were listed as common causes of death however since a similar incidence was observed in control animals compared to drug-treated animals they were not considered to be drug-related.

Table 52: Statistical analysis of selected tumors (Statistical Reviewer's tables)

The following table was excerpted from the statistics review (Dr. Hepei Chen).

Table 2. Summary Table of Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship and/or Pairwise Comparisons of Treated Groups and Combined Control Group in Rats

Organ name	Tumor name	Vehicle Control 1	Vehicle Control 2	Combined V Cont (C) P - Trend	Low (L) P - C vs. L	Mid (M) P - C vs. M	High (H) P - C vs. H
Male							
Skin	#B Fibroma	0/(60)	0/(60)	0/78 (120) 0.1966	1/39 (60) 0.3333	3/39 (60) 0.0351 $	1/33 (60) 0.2973
Soft Tissue- Abd	#B Lipoma	0/(60)	0/(58)	0/77 (118) 0.7674	3/39 (60) 0.0361 $	0/39 (60) NC	0/33 (60) NC
Systemic Tumors	#M Lymphoma, Malignant	1/(60)	1/(60)	2/79 (120) 0.0373	2/39 (60) 0.4023	3/40 (60) 0.2098	4/34 (60) 0.0658
Testes	#B Adenoma, Interstitial Cell	1/(60)	1/(60)	2/79 (120) 0.2230	2/39 (60) 0.4023	2/39 (60) 0.4023	2/33 (60) 0.3379
	#B Adenoma, Interstitial Cell, Multiple	0/(60)	0/(60)	0/78 (120) 0.0300	0/38 (60) NC	0/39 (60) NC	2/33 (60) 0.0865
	#B Adenoma, Interstitial Cell + Multiple	1/(60)	1/(60)	2/79 (120) 0.0324	2/39 (60) 0.4023	2/39 (60) 0.4023	4/33 (60) 0.0610
	#M Carcinoma, Interstitial Cell	0/(60)	0/(60)	0/78 (120) 0.3830	1/38 (60) 0.3276	0/39 (60) NC	0/33 (60) NC
	#B+M Interstitial Cell	1/(60)	1/(60)	2/79 (120) 0.0488	3/39 (60) 0.2014	2/39 (60) 0.4023	4/33 (60) 0.0610
Female							
Cervix	#B Granular Cell Tumor, Benign	0/(60)	1/(60)	1/82 (120) 0.0486	3/42 (60) 0.1123	2/43 (60) 0.2719	4/42 (60) 0.0445
Cervix/Vagina	#B Granular Cell Tumor, Benign	0/(60)	1/(60)	1/82 (120) 0.0561	3/41 (59) 0.1074	3/43 (60) 0.1172	4/42 (60) 0.0445
Cervix/Vagina/Ovaries	#B Granular Cell Tumor, Benign	0/(60)	1/(60)	1/82 (120) 0.0797	4/42 (60) 0.0445	3/43 (60) 0.1172	4/42 (60) 0.0445

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
$ = Statistically significant at 0.025 and 0.05 level in rare tumor for tests of dose response relationship and pairwise comparison, respectively; NC = Not calculable.

The following is excerpted from the statistical review.

The tumor types with p-values less than or equal to 0.05 for dose response relationship and/or pairwise comparisons of treated groups and combined control are reported in Table 2.

Based on the criteria of adjustment for multiple testing discussed above, the reviewer's analysis showed that in males, the incidence rate of benign fibroma in skin for animals in mid dose group was significantly higher than incidence in the combined vehicle control group (p = 0.0351), if this tumor was considered as a rare tumor. Also in males, the incidence rate of benign lipoma in Soft Tissue-Abd for animals in the low dose group was significantly higher than incidence in the combined vehicle control group (p = 0.0361). In both of these two cases, because no significant trend was noted, and the high dose group did not indicate any significant increases, these increases in the low and mid-dose group were not considered to be test article-related.

No other observed tumor types were noted to be statistically significant for the dose response relationships or pairwise comparisons in both male and female rats.

Non Neoplastic:
Systemic cytoplasmic vacuolation consistent with widespread phospholipidosis was observed in multiple tissues/organs in 10 males at 30 mg/kg/day and in 45 females at 50 mg/kg/day. The sponsor defined systemic phospholipidosis as animals that *"have cytoplasmic vacuoles morphologically consistent with phospholipidosis; the extent of vacuolation had to exceed 'background' severity levels of concurrent control group tissues that may manifest cytoplasmic vacuolation due to other pathologic processes or altered physiology unrelated, but histopathologically similar to, phospholipidosis; and 2 or more tissues had to be affected".* All animals that were considered to have systemic phospholipidosis had findings in the lung.
The following description is an excerpt from the pathology report describing the microscopic findings in the lungs.
"With the exception of the lungs in the 50 mg/kg/day group females, the presence of cytoplasmic microvacuoles consistent with phospholipidosis within macrophages, parenchymal cells, or epithelial cells appeared to be innocuous. However, moderate to severe involvement of the lungs (by 'macrophages, vacuolated') was characterized by numerous microvacuolated to foamy alveolar macrophages admixed with abundant extracellular material that filled alveolar spaces. This extracellular material was similar in appearance to the cytoplasm of the vacuolated macrophages and was considered to represent macrophage lysis with release of cellular contents. The filling of confluent regions of the lungs with these macrophages and/or extracellular material commonly corresponded to the gross findings of not fully collapsed, pale, mottled, white areas and/or firm; severe cases were often considered to be the cause of death in found dead or moribund animals. In addition, the accumulation of this material in the lungs likely would have created an increased workload on the heart and was considered to be the most likely explanation for the increased incidence and severity of cardiomyopathy seen in the 50 mg/kg/day group females. There also were higher incidences of mixed inflammatory cell infiltrates seen surrounding blood vessels and/or bronchioles and inflammation within the lung parenchyma in the 50 mg/kg/day group females. Although similar changes were seen across all treatment groups (including control groups) from both sexes, the higher incidences seen in the 50 mg/kg/day group females seemed to be associated with many cases of moderate to severe infiltrates of vacuolated macrophages and were therefore considered test article-related effects. Also seen in the lungs, but at a lower incidence in both the 30 mg/kg/day group males and 50 mg/kg/day group females, was cytoplasmic vacuolation of bronchial and/or bronchiolar epithelial cells. Similar findings were often seen in the respiratory epithelium of the trachea. It is not known if involvement of the respiratory epithelium influenced muco-ciliary clearance of foreign material from the lungs and may have been a contributing factor to the moderate to severe accumulations of macrophages and material seen in the 50 mg/kg/day group females."
The open sores (cage sores) on the paws and nodules of the tail observed in several animals at necropsy, corresponded to ulcerative pododermatitis and cystic dilatation of hair follicles, respectively observed microscopically. However, since the tail and paws were not protocol-required tissues, they were only examined histologically if a gross lesion was present and the same trend seen at necropsy was present with the microscopic evaluations. The toxicological relevance of these findings is unknown.

Table below from sponsor, data for drug groups only.

Table 53: Prevalence of cytoplasmic vacuolation in organs from all animals

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	Males					Females				
Affected animals (range)	1-2	3-10	11-20	21-30	31+	1-2	3-10	11-20	21-30	31+
Lung										
Vacuolated (alveolar) macrophages[a]					X					X
Epithelium (airways)		X							X	
Liver - biliary epithelium		X								X
Epididymides - epithelium[a]					X					
Uterus - epithelium										X
Adrenal cortex[a]			X						X	
Trachea - epithelium		X								X
Kidney										
Tubular epithelium		X							X	
Pelvic epithelium	X						X			
Urinary bladder - epithelium	X							X		
Thyroid gland - follicular cells	X							X		
Parathyroid gland	X						X			
Pituitary gland	X						X			
Lymph nodes - macrophages	X						X			
Vagina/cervix - epithelium							X			
Bile duct - epithelium							X			
Pancreas - ductal epithelium	X					X				
Spleen - macrophages						X				
Marrow, femur - macrophages						X				
Mammary gland - epithelium						X				
Oviduct - epithelium							X			
Small intestine - epithelium						X				
Brain										
Choroid plexus						X				
Neurons	X									
Prostate - epithelium	X									
Testes - interstitial cells	X									
Spinal cord - neurons	X									
Heart - myocardium	X									
Skin - follicular epithelium	X									

[a] = Findings also commonly seen in control group animals of 1 or both sexes.

Table 54: Incidence of selected histopathological findings from all animals

	Males					Females				
Dosage (mg/kg/day):	**0**	**0**	**3**	**10**	**30**	**0**	**0**	**5**	**15**	**50**
Systemic Lesions [a]	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**
Vacuolation, cytoplasmic	0	0	0	0	10	0	0	0	0	45
Lung [a]	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**
Macrophages, vacuolated	20	22	21	22	33	20	19	11	19	56
Minimal	19	20	20	22	28	20	19	11	19	7
Mild	1	2	1	0	4	0	0	0	0	18
Moderate	0	0	0	0	1	0	0	0	0	21
Severe	0	0	0	0	0	0	0	0	0	10
Vacuolation, epithelium	0	0	0	0	6	0	0	0	0	30
Minimal	0	0	0	0	6	0	0	0	0	23
Mild	0	0	0	0	0	0	0	0	0	7
Infiltrate, mixed inflammatory cell	2	0	4	4	8	5	5	2	1	15
Minimal	2	0	4	4	6	5	5	2	0	14
Mild	0	0	0	0	2	0	0	0	1	1
Inflammation	10	2	5	4	9	5	5	3	4	14
Minimal	8	2	4	3	9	5	3	3	3	13
Mild	2	0	1	1	0	0	2	0	1	0
Moderate	0	0	0	0	0	0	0	0	0	1
Heart [a]	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**
Cardiomyopathy	51	52	51	46	49	31	41	37	40	52
Minimal	38	41	37	32	37	30	38	31	37	33
Mild	10	10	12	10	10	1	3	6	3	14
Moderate	3	1	2	3	2	0	0	0	0	4
Severe	0	0	0	1	0	0	0	0	0	1
Paws [a]	**32**	**27**	**25**	**29**	**35**	**11**	**11**	**6**	**9**	**24**
Pododermatitis, ulcerative	31	27	25	27	34	9	10	6	8	23
Minimal	8	11	9	5	7	5	7	1	5	11
Mild	10	7	7	9	12	3	1	4	3	10
Moderate	8	6	7	6	11	1	2	1	0	1
Severe	5	3	2	7	4	0	0	0	0	1
Tail [a]	**36**	**26**	**30**	**27**	**23**	**11**	**13**	**7**	**17**	**33**
Cyst, follicular (present)	35	26	25	25	20	8	10	3	13	28

[a] = Number of tissues examined from each group.

Toxicokinetics

Blood samples for toxicokinetic analysis of ACP-103, and metabolites AC-260279, AC-260423, and AC-269527 were taken from 3 animals/sex/group satellite animals on days 89, 182, and 364 at 0.5, 1, 2, 4, 8, and 24 hrs postdose and at 2 hrs postdose from control group animals. Metabolite AC-260279 (AC-279) was identified as major circulating metabolite in humans. Exposures to ACP-103 and metabolite AC-260279 increased much greater than dose-proportional for both males and females e.g. for the parent there was a 371-fold and 523-fold increase in exposure in females dosed 50 vs. 5 mg/kg/day and in males dosed 30 vs. 3 mg/kg/day. The half-life ($t_{1/2}$) for parent and all metabolites increased with increasing dose and also increased over time. Most significant was the half-life for ACP-103 in high dose females of 27 hrs on day 364. This

prolonged half-life could potentially lead to extensive uptake/accumulation in tissues/organs. There was very little, if any, drug accumulation for parent or metabolites in males and females after 3-months of repeat dosing, as exposures were similar on day 89 compared to day 364 indicating steady state was achieved by 3 months of repeated dosing. There is a marked difference in exposure and Cmax between sexes with higher levels in females relative to males.

Table 55: Toxicokinetic parameters of ACP-103 in rats

Day	Dose (mg/kg/day)		T_{max} (h)		C_{max} (ng/mL)		AUC_{24h} (ng•h/mL)		$t_{1/2}$ (hr)		AR	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
89	3	5	0.500	1.00	3.56	37.4	10.2	79.3	0.945	1.31	NA	NA
	10	15	2.00	4.00	57.6	260	567	2220	7.38	1.99	NA	NA
	30	50	4.00	8.00	436	1570	5350	29400	4.58	NC	NA	NA
182	3	5	1.00	2.00	8.44	26.6	13.9	69.6	0.747	0.890	1.37	0.877
	10	15	2.00	4.00	80.9	256	887	2940	2.87	2.35	1.56	1.32
	30	50	4.00	8.00	526	1710	6620	32000	5.54	NC	1.24	1.09
364	3	5	1.00	1.00	9.73	19.7	22.8	69.1	NR	1.44	2.24	0.871
	10	15	2.00	4.00	158	361	1140	3200	3.27	2.19	2.02	1.44
	30	50	4.00	4.00	571	1430	6340	25900	6.19	27.1	1.18	0.878

AR = Accumulation ratio (AUC_{24hr} [study day 364 or 182]/AUC_{24hr} [study day 89])
NA = Not applicable
NC = Not calculated due to insufficient data in the apparent terminal elimination phase
NR = Not reportable due to insufficient data in the apparent terminal elimination phase

Table 56: Toxicokinetic parameters of metabolites in rats

Day	Dose (mg/kg/day)		T_{max} (h)		C_{max} (ng/mL)		AUC_{24h} (ng•h/mL)		$t_{1/2}$ (hr)	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
AC-260279										
89	3	5	NA	NA	NA	NA	NA	NA	NA	NA
	10	15	2.00	4.00	6.91	12.6	89.5	91.4	NC	NC
	30	50	8.00	0.00	80.5	321	1000	5740	6.66	NC
182	3	5	NA	NA	NA	NA	NA	NA	NA	NA
	10	15	4.00	4.00	8.90	11.5	81.1	135	3.69	NC
	30	50	2.00	1.00	85.8	376	936	5820	4.28	NC
364	3	5	NA	1.00	NA	0.431	NA	0.768	NA	NC
	10	15	2.00	4.00	24.7	18.5	147	185	NR	NC
	30	50	4.00	4.00	100	314	1540	3970	12.9	13.1
AC-260423										
89	3	5	2.00	1.00	90.1	70.5	840	378	4.16	3.53
	10	15	4.00	2.00	352	209	3830	1360	4.04	3.73
	30	50	8.00	4.00	707	268	8790	5180	NC	28.7
182	3	5	4.00	2.00	105	59.2	992	316	4.44	3.64
	10	15	2.00	2.00	338	161	4040	1280	4.78	3.78
	30	50	8.00	4.00	771	249	10300	5170	7.18	41.0
364	3	5	4.00	2.00	140	56.2	1010	399	4.01	3.47
	10	15	4.00	2.00	378	163	3720	1630	4.78	5.90
	30	50	4.00	4.00	888	225	2100*	4540	NC	35.0
AC-269527										
89	3	5	1.00	1.00	0.358	3.21	2.99	19.1	4.25	2.88
	10	15	4.00	2.00	2.24	10.6	25.1	72.2	NC	4.87
	30	50	4.00	8.00	10.5	17.9	98.5	356	4.99	NC
182	3	5	1.00	1.00	0.661	3.83	3.99	20.0	5.54	3.00
	10	15	1.00	2.00	2.31	8.26	25.2	65.9	10.1	4.38
	30	50	4.00	8.00	10.9	17.2	110	367	4.94	NC
364	3	5	4.00	1.00	0.741	3.40	5.20	20.0	NC	3.51
	10	15	2.00	2.00	3.90	9.47	25.0	90.4	3.29	5.77
	30	50	4.00	4.00	12.9	19.1	125	307	7.32	13.7

* = AUC_{4hr}, NA = <LLOQ or not reportable at all time points or at all but one time point
NC = Not calculated due to insufficient data in the apparent terminal elimination phase
NR = Not reportable due to insufficient data in the apparent terminal elimination phase

Dosing Solution Analysis

Most of the analyzed dosing formulations were within [redacted] (b) (4) % of ACP-103 which is within the acceptable range. In a few instances, dosing formulations were slightly outside that range ([redacted] (b) (4) % and [redacted] (b) (4) %). Since the differences were slight, they were not considered to have had an impact on the study.

8.2 24-month mouse

Study title: A 24-month oral (gavage) carcinogenicity study of ACP-103 in mice

Study no.:	(b) (4)-616006
Study report location:	EDR SDN 1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	December 4, 2007
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	ACP-103 (pimavanserin tartrate), batch 1046433, 98.8-100.3%
CAC concurrence:	Yes

Key Study Findings

- ACP-103 was not carcinogenic in males up to 15 mg/kg/day and in females up to 50 mg/kg/day pimavanserin free base. There were no drug-related neoplasms identified. The highest dose tested for males and females is approximately 2- and 6-fold the maximum recommend human dose (MRHD) of 34 mg/day pimavanserin free base based on mg/m^2. AUC values at the highest dose for males and females are 1,560 ng.hr/ml and 11,800 ng.hr/ml, respectively, which is ~1-fold and 7-fold the MRHD based on AUC (based on predicted human AUC value of 1,606 ng.hr/ml).
- AUC values for the major human metabolite, ACP-260279 (ACP-279), at the highest dose in males and females are 1,220 and 12,100 ng.hr/ml, respectively. The predicted AUC for ACP-279 in humans at the MRHD of 34 mg pimavanserin is 847 ng.hr/ml).
- There was a statistically significant decrease in survival rates for males at the high dose of 15 mg/kg/day compared to controls; no clear drug-related causes of death were identified.
- The NOAEL for systemic toxicity was 7 mg/kg/day for males and 10 mg/kg/day for females due to mortality and decreases in body weight respectively.

Adequacy of Carcinogenicity Study

The carcinogenicity study was adequately conducted according to the protocol and protocol amendments. No deviations impacted study integrity.

Appropriateness of Test Models

The species and strain used in the study (CD1 mouse) is appropriate for long-term study and there is significant historical control data.

Evaluation of Tumor Findings

A separate statistical review was conducted by Dr. Hepei Chen from the Division of Biometrics.

Methods

Doses:	Males: 0, 0, 3, 7, 15 mg/kg/day pimavanserin tartrate (0, 0, 2.6, 6.0, 13 mg/kg/day pimavanserin free base) Females: 0, 0, 10, 25, 50 mg/kg/day pimavanserin tartrate (0, 0, 8.5, 21, 43 mg/kg/day pimavanserin free base)
Frequency of dosing:	Once daily
Dose volume:	10 ml/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	Deionized water
Basis of dose selection:	13-week dose range-finding study. The high doses were selected on basis of mortality (1/2 the lethal dose). The doses used in the study were the doses recommended by the ECAC on December 13, 2007 (see ECAC meeting minutes in the appendix).
Species/Strain:	Mouse/CD1(ICR) (b) (4)
Number/Sex/Group:	60/sex/group
Age:	At dose initiation: ~6 weeks old
Animal housing:	Individual
Paradigm for dietary restriction:	NA
Dual control employed:	Yes (both controls were the same: deionized water)
Satellite groups:	TK: 21/sex/treated groups, 6/sex/control TK animals were dosed once daily for 182 consecutive days.
Deviation from study protocol:	None of the protocol deviations affected the integrity of the study.

*All tables and figures excerpted from sponsor's study report, unless stated otherwise.

Observations and Results

Mortality

There was no early termination of any control or dose groups except dosing was terminated during study week 101 (study day 710) for high dose males (15 mg/kg/day) due to the number of surviving animals reaching 20. The sponsor received agreement from the division and the ECAC prior to the cessation of dosing for this group. There was a statistically significant dose-related decreasing trend in survival rates for males when compared to pooled control groups and control group 1 alone. In addition, there was a statistically significantly lower survival rate in the 15 mg/kg/day group males compared to pooled control groups and control group 1 alone. The same statistical finding was found by the statistical reviewer; Dr. Hepei Chen. There was no statistically significant effect on survival rates for females. There were a higher number of

undetermined deaths for high dose females at 50 mg/kg/day (16/35 or 47% compared to 6/38 or 16% and 1/29 or 3% for control groups 1 and 2, respectively).

Table 57: Statistical analysis of survival rates for males and females

		Kaplan-Meier Estimates and P-values					Overall / Trend
Sex	Week	Control 1	Control 2	Low	Mid	High	
M	52	97	93	98	93	81	
	78	85	73	74	69	63	
	92	65	54	55	59	42	
	End of Study	47	41	36	39	29	
	p-value (p)			0.4401	0.3499	0.0045 *	0.0330 * (O) 0.0217 * (T)
	p-value (1)		0.1938	0.1594	0.1396	0.0034 *	0.0193 * (O) 0.0130 * (T)
	p-value (2)			NT	NT	NT	0.1540 (O) 0.1531 (T)
F	52	92	95	93	88	73	
	78	76	88	76	78	64	
	92	51	66	57	60	53	
	End of Study	38	53	38	41	46	
	p-value (p)			NT	NT	NT	0.4408 (O) 0.4075 (T)
	p-value (1)		0.0654	NT	NT	NT	0.8127 (O) 0.8331 (T)
	p-value (2)			NT	NT	NT	0.1735 (O) 0.1672 (T)

p-values:
(p): Comparisons using pooled control
(1): Comparisons using control group 1
(2): Comparisons using control group 2
* - statistically significant at the 0.05 significance level. NT = Not tested per statistical methodology.

Table 58: Survival of animals during study (number and percent)

	Males					Females				
Group (mg/kg/day)	0	0	3	7	15 [b]	0	0	10	25	50
Study Week										
25	60/60 100%	60/60 100%	58/58 100%	60/60 100%	57/60 95%	58/59 98%	60/60 100%	59/60 98%	57/59 97%	55/59 93%
50	57/59 97%	56/59 95%	57/58 98%	55/59 93%	49/59 83%	54/59 92%	56/59 95%	56/59 95%	52/59 88%	44/58 76%
83	42/57 74%	41/59 69%	40/58 69%	38/57 67%	30/59 51%	41/59 69%	48/58 83%	41/58 71%	41/57 72%	34/57 60%
92	37/57 65%	32/59 54%	32/58 55%	33/57 58%	25/59 42%	29/58 50%	38/58 66%	33/58 57%	34/57 60%	30/57 53%
101	30/57 53%	28/59 47%	22/58 38%	24/57 42%	20/59 34%	22/58 38%	32/58 55%	25/58 43%	24/57 42%	27/57 47%
104	28/57 49%	24/59 41%	21/58 36%	22/57 39%	18/59 31%	22/58 38%	31/58 53%	22/58 38%	23/57 40%	26/57 46%

[a] = Mortality data corrected for accidental deaths by dividing the number of surviving animals by the total number of animals minus the accidental deaths (no. alive/[60-no. accidental deaths]).

[b] = Dosing was terminated during study week 101.

Figure 11: Percent survival: males

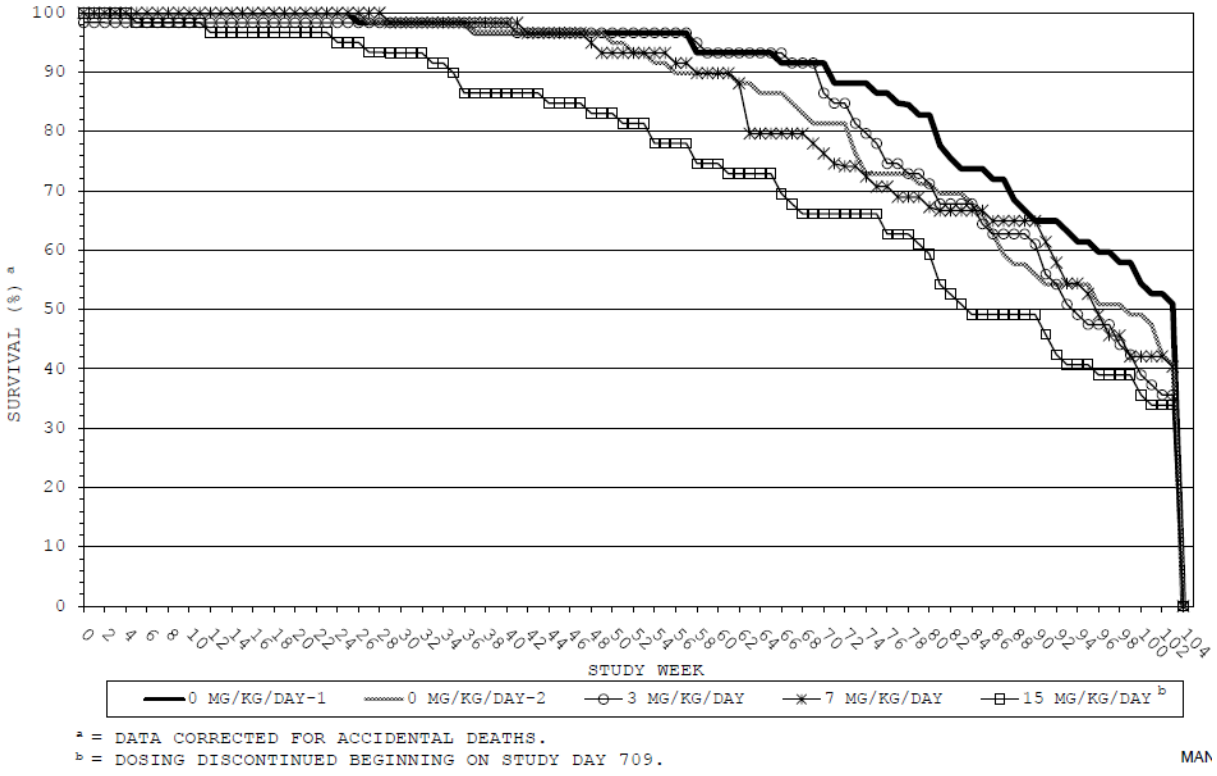


Figure 12: Percent survival: females

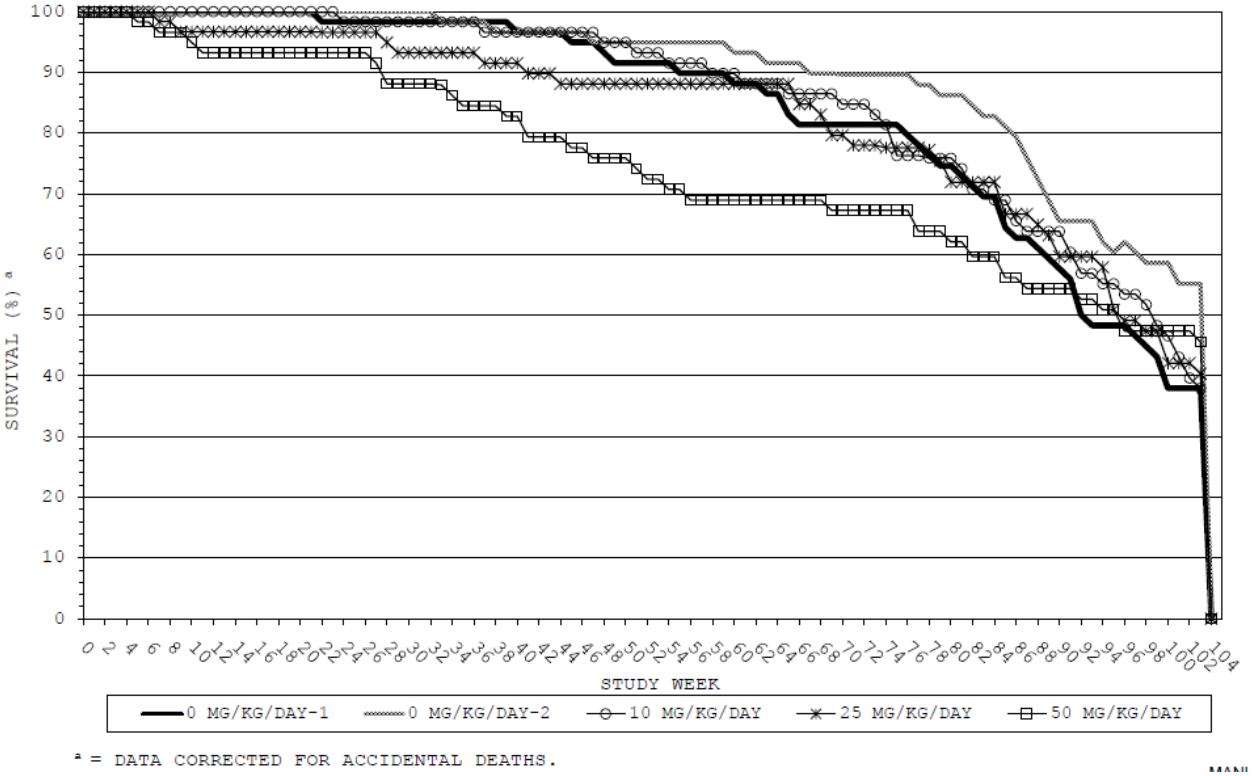


Table 59: Selected causes of unscheduled death for males

	Males					
Group (mg/kg/day):	**0**	**0**	**3**	**7**	**15**	**Total**
Animals [a]	**32**	**36**	**38**	**38**	**42**	**186**
Urogenital Tract Inflammation or Urinary Tract Obstruction	10	21	14	16	18	**79**
(Incidence as a %)	*(31)*	*(58)*	*(37)*	*(42)*	*(43)*	*(42)*
Undetermined	0	6	4	5	8	**23**
(Incidence as a %)	*(0)*	*(17)*	*(11)*	*(13)*	*(19)*	*(12)*
Amyloidosis	4	1	5	2	5	**17**
(Incidence as a %)	*(13)*	*(3)*	*(13)*	*(5)*	*(12)*	*(9)*
Lymphoma, Malignant	4	1	2	2	2	**11**
(Incidence as a %)	*(13)*	*(3)*	*(5)*	*(5)*	*(5)*	*(6)*
Nephropathy	2	0	4	2	0	**8**
(Incidence as a %)	*(6)*	*(0)*	*(11)*	*(5)*	*(0)*	*(4)*

[a] = Number of animals not surviving to the scheduled necropsy from each group.

Table 60: Selected causes of unscheduled death for females

	Females					
Group (mg/kg/day):	**0**	**0**	**10**	**25**	**50**	**Total**
Animals [a]	**38**	**29**	**38**	**37**	**34**	**176**
Undetermined	6	1	6	7	16	**36**
(Incidence as a %)	*(16)*	*(3)*	*(16)*	*(19)*	*(47)*	***(20)***
Lymphoma, Malignant	8	6	9	10	2	**35**
(Incidence as a %)	*(21)*	*(21)*	*(24)*	*(27)*	*(6)*	***(20)***
Nephropathy	5	3	5	3	5	**21**
(Incidence as a %)	*(13)*	*(10)*	*(13)*	*(8)*	*(15)*	***(12)***
Amyloidosis	5	3	4	7	1	**20**
(Incidence as a %)	*(13)*	*(10)*	*(11)*	*(19)*	*(3)*	***(11)***

[a] = Number of animals not surviving to the scheduled necropsy from each group.

Clinical Signs

A slightly higher incidence of dried yellow material was observed around the mouth and neck of mid and high dose males and females. The significance of this finding is unknown. Gasping was observed in a few high dose females compared to no findings in control females. In addition, a higher incidence of rales was observed in high dose males and in mid and high dose females compared to controls. Detailed physical examinations and palpable mass observations were performed approximately weekly; clinical observations were recorded daily. There was no clear drug-related effect on the incidence of palpable masses.

Body Weights

Mean body weights and body weight gains were lower for high dose males (15 mg/kg/day) and for mid and high dose females (25 and 50 mg/kg/day). At week 100, mean body weights were 6.2% lower for males at 15 mg/kg/day compared to the mean combined control groups. Overall body weight gain from weeks 0 to 100 (the dosing period for high dose males) was significantly decreased for males at 15 mg/kg/day, 21% compared to the mean combined control groups. For females during week 104, mean body weights were 12.2% and 14.9% lower at 25 and 50 mg/kg/day, respectively compared to the mean combined control groups. Overall body weight gain from weeks 0 to 104 was significantly decreased for females at 25 and 50 mg/kg/day, 32% and 44% compared to the mean combined control groups, respectively.
Body weights were recorded once weekly through study week 12 and biweekly thereafter. The drug effect on body weight slightly correlated with changes in food intake for females only.

Figure 13: Mean body weight: males

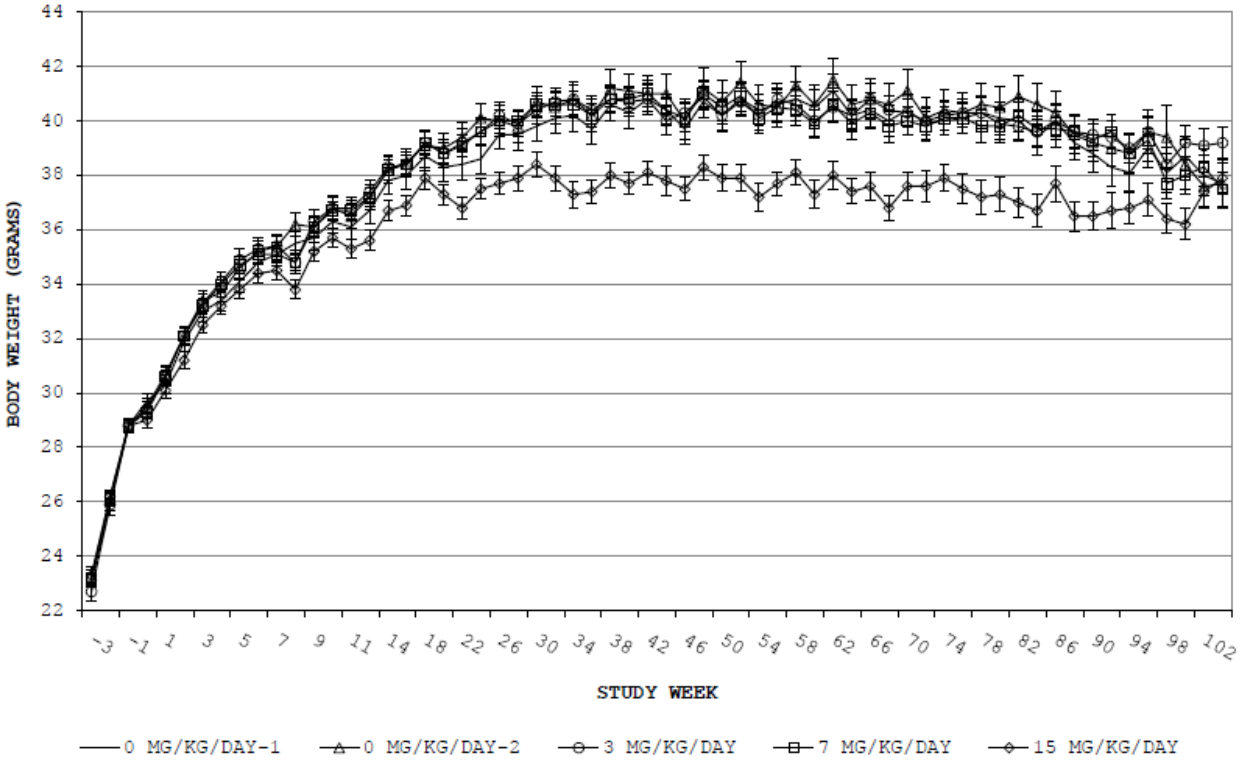
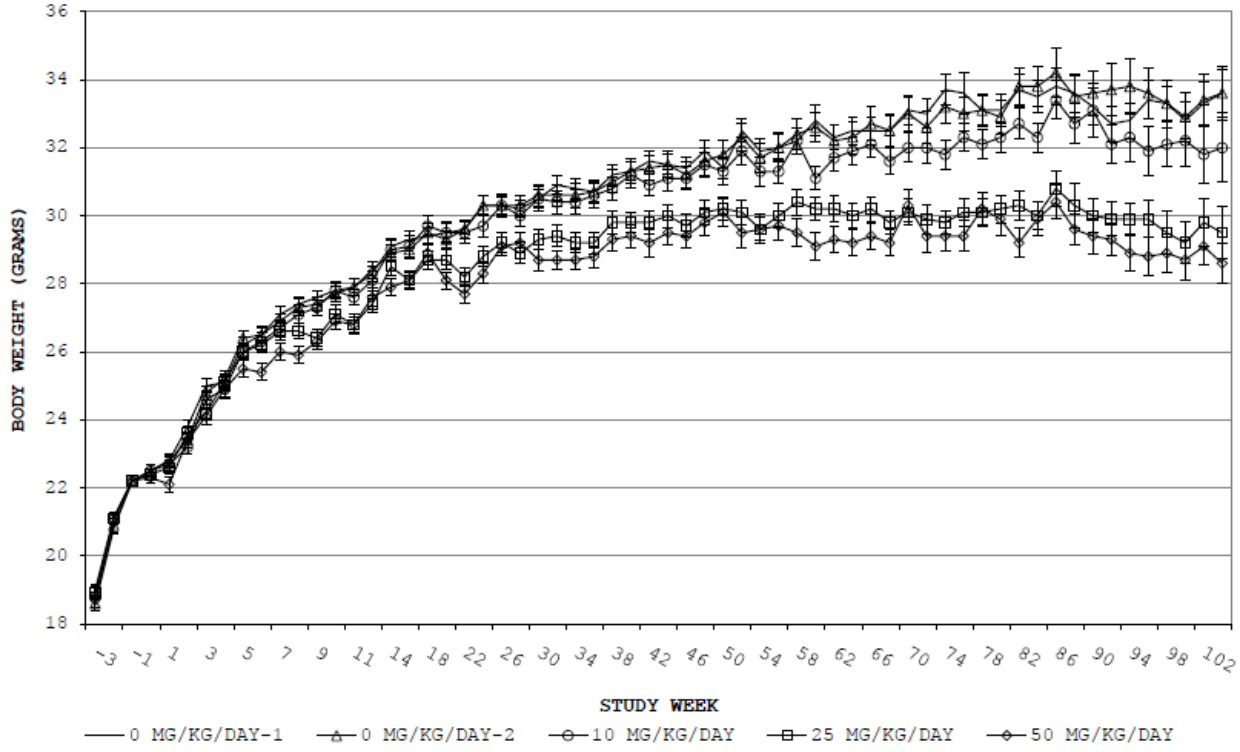


Figure 14: Mean body weight: females



Food Consumption

There was a decrease in mean food consumption for females at 25 and 50 mg/kg/day during the first part of the study, but values were comparable to the control groups throughout the remainder of the study. At weeks 25 to 26, there was a non-statistically significant decrease in food consumption of 8% for females at 50 mg/kg/day compared to controls. The effect on food consumption for females correlated with decreased body weights. There was no effect on food consumption for males. Food consumption was recorded once weekly through study week 12 and biweekly thereafter.

Gross Pathology

There were no clear drug-related macroscopic findings. All findings in drug-treated groups were at a similar incidence in control groups, and/or not dose-related and common background findings. Necropsies were performed on all animals found dead, euthanized moribund and all surviving animals during week 104. Blood smears were taken from all animals.

Histopathology

Peer Review: Yes

The peer review statement states that the pathology data and report reflect the consensus opinions of the study pathologist and peer review pathologist.

Neoplastic:
No drug-related neoplastic findings were found in males or females from any dose group. The only statistically significant finding was for hemangiosarcomas in control group 2 and low dose males compared to control group 1 males, but since none were observed in high dose males and the finding was not statistically significant when the control groups were combined, this finding was not considered drug-related. A separate statistical review was conducted by Dr. Hepei Chen from the Division of Biometrics.

The following is an excerpt from Dr. Chen's review.
***Reviewer's findings**:*

In this mouse study, relatively large differences in tumor bearing animals between the two vehicle control groups were noted for some tumors such as systemic hemangiosarcoma in males (0 and 6 for control 1 and 2, respectively), systemic lymphoma in males (6 and 2 for control 1 and 2, respectively), and liver carcinoma hepatocellular in males (6 and 1 for control 1 and 2, respectively). Following the guidance recommendation indicated above, in the reviewer's analysis the two vehicle control groups were combined, without the separate analysis for each single control group.

Reviewer's findings:

The tumor types with p-values less than or equal to 0.05 for dose response relationship and/or pairwise comparisons of treated groups and combined control are reported in Table 4.

Based on the criteria of adjustment for multiple testing discussed above, no dose response relationship or pairwise comparisons were noted in the reviewer's analysis for the mice study.

Table 4. . Summary Table of Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship and/or Pairwise Comparisons of Treated Groups and Combined Control Group in Mice

		Vehicle		Vehicle (C)	Low (L)	Mid (M)	High (H)
		0 mg	0 mg	0 mg (1+2)	10 mg	25 mg	50 mg
Organ name	Tumor name	1	2	P - Trend	P - C vs. L	P - C vs. M	P - C vs. H
Female Lungs	#B Adenoma, Bronchiolo-Alveolar	3/(60)	3/(60)	6/87 (120)	5/42 (60)	7/41 (60)	6/36 (60)
				0.0479#	0.2623	0.0746	0.0953
Ovaries	#B Cystadenoma	1/(60)	0/(60)	1/86 (120)	2/42 (60)	2/40 (60)	3/34 (59)
				0.0414#	0.2505	0.2364	0.0683
Pituitary	#B Adenoma, Pars Distalis+Intermedia	0/(60)	1/(60)	1/86 (120)	4/42 (60)	2/40 (60)	1/34 (59)
				0.3602	0.0396#	0.2364	0.4881

& X/YY (ZZ): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
$ = Statistically significant at 0.025 and 0.05 level in rare tumor for tests of dose response relationship and pairwise comparison, respectively;
NA = Not calculable.

Non Neoplastic:
There were no clear drug-related non-neoplastic microscopic findings for males or females.

Toxicokinetics

Blood samples for toxicokinetic analysis of ACP-103 and metabolites AC-260279, AC-260423, and AC-269527 were collected from satellite animals, 3 animals/sex/group/time point at 0.5, 1, 2, 4, 8, and 24 hours post-dosing (collected from Group 2A at 2 hours post-dosing only) on study day 182. Metabolite AC-260279 (AC-279) was identified as a major circulating metabolite in humans. Similar to the rat, exposure levels increased much greater than dose proportional from the low to mid dose groups for both males (up to 68x) and females (up to 16x), but then increased roughly dose proportional from the mid to high dose groups.

Table 61: Toxicokinetic parameters of ACP-103 in 24-month mouse study

Dosage	$AUC_{0\text{-}24\ h}$ (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)
Males			
3 mg/kg/day	22.9	16.5	0.500
7mg/kg/day	387	128	0.500
15 mg/kg/day	1560	339	0.500
Females			
10 mg/kg/day	754	239	0.500
25 mg/kg/day	4850	703	1.00
50 mg/kg/day	11,800	1510	0.500

Table 62: Toxicokinetic parameters of Metabolites in 24-month mouse study

Dosage	$AUC_{24\ h}$ (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)
ACP-260279			
Males			
3 mg/kg/day	NA	NA	NA
7 mg/kg/day	174	36.9	2.00
15 mg/kg/day	1220	153	0.500
Females			
10 mg/kg/day	523	51.3	2.00
25 mg/kg/day	2790	317	2.00
50 mg/kg/day	12100	889	1.00
ACP-260423			
Males			
3 mg/kg/day	535	103	1.00
7 mg/kg/day	1720	198	4.00
15 mg/kg/day	2490	434	2.00
Females			
10 mg/kg/day	2350	330	4.00
25 mg/kg/day	3980	521	1.00
50 mg/kg/day	6730	759	0.500
ACP-269527			
Males			
3 mg/kg/day	NA	NA	NA
7 mg/kg/day	7.55	1.82	0.500
15 mg/kg/day	20.0	6.51	0.500
Females			
10 mg/kg/day	12.4	2.98	0.500
25 mg/kg/day	40.0	6.76	0.500
50 mg/kg/day	96.8	15.5	0.500

NA = Not Applicable

Dosing Solution Analysis

All analyzed dose formulations were within [redacted] (b) (4) % of nominal ACP-103 concentrations, within the acceptable SOP range.

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

Study title: ACP-103: Oral study of male and female fertility and early embryonic development to implantation in rats

Study no.:	1612-05314
Study report location:	EDR SDN 1, supplemental information in SDN 7
Conducting laboratory and location:	(b) (4) [redacted]
Date of study initiation:	April 12, 2006
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	ACP-103, lot no. 981756, 100%

Key Study Findings

Clinical signs of rales, rough hair-coat and thinness at 60 and 90 mg/kg/day in males and females. Decreased body weight and food consumption for males and females at 60 and 90 mg/kg/day and decreased body weight gain in females at 10 mg/kg/day. Maternal reproductive and/or embryotoxicity observed at 90 mg/kg/day, but no effects on fertility parameters at any dose level. Male reproductive toxicity observed at ≥60 mg/kg/day with dose-related changes in sperm motility and decreased sperm density and microscopic changes in epididymis (vacuolation).

- Systemic toxicity NOEL = 10 mg/kg/day pimavanserin tartrate
- Maternal reproductive and/or embryotoxicity NOAEL = 60 mg/kg/day
- Male reproductive toxicity NOAEL* = 10 mg/kg/day
- 10 mg/kg/day (8.5 mg/kg/day pimavanserin free base) = 2-fold MRHD of 34 mg pimavanserin free base based on mg/m^2

*No sperm density measurements taken at 10 and 60 mg/kg/day, so an accurate NOEL sperm density could not be determined in this study. However, based on the lack of organ weight changes and microscopic findings in males at 10 mg/kg/day, the NOAEL for male reproductive toxicity is most likely 10 mg/kg/day.

Methods

Doses:	0, 10, 60, 90 mg/kg/day pimavanserin tartrate 0, 8.5, 51, 77 mg/kg/day pimavanserin free base
Frequency of dosing:	Once daily
Dose volume:	10 ml/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	0.9% saline
Species/Strain:	Rat/Sprague-Dawley (b) (4)
Number/Sex/Group:	25/sex/group
Satellite groups:	NA
Study design:	Males were dosed during the 4-week pre-cohabitation period, during cohabitation, and the post-cohabitation period for a total of 64 consecutive days. Females were dosed for 2 weeks prior to cohabitation, during cohabitation, and from gestation day (GD) 1 to 7. During cohabitation (up to 2 weeks), each male was paired with one female, and the day of confirmed mating was set as GD 1.
Deviation from study protocol:	None that affected the integrity of the study.

Observations and Results

Mortality

One male at 10 mg/kg/day was found dead on study day 47. There were no clinical signs prior to death and no abnormal findings were observed at necropsy (i.e. no signs of a dosing error). Since no deaths occurred at higher doses, this death was not considered to be drug-related.

Clinical Signs

Drug-related clinical signs of rales, rough hair-coat, and thinness were observed in males and females. Rales (noisy breathing) were noted in 3 males and 1 female at 90 mg/kg/day and in 1 male at 60 mg/kg/day. Rough hair-coat was observed in 7 males and 4 females at 90 mg/kg/day. Thinness, which correlated with body weight loss, was observed in one male and one female at 10 mg/kg/day and 90 mg/kg/day. Cage-side observations were conducted at least twice daily and clinical observations were recorded at each body weight interval.

Body Weight

There was a statistically significant decrease in mean body weight for males at 60 and 90 mg/kg/day at the end of the dosing period (7% and 18% decrease compared to controls, respectively) and also a significant decrease in body weight gain at 90 mg/kg/day (27% decrease compared to controls. There was a dose dependent decrease in mean body weight on GD 7 (last day of dosing), 8% decrease compared to controls at 90 mg/kg/day. High dose females also lost weight during the pre-cohabitation period. . Decreases in body weight and body weight gain correlated with

decreased food consumption. For males, body weights were recorded twice weekly and prior to necropsy. For females, body weights were recorded once weekly prior to cohabitation and during cohabitation, and after mating on GDs 1, 4, 7, 10, 13 and prior to necropsy.

Males

Dose (mg/kg/day)	Mean body weight g (% control)	Body weight gain (days 1-65 g (% control)
0	528 (100%)	234 (100%)
10	509 (96%)	224 (96%)
60	490 (93%)	196 (84%)
90	431 (82%)	170 (73%)

Females

Dose (mg/kg/day)	Mean body weight g (% control)	Body weight gain (pre-cohab. 1-15) g (% control)	Body weight gain (GD 1-13) g (% control)
0	274 (100%)	17 (100%)	57 (100%)
10	268 (98%)	7 (41%)	59 (104%)
60	260 (95%)	4 (24%)	39 (68%)
90	251 (92%)	-2	50 (88%)

[Mean body weight values on day 64 for males, GD 13 for females. Body weight tables generated by reviewer.]

Food Consumption

There was a statistically significant decrease in food consumption for males at all dose levels and for females at 60 and 90 mg/kg/day. Decreases in food consumption correlated with decreased in body weights.

Table 63: Food consumption in males and females in fertility study

Dosage (mg/kg)	Sex	Food Consumption	
10	Male	↓ SD 15-22 (7%)	
60	Male	↓ SD 1-8 (7%) ↓ SD 50-57 (11%) ↓ SD 36-64 (10%)	↓ SD 43-50 (11%) ↓ SD 57-64 (11%)
	Female	↓ SD 1-8 (16%) ↓ SD 1-14 (14%) ↓ GD 4-7 (15%) ↓ GD 10-13 (19%)	↓ SD 8-14 (10%) ↓ GD 1-4 (11%) ↓ GD 7-10 (29%) ↓ GD 1-13 (19%)
90	Male	↓ SD 1-8 (14%) ↓ SD 22-28 (9%) ↓ SD 36-43 (12%) ↓ SD 50-57 (25%) ↓ SD 36-64 (20%)	↓ SD 15-22 (8%) ↓ SD 1-28 (9%) ↓ SD 43-50 (25%) ↓ SD 57-64 (16%)
	Female	↓ SD 1-8 (24%) ↓ SD 1-14 (20%) ↓ GD 4-7 (20%) ↓ GD 10-13 (11%)	↓ SD 8-14 (16%) ↓ GD 1-4 (12%) ↓ GD 7-10 (15%) ↓ GD 1-13 (14%)

↑ = Statistically higher than control means ↓ = Statistically lower than control means

For males, food consumption was recorded once weekly except during cohabitation. For females, food consumption was recorded once weekly prior to cohabitation and after mating on GDs 1 to 4, 4 to 7, 7 to 10, and 10 to 13.

Toxicokinetics

NA

Dosing Solution Analysis

All dose formulations were within the acceptable range, (b) (4) % to (b) (4) %. No test article was detected in any control samples.

Necropsy

Males at 90 mg/kg/day were observed with enlarged adrenal glands (4/25), enlarged kidneys (3/25), and enlarged lymph nodes (4/25). The sponsor did not consider these findings to be drug-related, but this reviewer disagrees since enlargement of these organs were observed in previous rat studies, and correlated with phospholipidosis in those organs, and the findings occurred only in high dose animals. There were no drug-related macroscopic findings in females.
All confirmed mated females were sacrificed on GD 14±1. Surviving males were sacrificed ~24 to 48 hrs after the last dose. All animals were necropsied.

Table 64: Male organ weight changes from control

Dosage (mg/kg)	Organ	
	Absolute	Organ-to-Body Weight Ratios
60	↓ Prostate (15%)	↑ Right Cauda Epididymis (14%)
90	↓ Prostate (21%) ↓ Seminal Vesicles (26%)	↑ Left Testis with Epididymis (17%) ↑ Right Cauda Epididymis (25%) ↑ Right Epididymis (20%) ↑ Right Testis (17%)

↑ = Statistically higher than control means ↓ = Statistically lower than control means

There were significant and dose-related effects on male reproductive organ weights at 60 and 90 mg/kg/day. Absolute prostate weights were decreased at ≥60 mg/kg/day up to 21% compared to controls and absolute seminal vesicle weights were decreased at 90 mg/kg/day (26% compared to controls). Relative epididymis weights were increased at ≥60 mg/kg/day (up to 25% compared to controls) and testis weights were increased at 90 mg/kg/day (17% compared to controls).The changes in epididymis weights correlated with microscopic findings.

Fertility Parameters (Mating/Fertility Index, Corpora Lutea, Preimplantation Loss, etc.)

There were no effects on mating or fertility indices (number of pregnant females, length of pre-coital period) or the number and length of estrous cycles.
There was a significant decrease in the number of corpora lutea, implantations and percent viable implants. Three was also a slight increase in the percentage of pre-implantation loss and increased early resorptions all at 90 mg/kg/day that was outside the historical control range for this laboratory. The changes observed at 10 mg/kg/day, decrease in number of implantations and increase in non-pregnancies, was not considered drug-related since similar effects were not observed at the 60 mg/kg/day dose.

Table 65: Summary of uterine data

Group	Sex	Number of Corpora Lutea	Number of Imp.	% Pre-Imp.	Late Resorption	Early Resorption	Aborted Fetuses	Total Deaths	% Post-Imp. Loss	Number of Live Fetuses	% of Viable Imp.
1f	TOTAL	349	328		0	18	0	18		310	
	MEAN	15.9	14.9	6.4(6.0)	0.0	0.8	0.0	0.8	5.9(5.5)	14.1	94.1(94.5)
	SD	2.05	2.54		0.00	0.85	0.00	0.85		2.81	
	N	22	22		22	22	22	22		22	
2f	TOTAL	281	236		0	16	0	16		220	
	MEAN	14.8	12.4*	17.4(16.0)	0.0	0.8	0.0	0.8	8.8(6.8)	11.6	91.2(93.2)
	SD	3.49	4.69		0.00	1.57	0.00	1.57		4.79	
	N	19	19		19	19	19	19		19	
3f	TOTAL	380	359		0	23	0	23		336	
	MEAN	15.2	14.4	5.4(5.5)	0.0	0.9	0.0	0.9	6.2(6.4)	13.4	93.8(93.6)
	SD	2.20	2.20		0.00	1.08	0.00	1.08		2.08	
	N	25	25		25	25	25	25		25	
4f	TOTAL	282	241		0	28	0	28		213	
	MEAN	12.3*	10.5*	16.2(14.5)	0.0	1.2	0.0	1.2	10.4(11.6)	9.3	89.6(88.4)
	SD	2.85	3.34		0.00	1.51	0.00	1.51		3.12	
	N	23	23		23	23	23	23		23	

f - Female Imp. - Implantation

Note: Mean percentages are the average of individual percentages. Numbers in parenthesis are the calculated means from the group totals. Calculated values do not include non-pregnant animals.

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 - 10 mg/kg/day Group 3 - 60 mg/kg/day Group 4 - 90 mg/kg/day

* Statistically significant difference from control group, p<0.05
[Table excerpted from sponsor's study report.]

There was a decrease in sperm motility parameters at 60 and 90 mg/kg/day, and a decrease in sperm density at 90 mg/kg/day (sperm density and spermatid concentration were not measured at 10 and 60 mg/kg/day). There was also a dose-related increase in epididymis weights at 60 and 90 mg/kg/day with corresponding microscopic findings of minimal to moderate cytoplasmic vacuolation of the tubular epithelium, primarily in the body (isthmus) of the epididymis. Testes weights were increased only at 90 mg/kg/day but without corresponding microscopic findings. The NOEL for male organ weight changes and microscopic findings and effects on sperm motility is 10 mg/kg/day.

Table 66: Sperm Motility Parameters

Group Sex		Path Velocity (µm/second)	Progressive Velocity (µm/second)	Track Speed (µm/second)	Lateral Amplitude	Beat Cross Frequency	Straightness	Linearity	Motility (%)
1m	Mean	209.2	141.4	316.5	13.6	9.4	66	46	91
	SD	16.6	13.8	23.1	1.0	1.3	3	3	11
	N	25	25	25	25	25	25	25	25
2m	Mean	210.6	140.4	320.3	13.6	9.1	65	46	90
	SD	21.9	17.5	33.2	1.2	1.6	3	2	14
	N	24	24	24	24	24	24	24	24
3m	Mean	189.1*	128.5*	284.6*	12.5*	10.2	66	47	86
	SD	23.0	14.8	36.4	1.5	1.6	3	3	21
	N	25	25	25	25	25	25	25	25
4m	Mean	184.5*	123.3*	279.1*	12.6*	10.8*	65	45	88
	SD	21.2	18.3	28.7	1.3	1.5	4	4	16
	N	23	23	23	23	23	23	23	23

m - Male * - Statistically significant difference from control group, p<0.05

Nominal Dose: Group 1 - 0 mg/kg/day Group 2 - 10 mg/kg/day Group 3 - 60 mg/kg/day Group 4 - 90 mg/kg/day

[The above table is excerpted from the sponsor's study report]

Table 67: Sperm density and spermatid head counts

Group Sex		Right Cauda Epididymis Weight (g)	Total Sperm $x10^6$/cauda	Sperm Density $x10^3$/mg cauda	Right Testis Weight (g)	Total Spermatid $x10^6$/testis	Spermatid Density $x10^3$/mg testis
1m	Mean	0.304	140.850	464.431	1.676	192.350	115.273
	S.D	0.031	23.141	69.376	0.146	19.071	12.474
	N	25	25	25	25	25	25
4m	Mean	0.313	127.510	398.399*	1.588	195.900	120.701
	S.D	0.054	41.035	99.675	0.238	47.909	28.665
	N	25	25	25	25	25	25

m - Male * - Statistically significant difference from control group, p<0.05

Nominal Dose: Group 1 - 0 mg/kg/day Group 4 - 90 mg/kg/day

[The above table is excerpted from the sponsor's study report]

Sperm density and spermatid concentrations were not measured in the low and mid dose groups (10 and 60 mg/kg/day). Therefore a NOEL for decreased sperm density could not be determined from this study and an accurate NOAEL for effects on male fertility could not be determined for this study. In a September 30, 2015 information request to the sponsor, the sponsor was asked to analyze sperm density and spermatid head counts from the 10 and 60 mg/kg/day groups. The sponsor informed the division that those tissues could not be located. The sponsor re-evaluated all data from the

study report and concluded the following and submitted an additional table summarizing the overall findings:
"Overall, the data suggest that no drug-related effects are likely on sperm parameters at the lowest dose of 10 mg/kg/day. The exposure at 10 mg/kg/day (AUC of 1030 h.ng/mL, Study (b) (4) 146.02) is well below that of the no effect level for histological change in the epididymis (AUC of 8670 h.ng/mL, Study (b) (4) 146.02) and 15-fold (AUC of 15,900 h.ng/mL, Study (b) (4)-616007) below that at 60 mg/kg/day where effects on sperm motility and cytoplasmic vacuolation of the epididymis were noted."

Table 68: Effects on sperm parameters and male reproductive organs in rats

Dose (mg/kg/day)	Sperm Motility	Sperm Density/ Spermatid Concentration	Organ to Body Weight Ratios	Histology
10	No significant effects	Not measured	No significant effects	Testis - not examined Epididymis - no findings
60	↓ Path Velocity (10%) ↓ Progressive Velocity (9%) ↓ Track Speed (10%) ↓ Lateral Amplitude (8%)	Not measured	↑ Right Cauda Epididymis (14%)	Testis - not examined Epididymis – minimal to mild cytoplasmic vacuolation (21/25 animals)
90	↓ Path Velocity (12%) ↓ Progressive Velocity (13%) ↓ Track Speed (12%) ↓ Lateral Amplitude (7%) ↑ Beat Cross Frequency (15%)	↓ Sperm Density (14%) ↑ Spermatid Density (5%)	↑ Left Testis with Epididymis (17%) ↑ Right Cauda Epididymis (25%) ↑ Right Epididymis (20%) ↑ Right Testis (17%)	Testis - no findings Epididymis – moderate cytoplasmic vacuolation (25/25 animals)

[The above table is excerpted from the NDA submission, SDN 7: response to information request.]

9.2 Embryonic Fetal Development

Study title: ACP-103: Oral Study for Effects on Embryo-Fetal Development in Sprague Dawley Rats

Study no.:	1612-05791
Study report location:	EDR SDN
Conducting laboratory and location:	(b) (4)
Date of study initiation:	May 5, 2006
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	ACP-103, lot no. 981756, 100%

Key Study Findings

There were no drug-related effects on any pregnancy parameters measured or fetal morphology. ACP-103 is considered non-teratogenic under the conditions of this study.

- Maternal NOAEL was 10 mg/kg/day pimavanserin tartrate due to a significant decrease in body weight, body weight gain and food consumption at 60 mg/kg/day.
- Fetal NOEL = 60 mg/kg/day
  AUC and Cmax at fetal NOEL = 34,800 ng.hr/ml and 909 ng/ml, respectively.

Methods

Doses:	0, 1, 10, 60 mg/kg/day pimavanserin tartrate 0, 0.9, 8.5, 51 mg/kg/day pimavanserin free base
Frequency of dosing:	Once daily from gestation day (GD) 7-20
Dose volume:	10 ml/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	0.9% saline
Species/Strain:	Rat (time-mated)/Sprague Dawley (b) (4)
Number/Sex/Group:	20/sex/group
Satellite groups:	Toxicokinetic (9/drug-treated group) dosed from GD 7-13.
Study design:	Animals were dosed once daily from GD 7-20 and sacrificed and necropsied on GD 22. Full uterine examinations were conducted.
Deviation from study protocol:	None that affected the outcome of the study.

Dose selection was based on an oral dose range-finding study in time-mated female rats (study no. 1612-05308) using doses of 10, 30, 60 and 90 mg/kg/day. Clinical signs of nasal discharge, rales and/or rough hair coat were observed at 60 and 90 mg/kg/day. There was a dose-dependent decrease in body weight and body weight gain at ≥30 mg/kg/day with a corresponding decrease in food consumption. Fetal body weights were reduced, but there were no external morphologic fetal effects. Based on the maternal toxicity findings of clinical signs and decreased body weight, the high dose of 60 mg/kg/day was selected for the definitive study.

Observations and Results

Mortality

One 60 mg/kg/day TK animal was found dead after the 24-hr blood collection, however the death was most likely related to the blood collection procedure and not drug-related.

Clinical Signs

There were no abnormal clinical or cage-side observations as no findings were reported in the clinical observation tables.

Cage-side observations were conducted twice daily and more detailed clinical observations were recorded on GDs 7, 10, 13, 16, 20, and 22. The time observations were recorded after dosing was not included in the study protocol.

Body Weight

There was a statistically significant decrease in absolute body weight for dams at 60 mg/kg/day during the entire study period (GD 7-22), maximum decrease of10% compared to controls. Mean body weight values at the end of dosing on GD 20 were 354, 350, 349, and 320 g at 0, 1, 10, and 60 mg/kg/day, respectively. Body weight gains were also significantly decreased at 60 mg/kg/day, with an overall decrease during the dosing period from GD 7-20 of 30% compared to controls. Body weight gain values from GD 7-20 were 104, 102, 101, and 72 g at 0, 1, 10, and 60 mg/kg/day, respectively. After dosing cessation from GD 21-22, there was a statistically significant increase in body weight gain at 60 mg/kg/day, 13% compared to controls. The effects on body weight correlated with effects on food consumption observed in the 60 mg/kg/day group. There were no significant effects on body weight observed at 1 or 10 mg/kg/day.
Body weights were recorded daily.

Food Consumption

Food consumption was significantly decreased at 60 mg/kg/day during the entire dosing period, 15-24% compared to controls. From GD 21-22, after dosing cessation, there was a significant increase in food consumption of 18% compared to controls in the 60 mg/kg/day group. There was no significant effect on food consumption at 1 or 10 mg/kg/day. Food consumption was recorded daily.

Toxicokinetics

Exposure levels, both C_{max} and AUC, increased much greater than dose proportional from 10 to 60 mg/kg/day, and the half-life also increased with increasing dose. This may indicate a decrease in metabolism at higher doses. The TK parameters appear similar to those in non-pregnant female rats. All plasma concentrations of ACP-103 were <LLOQ for the 1 mg/kg/day dose.
Blood samples for TK analysis were taken from satellite animals on GD 13-14 at pre-dose, 0.5, 1, 4, 12, and 24 hrs postdose.

Table 69: Toxicokinetic parameters of ACP-103 in female rats

Group	Dose (mg/kg/day)	T_{max} (hr)	C_{max} (ng/mL)	$AUC_{(0\text{-}24\ hr)}$ (ng·hr/mL)	AUC_{∞} (ng·hr/mL)	$t_{½}$ (hr)
3	10	4.00	44.9	347	347	2.52
4	60	4.00	909	16800	34800	24.3

[Table excerpted from study report.]

Dosing Solution Analysis

All dose formulations were within the acceptable range ((b) (4) % of the target concentration).

Necropsy

There were no drug-related gross pathologic findings.

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.)

There were no drug-related effects on pregnancy status or any uterine parameters measured (uterine weights, numbers of corporal lutea, implantations, early or late resorptions, dead fetuses, total intra-uterine deaths or live fetuses).

Daily Dose (mg/kg/day):			0 (Control)	1	10	60
	Body Weight %:					
	Gestation Days 7 to 20	Absolute change (g)	103.81	101.57	101.29	72.46*
		% change	41.42	40.90	40.80	29.31*
	Gestation Days 21 to 22	% change	3.50	7.60	9.28	13.26*
	Food Consumption: total (g/animal)					
	Gestation Days 7 - 20		332.2	326.5	333.1	268.3
	Gestation Days 20 -21		25.8	24.5	24.4	21.6*
	Gestation Days 21 -22		18.1	18.5	18.9	21.4
	Gross Pathology:		-	-	-	-
	Mean No. Corpora Lutea:		14.6	14.5	14.4	14.8
	Mean No. Implantations:		13.6	12.7	13.3	13.1
	Mean % Pre-implantation Loss:		7.1	12.8	7.8	10.5
	Early Resorption:		0.3	0.6	0.4	0.3
	Late Resorption:		0.0	0.0	0.0	0.0
	Mean No. Live Conceptuses:		13.3	12.1	12.9	12.9
	Mean % of Viable Implants:		97.5	95.7	97.3	98.2

Offspring (Malformations, Variations, etc.)

There were no drug-related effects on fetal weights or fetal morphology (external, visceral or skeletal).

Daily Dose (mg/kg/day):		0 (Control)	1	10	60
Litters:					
	No. of Litters Evaluated:	20	20	20	20
	Mean No. Live Fetuses per litter:	13.3	12.1	12.9	12.9
	Early Resorption (%):	0.3	0.6	0.4	0.3
	Late Resorption (%):	0.0	0.0	0.0	0.0
	No. of Litters with Dead Fetuses:	0	0	0	0
	Mean % Post-implantation Loss:	2.5	4.3	2.7	1.8
	Mean Fetal Body Weight (g):	5.295	5.523	5.393	5.178
	Fetal Sex Ratios (% males):	49.9	49.9	53.0	50.7
	Fetal Anomalies:	-	-	-	-

- No noteworthy findings
NA = not applicable
* Statistically significant difference from control group, $p < 0.05$
[a] On gestation Day 14 only, the 24-hour post-dose sample was collected

[Above tables excerpted from toxicology tabulated summary section of NDA 207318.]

Study title: ACP-103: Oral study for effects on embryo-fetal development in New Zealand white rabbits

Study no.: 1612-05790
Study report location: EDR SDN 1
Conducting laboratory and location: (b) (4)
Date of study initiation: May 5, 2006
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: ACP-103, lot no. 981756, 100%

Key Study Findings

Severe maternal toxicity, including mortality, body weight loss and dyspnea, was observed at doses ≥150 mg/kg/day pimavanserin tartrate which required removal of the two highest dosing groups. Clinical signs of rales were observed at doses ≥50 mg/kg/day. Decreased body weight with a corresponding decrease in food consumption was observed at ≥100 mg/kg/day. Maternal gross macroscopic findings were observed in the heart, lungs and spleen from the 300 mg/kg/day group. Mortality and abortions occurred at 100 mg/kg/day. There were no drug-related effects on any other pregnancy or fetal parameters. ACP-103 was considered non-teratogenic under the conditions of this study.

- Maternal NOAEL = 50 mg/kg/day pimavanserin tartrate due to decreased body weight, food consumption, mortality and abortions at doses ≥100 mg/kg/day.
  AUC and C_{max} at 50 mg/kg/day on GD 14 = 6,600 ng.hr/ml and 611 ng/ml
- Fetal NOAEL = 100 mg/kg/day (fetuses were not evaluated from the 150 and 300 mg/kg/day groups).
  AUC and C_{max} at 100 mg/kg/day on GD 14 = 19,000 ng.hr/ml, 1,300 ng/ml

Methods

Doses:	0, 5, 50, 150*, 300* mg/kg/day pimavanserin tartrate 0, 4.3, 43, 128, 255 mg/kg/day pimavanserin free base Due to mortality and severe signs of toxicity at doses ≥150 mg/kg/day, animals in the 2 highest groups were removed from the study after administration of 1-3 doses. The remaining available 16 rabbits that had not received any drug (due to staggered dosing) were re-assigned to the study (13 to main group and 3 to TK groups) and administered ACP-103 at a dose of 100 mg/kg/day on the same schedule.
Frequency of dosing:	Once daily
Dose volume:	5 ml/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	0.9% saline
Species/Strain:	Rabbit/New Zealand white (b) (4)
Number/Sex/Group:	16/group
Satellite groups:	Toxicokinetic groups: 3/group. Dosed from GD 8-14.
Study design:	Time-mated female rabbits were administered test article or control from gestation day (GD) 8 through 20, and euthanized for reproductive and fetal evaluations on GD 30.
Deviation from study protocol:	None that affected the integrity of the study.

Dose selection was based on an oral dose range-finding study in time-mated female rabbits (study no. 1612-05306) using doses of 5, 30, 50, and 80 mg/kg/day treated by oral gavage from GD 8-20. Two rabbits (one each at 30 and 80 mg/kg/day were found dead on GD 9, possibly due to gavage error). No other mortality, no adverse clinical signs and no significant effects on body weight or food consumption. No maternal toxicity and no effects on fetal survival or external fetal morphology, although reduced fetal weights were observed at ≥30 mg/kg/day.
A separate maximum tolerated oral dose study was also conducted in female non-pregnant rabbits (study no. 1612-05305) using doses of 30, 100, 300, 600, and 1000 mg/kg/day for up to 13 consecutive days. Severe signs of toxicity (death, nasal/oral discharge, respiratory distress, body weight loss, and/or decreased food consumption) were observed at doses ≥100 mg/kg/day in a dose-related manner. Mortality was observed as early as dosing day 2 at 1000 mg/kg/day and after 9 days of dosing at 100 mg/kg/day. The NOEL was 30 mg/kg/day. No macro- or microscopic pathology was conducted.

Observations and Results

Mortality

Maternal mortality occurred at doses ≥100 mg/kg/day. One doe each at 100, 150 and 300 mg/kg/day was found dead on GD day 20, 9, and 9, respectively. Due to mortality and severe clinical signs of dyspnea and weight loss at 150 and 300 mg/kg/day, dosing was stopped after 1-3 days of dosing for the two highest groups and animals were euthanized. Pregnant rabbits were now dosed with 100 mg/kg/day. No fetal examinations were conducted for the 150 and 300 mg/kg/day groups.

Clinical Signs

Adverse clinical signs were observed in does at ≥50 mg/kg/day. Dyspnea was observed in 2 animals at 150 mg/kg/day and 4 animals at 300 mg/kg/day. Rales were observed in 3, 1 and 3 animals at 50, 100 and 300 mg/kg/day, respectively. Hunched or low posture, paleness and languid behavior were noted in the animals that were sacrificed moribund at 300 mg/kg/day. Cage side observations were conducted twice daily and clinical observations were conducted on GD 8, 11, 14, 17, 21, 24, 27 and 30.

Body Weight

There was significant body weight loss in animals dosed at 150 and 300 mg/kg/day for 1-3 days, which in part lead to the animals needing to be euthanized. A smaller, but not statistically significant, decrease in body weight and body weight gain was also observed at 100 mg/kg/day during the dosing period, 8-9% compared to controls. There was no effect on body weight at 5 or 50 mg/kg/day. The effects on body weight correlated with effects on food consumption. Body weights were recorded daily.

Food Consumption

Food consumption was decreased for animals treated at 150 and 300 mg/kg/day during GD 8-11, 51% and 97% compared to controls, respectively. Food consumption was also decreased during the entire dosing period at 100 mg/kg/day, 23% to 62% compared to controls. Food consumption continued to be decreased compared to controls at 100

mg/kg/day after dosing cessation between GD 21-26, up to 23% compared to controls. Food consumption was slightly decreased at 50 mg/kg/day, 9% to 13% compared to controls during the dosing period. Food consumption was recorded daily.

Toxicokinetics

Exposure levels, C_{max} and AUC, increased much greater than dose proportional from 5 to 50 mg/kg/day and only slightly greater than dose proportional from 50 to 100 mg/kg/day. T_{max} was comparable in low and high dose (2-2.5 hrs) but higher at the mid dose (4 hrs). Half-life increased with an increase in dose perhaps reflecting saturation of metabolism. Blood samples for TK analysis were collected from satellite animals on GD 14 prior to dosing and at 0.5, 1, 2, 4, 12 and 24 hrs post-dose.

Table 70: Toxicokinetic parameters of ACP-103 in rabbits on GD 14

Group	Dose (mg/kg/day)	T_{max} (hr)	C_{max} (ng/mL)	AUC_{∞} (ng·hr/mL)	$t_{½}$ (hr)
2	5	2.00	33.3	390	6.18
3	50	4.00	611	6600	5.01
6	100	2.50	1300	19000	9.30

[Table excerpted from study report.]

Dosing Solution Analysis

All dose formulations were within the acceptable range ((b) (4) % of nominal concentration).

Necropsy

Gross macroscopic drug-related findings were only observed in animals at 300 mg/kg/day. Findings included thickening, enlargement, and/or discoloration of the heart in 3 does. Discolored lungs, which did not collapse, was observed in an additional doe at 300 mg/kg/day that was euthanized moribund and a distended colon and irregularly shaped spleen in another doe at 300 mg/kg/day that was also sacrificed moribund. The above findings may be related to phospholipidosis that was observed in mice, rats and monkeys from other studies, although since histopathology was not conducted on these does, a definitive cause cannot be determined.

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.)

There were no drug-related effects on the mean numbers of corpora lutea, implantations, early or late resorptions, dead fetuses, total intra-uterine deaths or the numbers of live fetuses. In addition to the female that died in the 100 mg/kg/day group on GD 20, 3 additional females at 100 mg/kg/day aborted following termination of dosing between GD 24 and 28. The abortions may be due in part to maternal toxicity of decreased body weight and food consumption observed at 100 mg/kg/day. There were slight decreases (5% and 9%) in mean gravid uterine weights at 5 and 100 mg/kg/day compared to controls, respectively. These decreases were the result of one doe in each of these groups with a small number of implantation sites (1 and 4 in the 5 and 100 mg/kg/day groups, respectively) and therefore were considered incidental. Uteri and ovaries of animals from the 150 and 300 mg/kg/day

groups were examined only for implantations and corpora lutea; there were no clear drug-related findings.

Offspring (Malformations, Variations, etc.)

There were no clear drug-related effects on fetal morphology (external, visceral or skeletal) or any effects on fetal weights. A single fetus from the 5 mg/kg/day had multiple malformations of the cardiovascular system. Abnormal lung lobe formation was observed in two fetuses, from separate litters, in the 100 mg/kg/day group, but was also observed in one control fetus. One fetus from the 50 mg/kg/day group was observed with the skeletal malformation of thickened left ribs. Multiple skeletal variations were noted in fetuses from all groups. However, the incidence rates were similar across all dose groups including controls; therefore the skeletal variation findings were considered incidental and not drug-related. None of the other fetal findings were considered drug-related, due to their low incidence rates and lack of a dose-response. Fetuses were not examined from the 150 and 300 mg/kg/day groups.

Daily Dose (mg/kg/day):		0 (Control)	5	50	150	300	100
	Food Consumption: total (g/animal)						
	Gestation Days 8 - 20	1670.0	1683.9	1629.6	ND[1]	ND[1]	1276.4
	Gestation Days 20 - 30	1316.7	1310.2	1186.2	ND[1]	ND[1]	1276.4
	Gross Pathology:						
	Heart (rough, enlargement, thicken and/or discoloration)	0	0	0	0	3	0
	Lungs (discoloration/failure to collapse)	0	0	0	0	1	0
	Colon, distended	0	0	0	0	1	0
	Spleen, irregularly shaped	0	0	0	0	1	0
	Mean No. Corpora Lutea:	10.2	10.2	9.5	ND[1]	ND[1]	9.7
	Mean No. Implantations:	9.0	8.4	8.5	ND[1]	ND[1]	8.3
	Mean % Pre-implantation Loss:	10.7	17.8	10.1	ND[1]	ND[1]	12.6
	Early Resorption:	0.2	0.2	0.0	ND[1]	ND[1]	0.1
	Late Resorption:	0.1	0.2	0.1	ND[1]	ND[1]	0.2
	Mean No. Live Fetuses:	8.7	8.0	8.4	ND[1]	ND[1]	8.0
	Mean % of Viable Implants:	96.7	96.1	98.3	ND[1]	ND[1]	96.7
	No. of Litters Evaluated:	16	13	15	ND[1]	ND[1]	9
	Mean No. Live Fetuses per Litter:	8.7	8.0	8.4	ND[1]	ND[1]	8.0
	No. of Litters with Dead Fetuses:	0	0	0	ND[1]	ND[1]	0
	Mean % Post-implantation Loss:	3.3	3.9	1.7	ND[1]	ND[1]	3.3
	Mean Fetal Body Weight (g):	40.1	42.0	40.8	ND[1]	ND[1]	40.7
	Fetal Sex Ratios (% males):	41.8	43.4	51.9	ND[1]	ND[1]	46.2
	Fetal Anomalies:	-	-	-	ND[1]	ND[1]	-

- No noteworthy findings
[1] Dose groups at 150 and 300 mg/kg/day were terminated early (Gestation Day 9/10) due to excessive maternal toxicity

[Table excerpted from Toxicology Tabulated Summary of NDA 207318.]

9.3 Prenatal and Postnatal Development

Study title: A Developmental and Perinatal/Postnatal Reproduction Study of Pimavanserin Tartrate (ACP-103) by Oral Gavage in Rats, Including a Postnatal Behavioral/Functional Evaluation

Study no.:	(b) (4) 20046298
Study report location:	EDR SDN 1
Conducting laboratory and location:	(b) (4) [redacted]
Date of study initiation:	August 27, 2013
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	ACP-103, lot no. 0001157439, 100%

Key Study Findings

- Maternal mortality at 60 mg/kg/day pimavanserin tartrate, decrease in maternal body weight at ≥ 30 mg/kg/day, maternal clinical signs at ≥ 30 mg/kg/day including rales, hunched posture and dehydration.
- Maternal and reproductive NOAEL = 10 mg/kg/day, AUC = 233 ng.hr/ml, which is <1-fold the MRHD of 34 mg pimavanserin free base.
- Decrease in pup survival and pup body weight at ≥ 30 mg/kg/day.
- NOAEL for pup viability and growth = 10 mg/kg/day.
- No effects on sexual maturation, neurobehavioral or reproductive function in F_1 pups.

Methods

Doses:	0, 10, 30, 60 mg/kg/day pimavanserin tartrate 0, 8.5, 26, 51 mg/kg/day pimavanserin free base
Frequency of dosing:	Once daily
Dose volume:	10 ml/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	0.9% sodium chloride for injection
Species/Strain:	Rat/Sprague Dawley (b) (4)
Number/Sex/Group:	25 females/group
Satellite groups:	NA
Study design:	Dams were dosed once daily from gestation day (GD) 7 through lactation day (LD) 21, and allowed to deliver naturally. F_1 pups (1/sex/litter) were selected for continuation and evaluation for potential effects on growth, behavior, and reproductive capacity. F_1 pups that were not selected for continued evaluation were euthanized on day 21/22 postpartum and examined for gross lesions. F_1 males that were selected for mating with F_1 females were euthanized following the completion of the 14-day cohabitation period (days 116 – 121 postpartum). F_1 females that were selected for mating were euthanized on GD 13 and examined for ovarian/uterine contents.
Deviation from study protocol:	None that affected overall integrity of the study.

Observations and Results

F_0 Dams

Survival:

2 dams at 60 mg/kg/day died during the study. One 60 mg/kg/day female was found dead on LD 21. Clinical signs prior to death included: chromorhinorrhea, mild dehydration, ungroomed coat, hunched posture, thin body condition, and rales. Similar clinical signs were observed in other surviving animals at 60 mg/kg/day. This animal also had a more severe decrease in body weight and food consumption than other animals in the same group. No cause of death was determined, but the death is considered drug-related. Another animal at 60 mg/kg/day was euthanized moribund due to signs of respiratory distress (rales, dyspnea, and open mouth breathing) and a swollen neck on LD 20. The cause of death was not determined, no macroscopic findings, the sponsor considered it to be most likely due to a dosing error however, in absence of evidence, a drug cause cannot be ruled out.

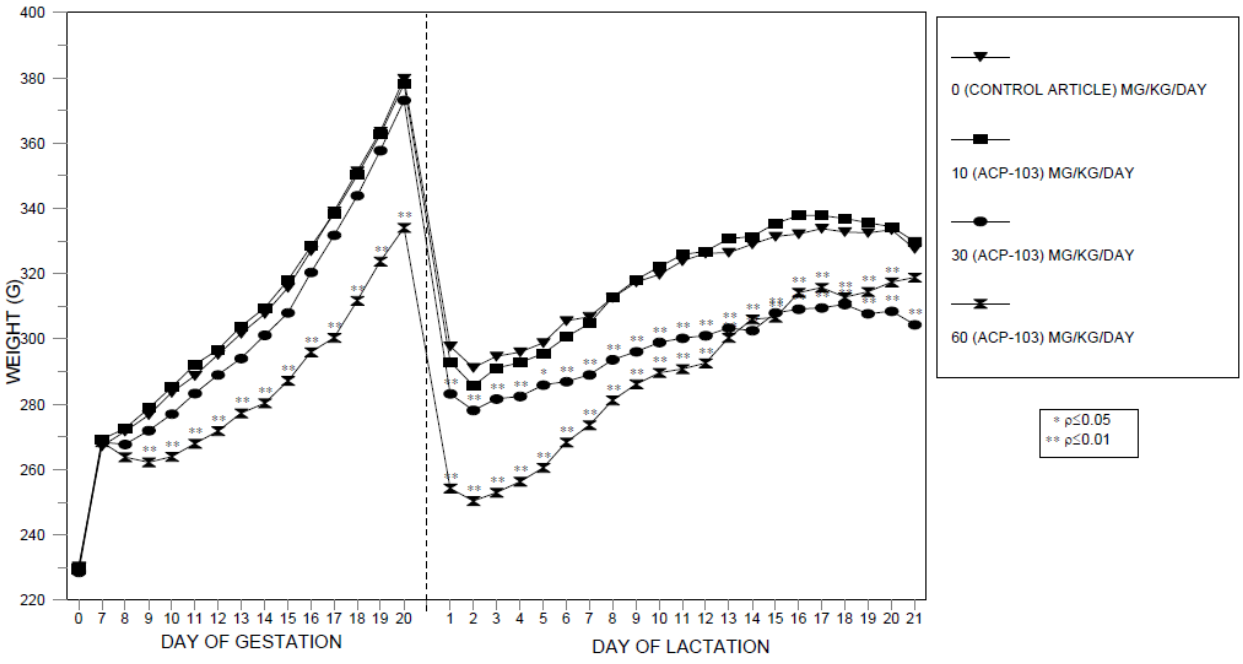
Clinical signs:

Clinical signs observed during both the gestation and lactation periods in animals at ≥30 mg/kg/day included hunched posture, rales, dehydration, sparse or ungroomed hair coat, chromorhinorrhea, salivation, decreased activity. The incidence and frequency increased with dose.

Body weight:

There was a significant decrease in maternal body weight at 60 mg/kg/day during the gestation and lactation periods and at 30 mg/kg/day during the lactation period. There was an average body weight loss at 60 mg/kg/day between GD 7-10 (-4.6 g compared to +16.4 g for controls), however after GD 10 average body weight gain at 60 mg/kg/day was comparable to controls. During the lactation period, average body weights were lower at 60 mg/kg/day (85-95% compared to controls), however body weight gain was significantly increased compared to controls. Body weight gain was significantly decreased at 30 mg/kg/day compared to controls during the lactation period (71% compared to controls). The effects on body weight correlated with decreased food consumption. Body weights for dams were recorded once on GD 0, and daily during the dose and post-dose periods, and on the day of euthanasia.

Figure 15: Maternal body weights: F_0 female rats



[Figure excerpted from (b) (4) 20046298 study report.]

Food consumption:
There was a dose-related decrease in food consumption at 30 and 60 mg/kg/day during both the gestation and lactation periods. During GDs 7-20, food consumption was

significantly decreased 68% to 94% compared to controls. During lactation days 1-14, food consumption was significantly 80% to 90% compared to controls. There were no effects on food consumption at 10 mg/kg/day.
Food consumption for dams was recorded on GDs 0, 7, 10, 12, 15, 18, and 20 and GD 25 (where necessary), and on days 1, 4, 7 and 14 postpartum.

Litter observations:
There were no drug-related effects on the numbers of dams delivering litters, the duration of gestation, averages for implantation sites per delivered litter, the gestation index (number of dams with one or more liveborn pups/number of pregnant rats), the numbers of dams with stillborn pups and of dams with all pups dying, litter sizes, and the percentage of male pups per number of pups sexed per litter. There were no dams with total litter losses.

Necropsy observation:

There were no drug-related macroscopic findings in the F_0 generation rats that survived to scheduled necropsy.

Toxicokinetics:

On the last day of dosing (LD 21) blood samples were collected from 3 control group females and 9 treated group females at predose, 0.5, 1, 4, 12, and 24 hrs postdose.

T_{max} was 20 fold higher at 60 mg/kg/day compared to 10 mg/kg/day, indicating a possible saturation of absorption. Exposure levels, both C_{max} and AUC, increased more than dose proportional.

Summary of Mean (SE) Pharmacokinetic Parameters in Female Sprague-Dawley Rat Plasma Following Oral Administration of 10, 30, and 60 mg/kg/day of Pimavansein Tartrate on DL 21

Dose (mg/kg/day)	T_{max} (hr)	C_{max} (ng/mL)	C_{max}/D (ng•kg/mL/mg)	AUC_{0-t} (ng•hr/mL)	AUC_{0-t}/D (ng•hr/mL/mg/kg)
10	0.500	31.7 ± 17.0	3.17	233 ± 39.7	23.3
30	1.00	347 ± 56.0	11.6	4010 ± 360	134
60	12.0	1070 ± 99.0	17.8	22100 ± 2630	367

[Table excerpted from (b) (4) 20046298 study report.]

Dosing solution analysis: All samples analyzed were within the acceptable range, (b) (4) % of target concentration.

F_1 Survival:

There was a significant decrease in pup survival compared to controls at 30 mg/kg/day during postpartum days 2-4 and at 60 mg/kg/day during postpartum days 2-14. Overall pup viability index was significantly decreased at 30 and 60 mg/kg/day, 90.2% and 94.3% respectively, compared to 99.4% for controls.

Table 71: F_1 pups: litter sizes and pup survival

GROUP		1	2	3	4
TEST MATERIAL		CONTROL ARTICLE	ACP-103	ACP-103	ACP-103
DOSE LEVEL (MG/KG/DAY)a		0	10	30	60
DELIVERED LITTERS WITH ONE OR MORE LIVEBORN PUPS	N	25	25	23	25
PUPS DELIVERED (TOTAL)	N	315	345	300	320
	MEAN±S.D.	12.6 ± 3.2	13.8 ± 1.8	13.0 ± 1.3	12.8 ± 2.6
LIVEBORN	MEAN±S.D.	12.6 ± 3.2	13.6 ± 1.9	12.8 ± 1.3	12.6 ± 2.8
	N(%)	314(99.7)	341(98.8)	295(98.3)	314(98.1)
STILLBORN	MEAN±S.D.	0.0 ± 0.2	0.2 ± 0.4	0.2 ± 0.6	0.2 ± 0.5
	N(%)	1(0.3)	4(1.2)	4(1.3)	5(1.6)
UNKNOWN VITAL STATUS b	N	0	0	1	1
PUPS FOUND DEAD OR PRESUMED CANNIBALIZED					
DAY 1	N/N(%)	1/314(0.3)	1/341(0.3)	2/295(0.7)	1/314(0.3)
DAYS 2- 4	N/N(%)	1/313(0.3)	4/340(1.2)	27/293(9.2)**	17/313(5.4)*
DAYS 5- 7	N/N(%)	1/312(0.3)	0/336(0.0)	0/266(0.0)	8/296(2.7)**
DAYS 8-14	N/N(%)	1/311(0.3)	0/336(0.0)	0/266(0.0)	4/288(1.4)**
DAYS 15-18	N/N(%)	0/310(0.0)	0/336(0.0)	1/266(0.4)	0/284(0.0)
DAYS 19-21	N/N(%)	0/310(0.0)	0/336(0.0)	0/265(0.0)	0/284(0.0)
DAYS 21-22	N/N(%)	----------	0/ 67(0.0)c	0/ 52(0.0)c	0/ 55(0.0)c
VIABILITY INDEX d	%	99.4	98.5	90.2**	94.3*
	N/N	312/314	336/341	266/295	296/314

DAY(S) = DAY(S) POSTPARTUM
a. Dose administration occurred on Days 7 of gestation through Day 21 lactation (rats that delivered a litter) or Day 24 of presumed gestation (rats that did not deliver a litter).
b. Maternal cannibalization or autolysis precluded identification of vital status at birth.
c. Includes litters from rats that were used for blood collection.
d. Number of live pups on Day 4 postpartum/number of liveborn pups on Day 1 postpartum.
* Significantly different from the control group value ($p \leq 0.05$).
** Significantly different from the control group value ($p \leq 0.01$).

Clinical signs:

There was an increased incidence of one or more pups from a litter that were cold to touch on one or more occasion at 30 and 60 mg/kg/day (6 and 7 litters compared to 3 control group litters). There were no drug-related clinical signs in the F_1 pups at 10 mg/kg/day.

Body weight:
There was a dose-related and significant decrease in pup body weight at all dose levels during postpartum day (PD) 1-4, and during PD 1-22 at 30 and 60 mg/kg/day (up to 26% compared to controls). There was also a dose-related and significant decrease in pup body weights for males at 30 and 60 mg/kg/day during most of the post-weaning period (PD 22 onwards); 6-15% at 30 mg/kg/day and 10-20% at 60 mg/kg/day compared to controls. Body weight gains for F_1 males at 30 and 60 mg/kg/day were also decreased compared to controls. There was a much smaller effect on body weight for F_1 females. Body weights were decreased 7-9% compared to controls at 30 mg/kg/day between PD days 22 and 36, and decreased 6-16% compared to controls at 60 mg/kg/day during PD days 22-57. The decrease in F_1 body weights correlated with a decrease in food consumption at the same dose levels.
Body weights were recorded at least once weekly during the post weaning period (including on the day that the sexual maturation criterion was met and on the first day of cohabitation), on GDs 0, 7, 10, and 13 (females only) and on the day of euthanasia (terminal weight).

Table 72: F_1 pup weights during PD 1-22

GROUP		1	2	3	4
TEST MATERIAL		CONTROL ARTICLE	ACP-103	ACP-103	ACP-103
DOSE LEVEL (MG/KG/DAY)a		0	10	30	60
DELIVERED LITTERS WITH ONE OR MORE LIVEBORN PUPS	N	25	25	23	25
LIVE LITTER SIZE AT WEIGHING					
DAY 1	MEAN±S.D.	12.5 ± 3.2	13.6 ± 1.8	12.7 ± 1.3	12.5 ± 2.8
DAY 4	MEAN±S.D.	12.5 ± 3.2	13.4 ± 1.7	11.6 ± 3.2	11.8 ± 2.8
DAY 7	MEAN±S.D.	12.4 ± 3.2	13.4 ± 1.7	11.6 ± 3.2	11.5 ± 2.8
DAY 14	MEAN±S.D.	12.4 ± 3.1	13.4 ± 1.7	11.6 ± 3.2	11.4 ± 2.9
DAY 18	MEAN±S.D.	12.4 ± 3.1	13.4 ± 1.7	11.5 ± 3.1	11.4 ± 2.9
DAY 21	MEAN±S.D.	12.4 ± 3.1	13.4 ± 1.7	11.5 ± 3.1	11.4 ± 2.9
PUP WEIGHT/LITTER (GRAMS)					
DAY 1	MEAN±S.D.	6.9 ± 0.8	6.5 ± 0.5*	6.3 ± 0.5**	5.8 ± 0.7**
DAY 4	MEAN±S.D.	9.5 ± 1.2	8.8 ± 0.8*	8.3 ± 1.2**	7.4 ± 1.3**
DAY 7	MEAN±S.D.	13.3 ± 2.0	12.7 ± 1.5	11.4 ± 1.4**	9.8 ± 2.0**
DAY 14	MEAN±S.D.	25.3 ± 4.3	24.6 ± 2.7	21.8 ± 2.3**	19.2 ± 3.7**
DAY 18	MEAN±S.D.	32.7 ± 5.5	31.8 ± 3.7	28.6 ± 2.9**	25.8 ± 4.1**
DAY 21	MEAN±S.D.	39.9 ± 6.8	38.7 ± 5.0	35.1 ± 4.1**	31.9 ± 5.3**

DAY = DAY POSTPARTUM
a. Dose administration occurred on Days 7 of gestation through Day 21 lactation (rats that delivered a litter) or Day 24 of presumed gestation (rats that did not deliver a litter).
b. Includes litters from rats that were used for blood collection.
* Significantly different from the control group value ($p \leq 0.05$).
** Significantly different from the control group value ($p \leq 0.01$).

Figure 16: Body weights: F1 generation male rats

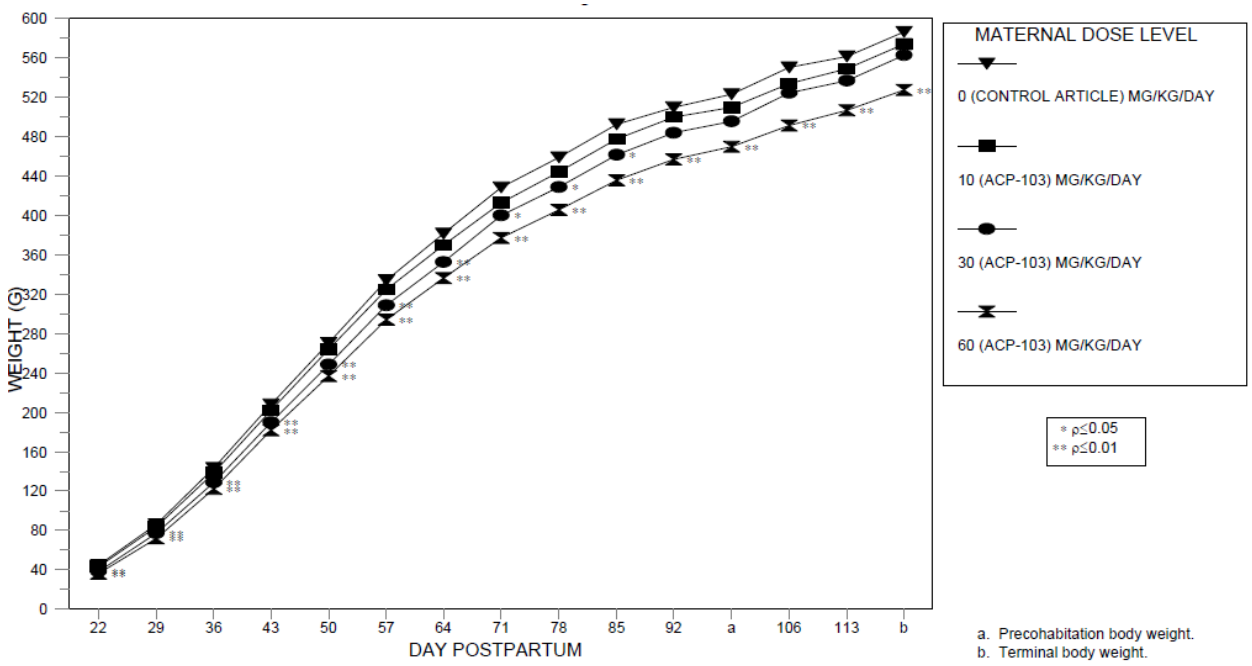
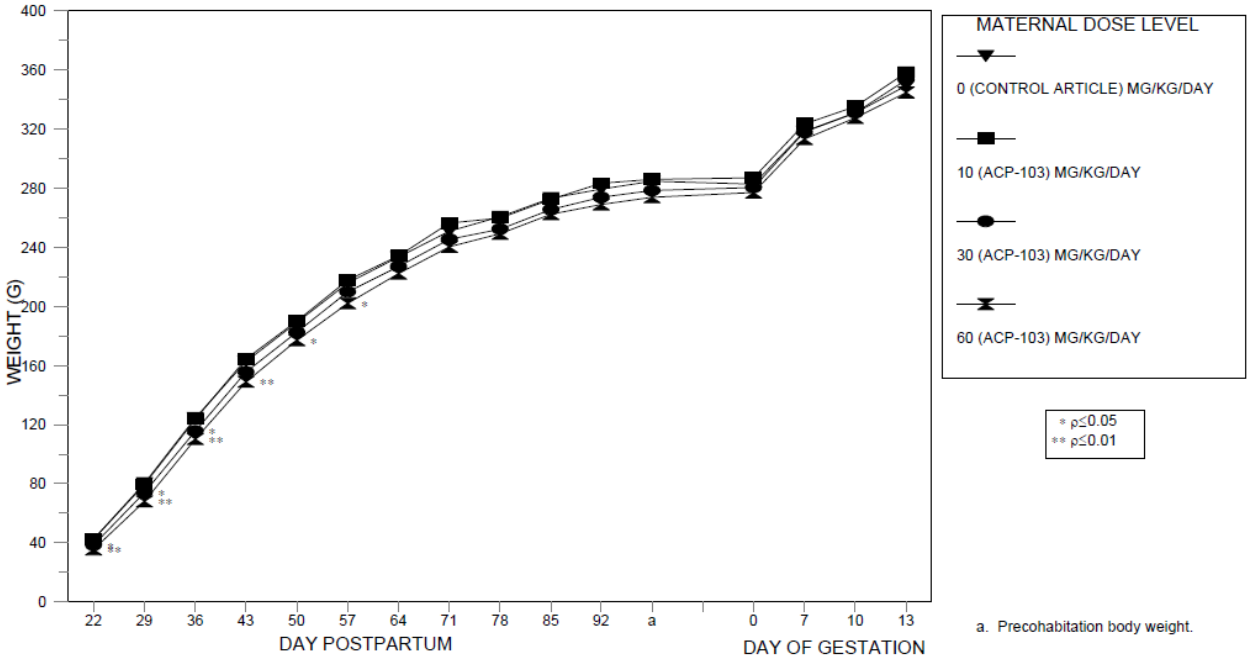


Figure 17: Body weights: F1 generation female rats



Food consumption:

There was a dose-related and significant decrease in food consumption for F_1 males at 30 and 60 mg/kg/day during postpartum days 43-71 (5-8% compared to controls). The decrease in food consumption correlated with decreased body weights. There was no effect on absolute food consumption for F_1 females at any dose level.

Physical development:
Sexual maturation in F_1 pups was assessed by time of balano-preputial separation for males and of vaginal patency for females. There was no drug-related effect on sexual maturation in F_1 pups; the mean day of observation of male balano-preputial separation (46.6 to 47.7 days) and of female vaginal patency (34.0 to 34.7 days) was comparable across all dose groups.

Neurological assessment:
There were no drug-related effects on short-term and long-term retention in the passive avoidance tests or on overt coordination, swimming ability, and learning and memory in the M-shaped water maze test in F_1 pups from any dose group.
Beginning on Day 24 postpartum ± 1 day, one male and one female rat from each litter were tested twice for passive avoidance evaluations. The test sessions were separated by a one-week interval, and the criterion was the same for both days of testing.
Beginning on Day 70 postpartum ± 2 days, one male and one female rat from each litter were evaluated in a water-filled M-maze for overt coordination, swimming ability, learning and memory.

Reproductive assessment:

There were no drug-related effects on F_1 generation offspring mating or fertility. The mating index was 100%, the number of days in cohabitation ranged from 2.5 to 2.6 days, and the male and female fertility index was 96.0% or 100%.
On Days 93 through 98 postpartum, within each dose group, consecutive order was used to assign rats to cohabitation (i.e., pairing), one male per one female. Sibling matings were excluded. The cohabitation period consisted of a maximum of 14 days. Females observed with spermatozoa in a smear of the vaginal contents and/or a copulatory plug observed *in situ* were considered to be at DG 0 and assigned to individual housing.

F_1 pup gross pathology:
There were no drug-related macroscopic findings in the F_1 pups at any dose level. Of the pups that were found dead and necropsied, 2, 0, 3, and 4 pups did not have any milk in their stomachs from the 0, 10, 30, and 60 mg/kg/day groups, respectively. This finding suggests that the pups failed to thrive due to a lack of nursing. There was a slight, but statistically significant, decrease in paired testes weights at 30 and 60 mg/kg/day, 8.4% and 7.4% compared to controls, respectively. However, the sponsor noted that the group means and individual testes weighs were generally within the historical control range for the laboratory. The testes were not examined microscopically; therefore the toxicological significance is unknown. There were no drug-related effects on the paired weights of the epididymides at any dose level or testes at 10 mg/kg/day.

F_1 ovarian and uterine examinations:
Pregnancy was confirmed in 100% (25/25) of F_1 females from all drug-treated groups. There were no drug-related effects on any ovarian and uterine parameters (% preimplantation loss, litter sizes, viable and non-viable embryos, and % postimplantation loss). No placental abnormalities were detected.

10 Special Toxicology Studies

10.1 Combination toxicity study

Study Title: ACP-103/L-Dopa/Carbidopa: 14-day oral gavage combination toxicity study in male rats
Study no. 1574-001
Testing Facility: (b) (4)
Study initiation date: May 1, 2008

Design: non-GLP
ACP-103 (b) (4) lot no. 1046433, 98.8%
Levodopa, lot no. 080202, 99.92%
Carbidopa, lot no. 20070503, 100%
Vehicle: 1% methylcellulose in deionized water

Rat/males only/Sprague-Dawley [redacted](b) (4) ~8 weeks old, 230-251 g at day of randomization
Dosed once daily by oral gavage in a volume of 10 ml/kg

Parameters evaluated: Clinical observations, body weights on Days -1, 1, 3, 7, and 14, food consumption recorded weekly started week -1, clinical chemistry, hematology and coagulation (blood samples taken prior to necropsy only), organ weights, gross and microscopic pathology. Blood for toxicokinetic analysis was taken from TK satellite animals prior to dosing and at 0.5, 1, 2, 4, 8, and 24 hours postdose on Days 1 and 14.

The following sponsor's table shows the dosing design for all groups. The doses for levodopa (LD) and carbidopa (CD) were the same for all treatment groups, 120 and 30 mg/kg/day, respectively. The doses for ACP-103 were 15, 30, 45 and 100 mg/kg/day. There was no control group in this study, and there was not a group dosed with ACP-103 alone to compare toxicities to the combination groups. *The overall study design was not optimal for assessing if LD/CD combined with ACP-103 exacerbated toxicities caused by ACP-103 alone*. Toxicities ideally should be compared within the same study.

Group Assignments

Group Number	Dose Level (mg/kg/day)	Number of Animals Male
Main Study		
1 15/120/30	ACP/LD/CD[a]	6
2 30/120/30	ACP/LD/CD[a]	6
3 45/120/30	ACP/LD/CD[a]	6
4 100/120/30	ACP/LD/CD[a]	6
TK		
5 15/120/30	ACP/LD/CD[a]	9
6 30/120/30	ACP/LD/CD[a]	9
7 45/120/30	ACP/LD/CD[a]	9
8 100/120/30	ACP/LD/CD[a]	9

[a] Animals were dosed with 120 mg/kg/day LD and 30 mg/kg/day CD on Days -7 to 14. Animals were dosed with ACP-103 on Days 1 to 14.

Organs/tissues collected and examined:

- Adrenal (2)
- Brain [cerebrum, midbrain, cerebellum, medulla/pons]*#
- Ep ididymis (2)
- Gonads: testis (2)*
- Gross lesions
- Kidney (2)*
- Liver [3 sections collected; 2 examined]*
- Lung with bronchi [collected whole; 2 sections exam ined]*
- Pro state*
- Skeletal muscle, biceps femoris
- Spl een*
- Thy mus*

#Not microscopically examined
*Organ weighed
(2) Paired organ

All tables and figures excerpted from study report, unless stated otherwise.

Results:

There were no deaths.

Clinical signs included dose-dependent piloerection and salivation, and to a lesser extent red/black/brown material around the nose/mouth, which was not dose-dependent. One high dose animal had breathing abnormalities of rales and audible sounds and two high dose animals had unkempt appearance.

There was an overall decrease in body weight gain at the high dose, 31% compared to the low dose group. This is consistent with decreases in body weight and body weight gain observed in rats treated with ACP-103 alone in previous studies. There was a corresponding decrease in food consumption in the high dose group.

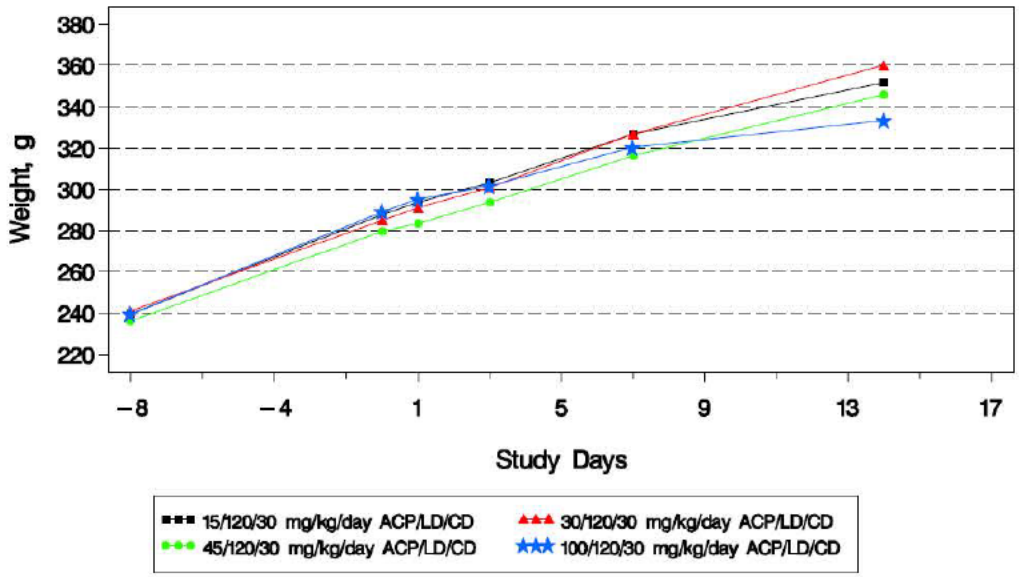
At the 45 and 100 mg/kg/day ACP-103 dose, lymphocytes and monocytes were increased 1.2-fold and 1.8-fold compared to the low dose group, respectively. At the high dose, eosinophils were decreased 0.54-fold compared to the low dose group. There were no major differences in any coagulation or clinical chemistry parameters between the groups.

There were no gross macroscopic findings. There was an increase in liver and lung weights in the high dose group compared to the low dose group. Microscopic findings were observed in the adrenal glands, liver, epididymides and lungs. Vacuolation was observed in the adrenal glands of the 45 and 100 mg/kg/day ACP-103 group animals and in the liver and epididymides of high dose animals. Vacuolated macrophages were observed in the lungs at 45 and 100 mg/kg/day. Lymphoid depletion of the thymus gland cortex was observed in one high dose animal. No adverse (inflammation, degeneration, hyperplasia, etc.) microscopic findings were observed at any of the dose combination groups.

Conclusions:

The microscopic findings observed in rats treated with the combination of ACP-103 and levodopa/carbidopa are consistent with systemic phospholipidosis observed with ACP-103 treatment alone in previous rat studies (28-day repeat dose study at doses up to 100 mg/kg/day). The addition of levodopa and carbidopa does not appear to exacerbate the findings or produce any additional toxicity or have a significant effect on plasma exposure of ACP-103, however this was done indirectly separate studies as no direct comparison could be done in this study due to the lack of an ACP-103 alone treated group. This study demonstrated that phospholipidosis in the lungs (including rales), and adrenal glands occurs in male rats after only 14-days of repeat dosing with 45 mg/kg/day of ACP-103 (AUC of 13,055 ng.hr/ml).

Figure 1 Mean Body Weight Values – MALE



Mean Body Weight Gain (g) With Percent Change Compared to Low Dose (Day -8 to -1, Day -1 to 7, and Day -1 to 14)		
Dose Group (mg/kg/day ACP/LD/CD)	Male Mean Body Weight (g) Gain Day -8 to -1 (%)	
15/120/30 +48.3	(NA)	
30/120/30	+44.0 (↓9%)	
45/120/30	+43.5 (↓10%)	
100/120/30 +49.6	(NC)	
Dose Group (mg/kg/day ACP/LD/CD)	Male Mean Body Weight (g) Gain Day -1 to 7 (%)	Day -1 to 14 (%)
15/120/30	+38.8 (NA)	+63.8 (NA)
30/120/30	+41.6 (NC)	+75.0 (↑17%)
45/120/30	+36.6 (↓6%)	+66.3 (↑3%)
100/120/30	+31.2 (↓20%) +44.2	(↓31%)
NA – Not Applicable; NC – No Change		

Selected Microscopic Findings,					
Dose level (mg/kg/day)		15/120/30 ACP/LC/CD	30/120/30 ACP/LC/CD	45/120/30 ACP/LC/CD	100/120/30 ACP/LC/CD
Sex		**M**	**M**	**M**	**M**
Number examined		**6**	**6**	**6**	**6**
Lungs					
macrophages, vacuolated					
-	minimal	0	0	2	5
-	mild	0	0	0	1
Adrenal gland					
vacuolation					
-	minimal	0	0	1	4
-	mild	0	0	0	2
Epididymides					
vacuolation					
-	minimal	0	0	0	4
-	mild	0	0	0	2
Liver					
vacuolation, centrilobular					
-	minimal	0	0	0	4

Toxicokinetics:

Daily Dose (mg/kg/day):		**15**	**30**	**45**	**100**
Number of Animals:		**M: 6**	**M: 6**	**M: 6**	**M: 6**
Toxicokinetics: No. of Animals		M: 9	M: 9	M: 9	M: 9
ACP-103 Toxicokinetics:					
C_{max} (ng/mL)	Day 1	17	191	251	905
	Day 14	63	536	745	2357
AUC_{all} (ng·h/mL)	Day 1	116	2441	3750	15917
	Day 14	815	7055	13055	44111
L-dopa (120 mg/kg/day) Toxicokinetics:					
C_{max} (ng/mL)	Day 1	11387	10207	10003	6993
	Day 14	9993	11827	10447	7233
AUC_{all} (ng·h/mL)	Day 1	87558	87014	90011	64636
	Day 14	55978	65621	84724	65087
Carbidopa (30 mg/kg/day) Toxicokinetics:					
C_{max} (ng/mL)	Day 1	288	274	242	191
	Day 14	404	395	293	227
AUC_{all} (ng·h/mL)	Day 1	2236	2058	2154	1547
	Day 14	2126	2516	1978	2165

[Table excerpted from Toxicology Tabulated summary section of NDA 207318.]

Dosing solution analysis:
Concentration analysis of dose formulation samples showed that ACP-103 concentrations were within the required specifications of (b) (4) % of the nominal concentrations (b) (4) % of theoretical). Carbidopa and L-dopa concentrations ranged slightly outside of the ±15% specifications (-9.33% to +19.33% for Carbidopa and -23.75% to +1.67% for L-dopa). The sponsor did not consider these variations to have affected either the quality or the integrity of the study.

Note:
As per discussion in the pre-NDA meeting minutes, the sponsor was not required to conduct an combination embryo-fetal toxicity study with pimavanserin and L-

dopa/carbidopa, due to the age of the patient population (most patients will be older and not of child-bearing potential). This reviewer concurs with this justification.

10.2 Local Tolerance

In SDN 12, dated December 9, 2015, the sponsor stated that the *"acute inhalation toxicity study in rats (Study 18244-14) was conducted, along with an acute dermal irritation study in rabbits (Study (b) (4) 14-22385.03), a bovine corneal opacity and permeability assay (Study (b) (4) 14-22385.59), a hen's egg chorioallantoic membrane test (Study (b) (4) 14-22385.09) and a local lymph node assay (Study (b) (4) 14-22385.26), to gather information for the pimavanserin material data safety sheet (MSDS) and to be used for setting occupational safety and health procedures. The acute inhalation toxicity study was a standard design for this type of study and no additional data were collected as part of that study."*

Species/ Strain	Method of Administration	Doses (mg/kg)	Gender and No. per Group	Noteworthy Findings	Study Number
Rabbit/NZW	Dermal	0.5 g	M: 1 ; F: 2	ACP-103 is not a dermal irritant	(b) (4) 14-22385.03
Hen`s White Leghorn egg	*in vitro*	300 µL of (b) (4) (b) (4) ACP-103 mixture, 0.9% saline, 0.1 N sodium hydroxide, 1% sodium dodecyl sulfate	6 eggs/group	Irritating potential of ACP-103 is severe/corrosive: Irritation Score of 6.43, 12.41 and 14.74 for (b) (4) (b) (4) mixture of ACP-103; Threshold Concentration was (b) (4) %.	14-22385.09
Bovine corneas	*ex vivo*	0.75 mL of (b) (4) ACP-103 mixture, 0.9% saline, minimal essential media, or 20% imidazole	3 corneas/ group	Irritating potential of ACP-103 is severe/corrosive: *in vitro* irritancy score of ACP-103 is 213.59.	(b) (4) 14-22385.59
Rat/SD	Inhalation	2.27, 5.14 mg/L	M: 5, F: 5	Mortality at concentration of 2 mg/L and MMAD of 4 - 6 µm. LC_{50} approximately 2 mg/L in males and >2 mg/L in females.	18244-14

F – Female; LC_{50} – median lethal concentration; M – Male; MMAD – Mass Median Aerodynamic Diameter; NZW – New Zealand White; SD – Sprague-Dawley

Antigenicity:

Species/ Strain	Method of Administration	Doses (mg/kg)	Gender and No. per Group	Noteworthy Findings	Study Number
Mice/CBA/J	Topical application	(b) (4) (b) (4) ACP-103 in DMSO, DMSO control, alpha-hexylcinnamaldehyde positive control	F: 5	Dermal sensitizing effect of ACP-103 in local lymph node assay as Stimulation Index values ≥ 1.6	(b) (4) 14-22385.26

[Tables excerpted from toxicology tabulated summary section of NDA 207318.]

Dermal toxicity:

Study no. (b) (4) 14-22385.26: Local Lymph Node Assay (LLNA-BrdU ELISA) Evaluation of pimavanserin tartrate (ACP-103) in mice

Design:

ACP-103 (lot no. 0001157439) at concentration of (b) (4) % were administered by topical application to the dorsum of each ear of CBA/J female mice

(5/group) for three consecutive days. A vehicle control of DMSO and a positive control of 25% alpha-hexylcinnamaldehyde were also used. Mice were given an i.p. injection of 5-bromo-2'-deoxy-uridine (BrdU) 4 days following the first dose and ~24 hrs prior to sacrifice. Ear thickness was measured and the auricular lymph nodes were isolated at sacrifice. Single-cell suspensions of lymph node cells were analyzed by ELISA for BrdU incorporation. The Stimulation Index (SI) was calculated for each group.

Results:

Table 2: Mean Stimulation Index

Treatment	SI	S.D.
DMSO (Vehicle Control)	1.0	0.5
25% HCA (Positive Control)	1.7[a,b]	0.5
[(b)(4)] (w/v) ACP-103, Lot# 0001157439	1.6[a,b]	0.2
w/v) ACP-103, Lot# 0001157439	1.4	0.2
(w/v) ACP-103, Lot# 0001157439	2.3[a]	0.8
(w/v) ACP-103, Lot# 0001157439	1.9[a,b]	0.3
(w/v) ACP-103, Lot# 0001157439	2.1[a]	0.5

a = SI ≥ 1.6 indicates a sensitizing response b = 1.6 ≤ SI ≤ 1.9 indicates a borderline sensitizing response

[Table excerpted from study report.]

"Treatment with the test article resulted in group SI values indicating a definitive positive response at [(b)(4)]% and [(b)(4)]% (w/v), a low borderline positive response at [(b)(4)]% (w/v), and a high borderline positive response at [(b)(4)]% (w/v). This is a dose-independent response; nonetheless the test article did produce a positive response indicative of sensitization. In addition, statistical analysis (ANOVA followed by the Students' t- Test) found that data from the [(b)(4)]%, [(b)(4)]% and [(b)(4)]% (w/v) dose groups were significantly different from the DMSO Vehicle Control Group (see Appendix G). There was no evidence at any dose level of systemic toxicity or excessive dermal irritation that might contribute to a "false positive" result." Therefore according to this study, ACP-103 is considered a dermal sensitizer.

Phototoxicity:
A phototoxicity assessment was made for pimavanserin tartrate by measuring the UV/visible (280-750 nm) spectrum at a concentration of 1 mg/ml (report ACP07). The maximum wavelength in two separate solvents (methanol and phosphate buffer pH 7.4) was 290 nm. The molar extinction coefficient (MEC) was calculated to be 376.1 and 251.9 L/mol/cm, respectively in each solvent. According to ICH S10, compounds with a MEC less than 1000 L/mol/cm do not present a significant photo safety concern in humans and additional nonclinical phototoxicity studies are not required.

10.3 Impurities

General Toxicology studies for Qualification of Impurities [(b)(4)]
The sponsor conducted two 4-eek repeat dose toxicity studies with ACP-103 spiked with either [(b)(4)]% of impurity [(b)(4)] or [(b)(4)]% of impurity [(b)(4)] in order to qualify these two impurities. However, in the pre-NDA meeting the sponsor was informed that the division typically

requests 90-day repeat dose toxicity studies in order to qualify impurities for chronic indications and that the adequacy of the 4-week studies would be a matter of review.

The following text and table is excerpted from the sponsor's response to an information request (SDN 7, October 14, 2015) regarding levels of impurities (b) (4) used in longer duration toxicity studies.

Impurity (b) (4) and Impurity (b) (4) data are available for two pimavanserin tartrate batches 981756 and 1046433 that were used in toxicity studies of 3 months or longer duration. These lot data and their corresponding use in toxicity studies are summarized in Table 2. Both lots were also used in clinical trials; batch 1046433, in particular, was used extensively throughout the Phase 3 PDP program, including in the 6-week placebo controlled studies (ACP-103-012, -014, and -020) and in both long-term open-label studies (ACP-103-010 and -015). In addition, this batch was used in the thorough QT study (ACP-103-018).

Table 73: Levels of impurities (b) (4) in toxicity studies 3 months or longer

Table 2 Impurity (b) (4) and Impurity (b) (4) Data for Drug Substance Lots Used in Toxicity Studies of 3 Months or Longer Duration

Batch Number	Date of Manufacture	Batch Size	Polymorphic Form	Study Number	Description of Use	Impurity (b) (4) (% w/w)	Impurity (b) (4) (% w/w)
981756	Apr-05	25 kg	(b) (4)	(b) (4)-146.01	A 12-Month Nasogastric Gavage Toxicity Study of ACP-103 in Cynomolgus Monkeys Followed by a 4-Month Recovery Period	< (b) (4)%	(b) (4)%[a]
				(b) (4)-146.02	A 6-Month Oral Administration Repeat Dosing Toxicity Study of ACP-103 in Sprague-Dawley Rats Followed by a 3-Month Recovery Period		
1046433	May-06	160 kg	(b) (4)	(b) (4)-616002	A 13-Week Oral (Gavage) Toxicity Study of ACP-103 in Mice With a 28-Day Recovery Period	< (b) (4)%	(b) (4)%[b]
				(b) (4)-616004	A 24-Month Oral (Gavage) Carcinogenicity Study of ACP-103 in Rat		
				(b) (4)-616006	A 24-Month Oral (Gavage) Carcinogenicity Study of ACP-103 in Mice		
				(b) (4)-616007	A 6-Month Oral Administration Repeat Dosing Toxicity Study of ACP-103 in Sprague-Dawley Rats Followed by a 6-Month Recovery Period		

a Tested in 2015

b Tested in 2014

[Table excerpted from SDN 7, response to information request.]

Study no. (b) (4) 20050631

Study title: A 4-week oral gavage qualification study of pimavanserin tartrate (ACP-103) and related substance D in rats, GLP and QA

Testing Facility: (b) (4)

Design:

Drug: ACP-103, lot no. 1157439, 100.2%

Related substance (b) (4) : lot no. 0251AS1, 99.69%

Male Sprague-Dawley rats: 10/group, ~8 weeks at dosing initiation

TK satellite animals: 9/treatment group, 3/control group

Dosing: once daily via oral gavage, 10 ml/kg
Doses: 0, ACP-103 (30 mg/kg/day), ACP-103 (10 mg/kg/day) + (b)% (b) (4) related substance (b) (4) ACP-103 (30 mg/kg/day) + (b)% (b) (4) related substance (b) (4)
Vehicle: 0.9% saline

Group No.	Test Material	ACP-103 Dose Level (mg/kg/day)	Dose Volume (mL/kg)	ACP-103 Dose Concentration (mg/mL)	Related Substance (b) (4) Dose Level (mg/kg/day)	No. of Animals	
						Main Study	Toxicokinetic Study
						Males	Males
1	0.9% Physiological Saline	0	10	0	0	10	3
2	ACP-103	30	10	3	0	10	9
3	ACP-103 + Related Substance (b) (4) at (b) (4)%	10	10	1	(b) (4)	10	9
4	ACP-103 + Related Substance (b) (4) at (b) (4)%	30	10	3	(b) (4)	10	9

[Table excerpted from study report.]

Parameters evaluated: clinical signs, body weight, food consumption, clinical pathology (hematology, coagulation, clinical chemistry and urinalysis), gross pathology, organ weights, histopathology, toxicokinetics.

Results:
No mortality occurred. There were no drug-related clinical signs. There was a decrease in absolute body weight and body weight gain across all groups compared to controls, but the addition of (b) (4)% impurity (b) (4) did not have any impact (no differences in group 2 and group 4 values). Absolute body weight values on day 28 were 6%, 4% and 5% decreased compared to controls at 30 mg/kg/day ACP-103, 10 mg/kg/day ACP-103+(b) (4)% impurity (b) (4) and 30 mg/kg/day+(b) (4)% impurity (b) (4) respectively. Body weight gain values were decreased 12%, 9% and 11% compared to controls at 30 mg/kg/day ACP-103, 10 mg/kg/day ACP-103+(b) (4)% impurity (b) (4), and 30 mg/kg/day+(b) (4)% impurity (b) (4) respectively. There was a slight decrease in food consumption (4-9% compared to controls) across all dose groups. However, there was no difference between the 30 mg/kg/day ACP-103 and 30 mg/kg/day ACP-103+(b) (4)% impurity (b) (4) groups. There were no drug-related effects on any hematology, clinical chemistry or urinalysis parameters. There were no significant drug-related effects on organ weights from any group, and no effect of the addition of (b) (4)% impurity (b) (4) on organ weight values. Possible drug-related macroscopic findings included one animal from the 30 mg/kg/day ACP-103 group with a pale focus in the lungs and one from the 30 mg/kg/day ACP-1-3+(b) (4)% impurity (b) (4) group with a “focus” in the lung. Liver necrosis was observed in 1 animal from the 30 mg/kg/day ACP-103 group and in 2 animals from the 30 mg/kg/day ACP-103+(b) (4)% impurity (b) (4) group, however given the low incidence and severity the study pathologist considered the effect to be an equivocal drug effect. This reviewer agrees with that conclusion. There was no finding in the 10 mg/kg/day ACP-103+(b) (4)% impurity (b) (4) group, therefore the effect is most likely not

directly related to impurity (b)(4) Findings consistent with phospholipidosis were observed in the lungs of rats from all groups (mixed cell infiltration characterized by *"small, focal infiltrates of mixed mononuclear cells in the alveolar septae coupled with increased numbers of alveolar histiocytes"*). The infiltrate in the lung were increased over controls in the 30 mg/kg/day ACP-103 group but the addition of (b)(4)% impurity (b)(4) did not exacerbate the effect. Inflammation in the lungs in 2 animals from the 30 mg/kg/day ACP-103 (b)(4)% impurity (b)(4) group was not discussed in the pathology report, except to say that all other findings are common background findings and most likely not drug-related. Since this finding was not also observed in the 10 mg/kg/day ACP-103+(b)(4)% impurity (b)(4) group the effect is most likely not directly related to impurity (b)(4).

Removal Reason: TERMINAL EUTHANASIA	Male			
	0 mg/kg/ day Group 1	30 mg/kg/ day Group 2	10+0.2 mg/kg/ day Group 3	30+0.6 mg/kg/ day Group 4
Number of Animals:	10	10	10	10
LUNG				
Examined	10	10	10	10
No Visible Lesions	8	4	9	6
Inflammation, granulomatous	0	0	0	2
.... minimal	0	0	0	2
Infiltration, mixed cell	2	6	1	2
.... minimal	2	5	1	2
.... mild	0	1	0	0
LIVER				
Examined	10	10	10	10
Necrosis	0	1	0	2
.... minimal	0	1	0	1
.... mild	0	0	0	1
Hepatodiaphragmatic nodule	0	0	0	1
Infiltration, mixed cell	10	10	10	10
LIVER (Continued...)				
.... minimal	10	10	9	9
.... mild	0	0	1	1
Fibrosis	0	0	1	0
.... minimal	0	0	1	0

[Table excerpted from study report.]

All analyzed dose formulations were within ± (b)(4)% of the nominal concentration, with the exception of day 1 group 3 sample which was (b)(4)% of nominal.

Toxicokinetics:
Exposure to ACP-103 was higher with the addition of impurity (b)(4) as compared to ACP-103. This is evident from the increased C_{max} and AUC values (almost 2-fold for AUC on day 28) at the 30 mg/kg/day dose of ACP-103 without the impurity compared to the addition of (b)(4)% impurity (b)(4) However, there was a fair amount of variability in the values within groups. The sponsor did not comment further on these changes.

Summary Mean (± SE) ACP-103 Toxicokinetic Parameters in Male Sprague-Dawley Rat Plasma Following 10 mg/kg/day and 30 mg/kg/day Oral Administration of Pimavanserin Tartrate + Related Substance (b)(4) at (b)(4)% on Day 1

Dose (mg/kg)	T_{max} (hr)	C_{max} (ng/mL)	$AUC_{(0-24h)}$** (ng•hr/mL)	$AUC_{(0-8h)}$ (ng•hr/mL)	C_{max}/D (ng•kg/mL/mg)	$AUC_{(0-24h)}$/D (ng•hr/mL/mg/kg)
10	4.00	18.7 ± 1.64	82.5 ± 10.5	82.5	1.87	8.25
30	8.00	258 ± 31.8	3510 ± 356	1440	8.61	117
30*	4.00	156 ± 14.1	2220 ± 105	1010	5.19	74.0

* Without Related Substance (b)(4) at (b)(4)%
** $AUC_{(0-24h)} = AUC_{(0-t)}$

Summary Mean (± SE) ACP-103 Toxicokinetic Parameters in Male Sprague-Dawley Rat Plasma Following 10 mg/kg and 30 mg/kg/day Oral Administration of Pimavanserin Tartrate + Related Substance (b)(4) at (b)(4)% on Day 28

Dose (mg/kg)	T_{max} (hr)	C_{max} (ng/mL)	$AUC_{(0-24h)}$** (ng•hr/mL)	$AUC_{(0-8h)}$ (ng•hr/mL)	C_{max}/D (ng•kg/mL/mg)	$AUC_{(0-24h)}$/D (ng•hr/mL/mg/kg)	R_{AUC}[a]
10	4.00	46.8 ± 13.2	232 ± 42.5	232	4.68	23.2	2.81
30	8.00	475 ± 70.1	6300 ± 802	2340	15.8	210	1.80
30*	4.00	348 ± 21.8	3750 ± 911	1940	11.6	125	1.69

[a] R_{AUC} = Day 28 $AUC_{(0-t)}$/ Day 1 $AUC_{(0-t)}$.
* Without Related Substance (b)(4) at (b)(4)%
** $AUC_{(0-24h)} = AUC_{(0-t)}$

[Toxicokinetic tables excerpted from study report.]

Conclusion: Overall, the addition of (b)(4)% impurity (b)(4) to 10 mg/kg/day or 30 mg/kg/day ACP-103 did not result in any new toxicities or exacerbate any toxicities due to ACP-103 alone. Consistent with previous studies with ACP-103, there was a reduction in body weight and microscopic findings of phospholipidosis in the lungs. There is no explanation for the increased exposure to 30 mg/kg/day ACP-103 when (b)(4)% impurity (b)(4) is added, and whether or not this is a real affect, or just a reflection of inter-animal variability in PK parameters.

Study no. (b)(4) 20055753
Study title: A 4-week oral gavage qualification study of pimavanserin tartrate (ACP-103) and related substance (b)(4) in rats, GLP and QA

Testing Facility: [redacted]

Design:
Drug: ACP-103, lot no. 1157439, 100.2%
Related substance [redacted] batch no. KMA 1423-ANARD 55822, 99.4%
Male Sprague-Dawley rats: 10/group, ~8 weeks at dosing initiation
TK satellite animals: 9/treatment group, 3/control group
Dosing: once daily via oral gavage, 10 ml/kg
Doses: 0, ACP-103 (30 mg/kg/day), ACP-103 (10 mg/kg/day) + [redacted]% [redacted] related substance [redacted] ACP-103 (30 mg/kg/day) + [redacted]% [redacted] related substance [redacted]
Vehicle: 0.9% saline

Group No.	Test Material	ACP-103 Dose Level (mg/kg/day)	Dose Volume (mL/kg)	ACP-103 Dose Concentration (mg/mL)	Related Substance [redacted] Dose Level (mg/kg/day)	No. of Animals	
						Main Study	Toxicokinetic Study
						Males	Males
1	0.9% Physiological Saline	0	10	0	0	10	3
2	ACP-103	30	10	3	0	10	9
3	ACP-103 + Related Substance [redacted] at [redacted]%	10	10	1	[redacted]	10	9
4	ACP-103 + Related Substance [redacted] at [redacted]%	30	10	3	[redacted]	10	9

[Table excerpted from study report.]

Parameters evaluated: clinical signs, body weight, food consumption, clinical pathology (hematology, coagulation, clinical chemistry and urinalysis), gross pathology, organ weights, histopathology, toxicokinetics.

Results:
No mortality occurred and there were no drug-related clinical signs in any group. Body weights were slightly decreased across all dose groups compared to controls, but the addition of [redacted]% impurity [redacted] did not have any effect on body weight changes compared to ACP-103 alone. Mean body weights at the end of dosing on study day 28 were decreased 4.0%, 3.5%, and 3.9% compared to controls from groups 2, 3 and 4, respectively. Overall food consumption was slightly decreased for all drug-treated groups, 7-11% compared to controls, which correlated with the decrease in body weight. There was no difference in food consumption between the 3 treated groups. There were no clear drug-related effects on any hematology, clinical chemistry or

urinalysis parameters. There were a few isolated instances of statistically significant changes compared to controls for various groups, however the values were within the historical control ranges and therefore were not considered toxicologically relevant. There were no drug-related macroscopic findings, effects on organ weights or microscopic findings from any dose group.

Toxicokinetics:

Summary Mean (± SE) ACP-103 Toxicokinetic Parameters in Male Sprague-Dawley Rat Plasma Following 10 mg/kg and 30 mg/kg Oral Administration of Pimavanserin Tartrate With or Whitout Related Substance (b) (4) on Day 1

Dose (mg/kg/day)	Related Substance (b) (4) (mg/kg/day)	T_{max} (hr)	C_{max} (ng/mL)	$AUC_{(0-8)}$ (ng•hr/mL)	$AUC_{(0-t)}$ (ng•hr/mL)	$AUC_{(0-24)}$ (ng•hr/mL)	C_{max}/D (ng•kg/mL/mg)	$AUC_{(0-t)}/D$ (ng•hr/mL/mg/kg)
10	(b) (4)	2.00	16.1 ± 4.68	60.4	60.4 ± 26.3	63.7 ± 26.7	1.61	6.04
30	0	8.00	154 ± 41.3	989	2220 ± 425	2220 ± 425	5.12	74.0
30	(b) (4)	4.00	149 ± 20.3	878	878 ± 115	1680 ± 422	4.97	29.3

Summary Mean (± SE) ACP-103 Toxicokinetic Parameters in Male Sprague-Dawley Rat Plasma Following 10 mg/kg and 30 mg/kg Oral Administration of Pimavanserin Tartrate With or Without Related Substance (b) (4) on Day 28

Dose (mg/kg)	Related Substance (b) (4) (mg/kg/day)	T_{max} (hr)	C_{max} (ng/mL)	$AUC_{(0-8)}$ (ng•hr/mL)	$AUC_{(0-t)}$ (ng•hr/mL)	$AUC_{(0-24)}$ (ng•hr/mL)	C_{max}/D (ng•kg/mL/mg)	$AUC_{(0-t)}/D$ (ng•hr/mL/mg/kg)	R_{AUC}[a]
10	(b) (4)	1.00	72.6 ± 28.9	316	316 ± 64.2	408 ± 81.3	7.26	31.6	5.24
30	0	8.00	292 ± 81.5	1820	4210 ± 831	4210 ± 831	9.74	140	1.90
30	(b) (4)	8.00	333 ± 53.2	2000	4680 ± 575	4680 ± 575	11.1	156	5.33

[a] R_{AUC} = Day 28 $AUC_{(0-t)}$/ Day 1 $AUC_{(0-t)}$.

[Toxicokinetic tables excerpted from study report.]

Conclusion: Overall, the addition of (b) (4)% impurity (b) (4) to 10 mg/kg/day or 30 mg/kg/day ACP-103 did not result in any new toxicity or exacerbate any toxicity due to ACP-103 alone. Consistent with previous studies with ACP-103, there was a reduction in body weight and food consumption. There were no other findings. There were no clear signs of phospholipidosis in any tissues from treated animals that was above the background rate; however this may be explained by the low incidence rate of phospholipidosis effects at 30 mg/kg/day.

10 Integrated Summary and Safety Evaluation

Pimavanserin is a new molecular entity being developed for the treatment of Parkinson's disease psychosis. A complete and adequate nonclinical package was submitted under NDA 207318 in order to conduct a thorough nonclinical safety evaluation of pimavanserin.

It should be noted that dosage information was expressed as pimavanserin tartrate in all nonclinical toxicity studies. However dosage information in the drug label is expressed as pimavanserin free base. Therefore, a conversion factor of 0.8507 was used to convert dosage levels from the salt to free base forms.

Pharmacology:
In vitro radioligand binding assays demonstrated that pimavanserin tartrate binds to the human recombinant serotonin 2A (5-HT_{2A}) receptor with a K_i of 0.087 nM and to the 2C (5-HT_{2C}) receptor with a lower affinity, K_i of 0.44 nM. Pimavanserin also binds to the human recombinant 5-HT_{2B} receptors though at a much lower affinity, K_i of 0.33 µM (330 nM). In vitro cell-based functional assays demonstrated that pimavanserin acts as an inverse agonist at 5-HT_{2A} and 5-HT_{2C} receptors, with greater potency at the 5-HT_{2A} receptor (pEC_{50s} of 8.7-9.4 for 5-HT_{2A} and 7.1-7.2 for 5-HT_{2C}). Pimavanserin also acts as a potent antagonist at both the 5-HT_{2A} and 5-HT_{2C} receptor, with greater potency at the 5-HT_{2A} receptor (pK_i values of 8.8-9.0 at 5-HT_{2A} and 7.6-8.3 at 5-HT_{2C}). Pimavanserin did not demonstrate any functional activity at the 5-HT_{2B} receptor in vitro. Similar to pimavanserin, the pimavanserin metabolites AC-279 (major human metabolite), AC-423, AC-527 and AC-627 displayed potent antagonistic activity at 5-HT_{2A} receptors, moderate antagonistic activity at 5-HT_{2C} receptors and no agonist or antagonist activity at 5-HT_{2B} receptors in in vitro assays. Therefore, these metabolites could contribute to the pharmacological activity of pimavanserin. Pimavanserin showed efficacious activity in several rodent models for antipsychotic activity. However, mice treated for two weeks with pimavanserin developed tolerance to its antipsychotic activity (attenuation of MK-801-induced hyperactivity). Pimavanserin also showed positive activity in a rodent model for Parkinson's disease in which rats with lesions induced in the substania nigra pars compacta were tested in several behavioral models for antipsychotic activity. There is very little potential for any significant off-target effects (pharmacological or toxicological) of pimavanserin due to its much greater affinity and functional activity at 5-HT_{2A} and 5HT_{2C} receptors as compared to numerous other receptors.

CNS, cardiovascular, respiratory and gastrointestinal (GI) safety pharmacology studies were conducted with pimavanserin tartrate. At the highest dose tested of 1000 mg/kg in the CNS study, mortality occurred in male rats along with clinical signs including gasping, decreased respiration, decreased locomotor activity, apathy, decreased alertness, piloerection and salivation. Necropsy findings in the animals that died included distended stomachs and signs of gastric damage. Pimavanserin has a modest inhibition of the hERG channel with an IC_{50} of 0.21 µM. There was also an increase in heart rate in dogs administered an i.v. dose of 1.8 mg/kg pimavanserin and a significant increase in the QT_c interval of 24-40 msec in monkeys after a 100 mg/kg oral dose. A signal for QT_c prolongation was also observed in humans. There was a significant decrease in respiratory rate in male rats after a single dose of 500 mg/kg pimavanserin, with a NOEL of 100 mg/kg. There were no effects on GI transit or GI peristalsis in mice, ferrets or rats, however there was a dose-dependent increase in emesis and nausea in male ferrets.

ADME:
Pimavanserin is a cationic amphiphilic drug (CAD), and its pharmacokinetic properties can be attributed in part to its physiochemical characteristics of a lipophilic amine (high pKa (8.6) and high logP (4.67)). Pimavanserin tartrate has (b) (4) high permeability across

cell bilayers and is highly absorbed from the GI tract. The volume of distribution is large in rats, >25 L/kg, which is consistent with its high rate of passive diffusion across cell membranes and ability to enter all tissues including brain and erythrocytes. Oral bioavailability in rats was dose-dependent and reached ≥61% after a 10 mg/kg oral dose. The elimination half-life ($t_{1/2}$) ranged from 8-16 hrs in all species tested after a single oral dose of 100 mg/kg and increased after repeated dosing in rats, up to 16 hrs in males and 38 hrs in females after 3 and 6-months of repeated dosing. The $t_{1/2}$ value in humans is higher than in animals, 25 hrs after a single 80 mg dose and 44 hrs at steady state. Pimavanserin is highly protein bound, >94% in all species including human. Based on its high lipid solubility and large volume of distribution, it is rapidly and widely distributed to organs/tissues, including brain, with the highest amount of tissue-to-plasma levels of drug-derived radioactivity in the liver, lung, and kidney. These three organs have a high content of phospholipids and lysosomes and consequently showed some of the more severe phospholipidosis (PLD) findings in repeat-dose toxicity studies. Drug-derived radioactivity was also found in high levels in the eye and uveal tract and remained high for a long time, suggesting binding to melanin. However, there were no corresponding histopathological findings or disturbances in ophthalmological parameters noted in toxicology studies, or significant drug-related effects in vision/eyes reported in clinical trials.
Pimavanserin is extensively metabolized in monkey, rabbit, rat, and mouse (39, 45, 52 and 55 metabolites detected, respectively) as well as in humans with 37 metabolites identified in plasma; but no human specific metabolites were identified. Metabolite AC-279 (*N*-desmethyl-pimavanserin) is the most abundant metabolite formed in mouse, rabbit, monkey and human, while metabolite AC-423 is the most abundant metabolite formed in rat. These metabolites are all pharmacologically active and bind to the target receptors. Based on metabolic profiles, the monkey appears to be the most similar species to human. Metabolite AC-279 qualifies as a major circulating human metabolite. Exposure to AC-279 is greater in all animal species used in toxicity studies compared to exposure in humans at the maximum recommended human dose (MRHD) of 34 mg/day pimavanserin (based on the predicted human exposure level for AC-279 of 847 ng.hr/ml), and therefore, its safety is adequately assessed. Pimavanserin is primarily excreted in feces, and to a lesser extent in urine.

General Toxicology:
Single dose toxicity studies were conducted with pimavanserin tartrate (ACP-103) in mice (subcutaneous) and rats (oral gavage and intravenous). Repeat dose toxicity studies were conducted in mice up to 13-weeks, rats up to 9-months and monkeys up to 12-months in duration.

Mice
14-day and 13-week repeat dose toxicity studies were conducted in CD-1 mice at doses of pimavanserin tartrate ranging from 50-300 mg/kg/day and 10-100 mg/kg/day, respectively. Drug related mortality and cytoplasmic changes consistent with phospholipidosis (PLD) (cytoplasmic vacuolation and vacuolated macrophages) were observed in the lungs, pituitary, kidneys, and spleen in the 14-day study at doses ≥200 mg/kg/day. Cytoplasmic alterations and/or hepatocellular necrosis were observed in the

livers of mice at ≥200 mg/kg/day which correlated with clinical pathology changes of increased ALT and AST and increased liver weights, although this finding may not be consistent with PLD. No recovery group was included in the 14-day study; therefore reversibility of the PLD at doses ≥200 mg/kg/day is unknown. The only microscopic finding observed in the13-week study was cytoplasmic homogeneity in the liver at doses of 10-100 mg/kg/day, which was not consistent with PLD, did not correlate with alterations in liver weight or clinical chemistry and was reversible at the end of 28 day recovery period. Mortality occurred in males at ≥30 mg/kg/day and in females at 100 mg/kg/day and there was a significant decrease in body weight in males at 100 mg/kg/day. The NOAEL doses were 10 and 30 mg/kg/day for males and females, respectively due to mortality at higher doses.

Rat

An oral dose range-finding and 7-day, 28-day with a 28-day recovery, 3-month with a 28-day recovery, and two separate 6-month repeat-dose toxicity studies, the first with a 3-month recovery and the second with a 6-month recovery, were conducted in rats. In the oral dose range-finding study, rats were orally administered pimavanserin tartrate starting at 50 mg/kg/day and increased up to 400 mg/kg/day; and in the 7-day repeat dose phase doses of 250 or 350 mg/kg/day were used. The maximum tolerated dose (MTD) was considered to be between 200 and 250 mg/kg/day due to body weight loss and decreased food consumption, adverse clinical signs including irregular breathing, unsteady gait, salivation, subdued behavior, agitated behavior, partially closed eyes and fur staining which resulted in premature sacrifice of animals at doses ≥250 mg/kg/day. No histopathology was conducted in this study. In the 28-day study rats were orally administered pimavanserin tartrate at 16.9, 84.7 and 126.8 mg/kg/day. PLD was observed at ≥84.7 mg/kg/day primarily in the lungs, liver, spleen, thymus, lymph nodes, cervix, uterus, ovaries, kidneys, jejunum and ileum. In addition, at the high dose, there was a higher incidence and severity of findings in the thyroid gland, prostate and vagina. After a 28 day recovery period there was some evidence of reversibility, however the findings in the lungs persisted at a lower level of severity in all recovery animals. Females were more severely affected than males from both main study and recovery groups, which correlated with increased exposure in females compared to males at equivalent doses. The *NOEL for PLD finding was 16.9 mg/kg/day.*

In the 3-month study, rats were administered oral doses of 10, 30 and 90 mg/kg/day. There was a decrease in body weight in males at ≥30 mg/kg/day and in females at 90 mg/kg/day. Most of the drug-related effects occurred at the high doses. Changes in clinical chemistry and hematology parameters included increased white blood cells, BUN, AST, ALT and creatinine. Adrenal, kidney, lung, spleen, epididymal and ovary weights were increased and macroscopic findings of discoloration and/or abnormal consistency were observed in the lungs. Most of these findings correlated with microscopic findings. Microscopic findings consistent with PLD were observed in multiple organs/tissues with the most widespread effects in the lungs and kidneys. Adverse microscopic findings observed at the high dose of both sexes included kidney nephrosis (degeneration), myofiber degeneration of skeletal muscle and cardiomyopathy (degeneration/fibrosis). After a 28-day recovery period, the clinical

chemistry, hematology and organ weight changes were fully or partially reversible with the exception of increased lung and kidney weights. The PLD was partially reversible, as evident by a lower incidence and severity at the end of the recovery period in most tissues; however PLD remained in several organs/tissues (adrenals, epididymides, liver, lung, spleen, ovaries, mesenteric lymph nodes, pituitary gland and skin). The skeletal muscle degeneration and cardiomyopathy was completely reversible while the nephrosis in the kidney was not. One new finding observed in high dose males and females at the end of the recovery period was *chronic inflammation in the lungs*. The overall NOAEL for the study was 10 mg/kg/day based on decreased body weight. The *NOEL for PLD was 30 mg/kg/day* for both males and females.

In the first 6-month study, doses of 3, 10, and 30 mg/kg/day were administered by oral gavage and included a 3-month recovery period. Drug-related findings were limited to the high dose of 30 mg/kg/day. These included a decrease in mean body weight and body weight gain in both sexes, signs of lethargy, sedation, hunched posture and few incidences of *raspy breathing*. Microscopic findings were limited to findings consistent with PLD in the lungs of females at 30 mg/kg/day (increased incidence and severity of macrophage infiltration in the alveoli), which was completely resolved following the 3-month recovery period. None of the effects adversely affected the overall well-being of the animals, therefore the highest dose of *30 mg/kg/day is the NOAEL* for both males and females. However, the *NOEL* for evidence of PLD in the lungs is *30 mg/kg/day for males and 10 mg/kg/day for females*.

A second 6-month study was conducted in rats to explore the chronic effects of higher doses of pimavanserin tartrate (60 and 90 mg/kg/day) and also extend the recovery period to 6-months. Drug-related deaths occurred in males dosed at 90 mg/kg/day and females dosed 60 and 90 mg/kg/day. Several deaths were attributed to tubular degeneration or vacuolation of the epithelium in the kidneys or in 1 case due to extensive vacuolated macrophages filling the alveoli of the lungs (PLD). Due to poor tolerability and mortality in females at 90 mg/kg/day, this dose group was euthanized during study week 13, although 10 females from that group still entered the 26-week recovery phase. Multi-organ PLD was observed in males and females at 60 and 90 mg/kg/day with only partial reversibility (decrease in severity only) observed in lungs, liver, lymph nodes, kidneys, adrenals, thyroids, spleen (males only), heart, epididymides, and ovaries. In this study only, drug-related PLD in the lungs was confirmed by transmission electron microscopy. The minimal to severe vacuolated macrophages in the lungs were characterized by collections of large foamy macrophages and multinucleated giant cells with lightly eosinophilic cytoplasm filling the alveoli and the macrophages were also accompanied by cholesterol clefts and variable amounts of extracellular eosinophilic proteinaceous material. The extracellular material in the lungs was consistent with cytoplasm of the macrophages and was most likely the result of macrophage lysis. This material filled the alveolar space and most likely impaired lung function, as was evident by cardio-pulmonary-related clinical signs including rales, labored respiration, gasping, blue extremities, cool bodies; no lung function analysis was conducted in any general toxicity study. *Lung fibrosis was also observed in recovery group males and females at 90 mg/kg/day and in recovery group*

females at 60 mg/kg/day. 1 female at 90 mg/kg/day also had lung fibrosis at the 13-week necropsy. The lung fibrosis was considered a permanent irreversible finding. The lung fibrosis is considered to be secondary to chronic inflammation, and not a direct fibrotic process consistent with human pulmonary fibrosis. Nonetheless, any PLD with accompanying chronic inflammation and fibrosis is considered adverse and relevant to humans (see histopathology consult in appendix 4, and Nikula et. al., 2014). PLD (vacuolation) was also observed in the brain of high dose males and females at the end of the dosing period, although it was absent at the end of the recovery period. Any evidence of PLD in the brain is also considered adverse. Similar to the 3-month study in rats, skeletal muscle degeneration was observed in high dose animals, but was again fully reversible. Cardio-pulmonary-related clinical signs were observed in many animals at both dose levels and correlated with the findings of severe PLD in the lungs and cardiomyopathy in the heart. This indicates that the extensive multi-organ PLD had a functional impact on the animals overall well-being. No NOAEL could be determined in this study (<60 mg/kg/day).

Monkey

A 7-day, 28-day with a 28-day recovery, 3-month with a 28-day recovery, and a 12-month with a 4-month recovery repeat-dose toxicity studies were conducted in cynomolgus monkeys. In an MTD and 7-day repeat-dose toxicity study, the MTD was determined to be between 40 and 64 mg/kg/day pimavanserin tartrate based on vomiting at higher doses. Doses of 5, 25 and 60 mg/kg/day were used in the 28-day study and toxicities were limited to the high dose which included vomiting and salivation at the high dose and a decrease in body weight gain in high dose females. PLD (alveolar macrophage infiltration) was observed in the lungs of high dose males and females which was increased in incidence over control levels. However, the PLD was completely reversible at the end of a 28-day recovery period. The same doses were used in the 3-month study as the 28-day study. There was a dose-related increase in lung weights for both males and females at end of dosing and at the end of the 28-day recovery period at the 25 and 60 mg/kg/day dose levels. Multi-organ PLD was observed in the adrenal glands, small intestines, spleen and thyroid at 25 mg/kg/day and in multiple other tissues and organs, including the lungs at 60 mg/kg/day. There was full reversibility of these findings at 25 mg/kg/day after a 28-day recovery period, with some suggestion of partial but not complete reversibility at 60 mg/kg/day (including incomplete recovery in the lungs). The *NOEL for PLD in any tissue was 5 mg/kg/day*.

In the 12-month study, dosing was initiated at 1, 5, and 25 mg/kg/day and then increased to 5, 25 and 60 mg/kg/day on day 43. Pimavanserin tartrate caused a decrease in body weight independent of food intake and emesis. Multi-organ PLD was observed, but only at the high dose of 25/60 mg/kg/day. It is unclear why PLD was not observed at the mid dose of 5/25 mg/kg/day, since 25 mg/kg/day resulted in PLD in the 3-month study. Atrophy of the testes with decreased sperm production and decreased sperm counts in the epididymis which may have potential clinical relevance was observed in high dose males, 9-times the MRHD of 34 mg/day based on AUC. All microscopic findings, including PLD, were completely reversible at the end of a 4-month

recovery period. The *NOAEL was 5/25 mg/kg/day*; AUC at 5/25 mg/kg/day = 6,680 ng.hr/ml in males and 6,230 ng.hr/ml in females.

Genetic Toxicology:
Pimavanserin was non-mutagenic in the in vitro Ames assay and in the in vitro mouse lymphoma assay. There was no evidence of clastogenicity in the in vivo mouse micronucleus assay when male mice were administered two consecutive doses of pimavanserin tartrate up to a MTD of 500 mg/kg/day.

Carcinogenicity:
Pimavanserin did not induce any significant increases in tumors in either rats or mice as assessed in long-term carcinogenicity studies. CD-1 mice were treated with pimavanserin tartrate up to 15 and 50 mg/kg/day in males and females, respectively which is approximately 1- and 7-times the MRHD based on estimated clinical AUC. There was however a statistically significant decrease in survival rates for males at the high dose of 15 mg/kg/day compared to controls. There was also a >10% decrease in body weight for females at 25 and 50 mg/kg/day, and a higher incidence of rales in both high dose males and females. The NOAEL for systemic toxicity was 7 mg/kg/day for males and 10 mg/kg/day for females due to mortality and decreases in body weight, respectively. Sprague-Dawley rats were treated with pimavanserin tartrate up to 30 and 50 mg/kg/day in males and in females respectively which are approximately 4- and 16-times the MRHD based on AUC. Exposures to the major metabolite ACP-279 at the highest doses are approximately 2- and 5-times the predicted AUC for ACP-279 in humans at the MRHD. Multi-organ PLD was observed in high dose males and females. Cardio-pulmonary-related clinical signs including rales, gasping, blue extremities and/or blue bodies were also observed at the high dose. PLD-related mortality (excessive vacuolated macrophages in the lungs and adverse respiratory-related clinical signs) occurred in females at 50 mg/kg/day. An increased incidence of *cardiomyopathy*, secondary to the pulmonary PLD, also occurred in high dose females. In addition, high dose females had an increased incidence compared to controls of open sores on the feet and nodules on the tails that corresponded to microscopic findings of ulcerative pododermatitis and cystic dilation of hair follicles, respectively. A >10% decrease in mean body weight was observed in high dose males and females. The NOEL for multi-organ PLD in males is 10 mg/kg/day, which is 0.7-fold the MRHD based on AUC. The NOEL for multi-organ PLD and PLD-related morbidity/mortality in females is 15 mg/kg/day, which is 2-fold the MRHD based on AUC.

Reproductive Toxicology:
Reproductive toxicity studies conducted with pimavanserin tartrate included a fertility and early embryonic development study in male and female rats, embryo-fetal development study in pregnant rats and rabbits and a pre- and post-natal development study in rats. In the fertility and early embryonic development study, male and female Sprague-Dawley rats were administered 10, 60, and 90 mg/kg/day pimavanserin tartrate before and during cohabitation, and from gestation days 1-7 for females. Clinical signs of *rales*, rough hair-coat and thinness, as well as decreased body weight and food consumption were observed at ≥60 mg/kg/day in males and females. Maternal

and embryotoxicity was observed at 90 mg/kg/day and consisted of a significant decrease in the number of corpora lutea, implantations and percent viable implants, as well as slight increases in the percentage of pre-implantation loss and increased early resorptions. Male reproductive toxicity was observed at ≥60 mg/kg/day with dose-related changes in sperm motility and decreased sperm density and microscopic changes in epididymis (vacuolation). Sperm density measurements were not taken at 10 or 60 mg/kg/day, so an accurate NOEL for sperm density could not be determined in this study. However, based on the lack of organ weight changes and microscopic findings in males at 10 mg/kg/day, the NOAEL for male reproductive toxicity is estimated to be 10 mg/kg/day. There were no effects on any mating or fertility parameters at any dose level. The NOAEL for maternal reproductive toxicity and/or embryotoxicity is 60 mg/kg/day. The estimated NOEL for systemic toxicity and male reproductive toxicity is 10 mg/kg/day, which is approximately 2-fold the MRHD based on mg/m^2.

Pimavanserin tartrate was not teratogenic to pregnant Sprague-Dawley rats administered oral doses of 1, 10 and 60 mg/kg/day from gestation days 7-20. There were no drug-related effects on maternal reproductive pregnancy parameters or fetal external morphology. The maternal NOAEL was 10 mg/kg/day pimavanserin tartrate due to a significant decrease in body weight, body weight gain and food consumption at 60 mg/kg/day. The fetal NOEL was 60 mg/kg/day, which corresponds to an AUC 34,800 ng.hr/ml and is approximately 22-fold the MRHD.

Pimavanserin was not teratogenic to pregnant New Zealand White rabbits administered oral doses up to 100 mg/kg/day. Severe maternal toxicity, including mortality, body weight loss and dyspnea, was observed at doses of 150 and 300 mg/kg/day. Clinical signs of *rales* were observed at doses ≥50 mg/kg/day. Decreased body weight with a corresponding decrease in food consumption was observed at ≥100 mg/kg/day. Mortality and abortions occurred at 100 mg/kg/day. Maternal gross macroscopic findings of thickening, enlargement, and/or discoloration of the heart, discolored lungs which did not collapse and irregularly shaped spleen were observed at 300 mg/kg/day. The findings may be related to PLD, consistent with findings observed in mice, rats and monkeys from other studies, although since histopathology was not conducted in this study, a definitive cause cannot be determined. The maternal NOAEL was 50 mg/kg/day which, corresponds to an AUC on gestation day 14 of 6,600 ng.hr/ml, which is approximately 4-times the MRHD. The fetal NOAEL was 100 mg/kg/day which, corresponds to an AUC on gestation day 14 of 19,000 ng.hr/ml, which is approximately 12-times the MRHD.

In the pre- and postnatal development study, pregnant Sprague-Dawley rats were administered oral doses of 10, 30 or 60 mg/kg/day pimavanserin tartrate from gestation day 7 through lactation day 21. Maternal mortality occurred at 60 mg/kg/day along with a decrease in maternal body weight at ≥ 30 mg/kg/day. Clinical signs including rales, hunched posture and dehydration were observed in F_0 dams at ≥ 30 mg/kg/day. There was a significant decrease in F_1 pup survival and pup body weight at ≥ 30 mg/kg/day. There were no effects on sexual maturation, neurobehavioral or reproductive function in

F_1 pups. The maternal and reproductive NOAEL was determined to be 10 mg/kg/day with a corresponding AUC of 233 ng.hr/ml, which is <1-times the MRHD. The NOEL for pup viability and growth was also 10 mg/kg/day.

Combination Toxicity:
A study was conducted in rats in order to characterize the toxicity and toxicokinetic properties of pimavanserin tartrate in combination with L-dopa/carbidopa. Male Sprague-Dawley rats were administered pimavanserin tartrate at oral doses of 15, 30, 45 or 100 mg/kg/day in combination with 120 mg/kg/day L-dopa and 30 mg/kg/day carbidopa. No pimavanserin alone group was included. The addition of levodopa and carbidopa did not appear to exacerbate any toxicity, produce any new toxicity or have a significant effect on plasma exposure of pimavanserin. However, this evaluation was done indirectly as no direct comparison could be done in this study due to the lack of pimavanserin-alone treated group. This study demonstrated that PLD in the lungs and adrenal glands occurs in male rats after only 14-days of repeat dosing with 45 mg/kg/day of pimavanserin (AUC of 13,055 ng.hr/ml).

In the pre-NDA meeting dated June 2, 2014, the sponsor was asked to conduct an embryo-fetal toxicity study with pimavanserin in combination with L-dopa/carbidopa. However, after further discussion it was decided that a combination embryo-fetal combination study was not required (meeting minutes dated July 2, 2014); although the sponsor was asked to submit a justification for not conducting this study. The sponsor submitted a justification in the nonclinical overview section and included the following reasons: the average mean age of onset of Parkinson's disease is 70.5 years for women (range of 31-93 years), however psychotic symptoms generally occur about 10 years after diagnosis is made, and for women, this would make it more likely to occur beyond the years of childbearing potential. This reviewer agrees with the sponsor's justification for not conducting a combination embryo-fetal development study for the indication of Parkinson's disease psychosis.

Local Tolerance:
A series of studies were conducted to assess the local tolerance effects of pimavanserin tartrate. Pimavanserin was not a dermal irritant in an acute dermal irritation/corrosion study when administered to the skin of rabbits. It was determined to be a severe/corrosive irritant in a Hen's eggs test using an alternative methodology to the Draize methodology. It was also considered to be a severe irritant in a bovine corneal opacity and permeability test. An acute inhalation toxicity study in rats using aerosols of pimavanserin tartrate at concentrations of (b) (4) resulted in mortality. Pimavanserin was considered a dermal sensitizer in a local lymph node assay when topically applied to mice.

Overall Conclusions and Recommendations:
Pimavanserin is a cationic amphiphilic drug (CAD). CADs are known to cause phospholipidosis (PLD), the excessive accumulation of phospholipids in cells, in animals and humans. Many marketed drugs are CADs and cause drug-induced PLD in animals and humans (e.g. fluoxetine, choroquine, amiodarone). PLD is usually reversible after

cessation of drug treatment, however high or prolonged exposures to CADs may lead to dose-limiting functional and structural tissue damage (e.g. nephrotoxicity, pulmonary toxicity, myopathy and retinopathy) (Halliwell, 1997; Vonderfecht, et. al., 2004).
In the case of pimavanserin, multi-organ PLD was observed in mice, rats and monkeys which was both dose and duration dependent and observed as early as after 14 days of daily administration. The number of tissues/organs affected in mice, monkeys and rats was extensive at 5, 15 and over 30, respectively, with the lungs and kidneys being the most severely affected. In mice and monkeys, there was no adverse tissue damage or functional impairment that was related to PLD and the findings were completely or partially reversible, however reversibility was not assessed in the 14-day mouse study in which PLD was observed in the lungs at doses ≥200 mg/kg/day. Conversely in rats, severe PLD correlated with adverse microscopic findings, impacted the general well-being of animals, had possible functional impairment, and resulted in morbidity/mortality. The adverse microscopic findings in rats included *chronic inflammation in the lungs with or without secondary lung fibrosis,* a permanent and irreversible finding (although it was minimal to mild in severity, therefore the fibrosis most likely did not cause any functional respiratory impairment) and type 2-pneumocyte hyperplasia. Severe PLD in several tissues of rats was not fully reversible, including the lungs, even after a 6-month recovery period, indicating no or very slow reversibility in the most sensitive tissues. Fibrosis that occurs in the lungs of rats after continued exposure to pimavanserin is most likely the end result of a chronic inflammatory response due to repeated injury to lung tissue and inability to clear phospholipids. It is not considered to be a direct fibrotic process consistent with human pulmonary fibrosis, although no special stains for collagen were included in any of the toxicity studies. The microscopic findings of PLD in the lungs, were verified by transmission electron microscopy in the second 6-month rat study, correlated with gross macroscopic findings and cardio-pulmonary-related clinical signs, indicating a possible functional impairment (although no lung function assessment was conducted in any toxicity study). Additionally, severe vacuolated macrophages in the lungs were also considered to be the cause of death of female rats at a dose of 50 mg/kg/day in the 2-year carcinogenicity study.

The sponsor considered the severe PLD in rats that leads to chronic inflammation and fibrosis in the lungs and morbidity/mortality to be only dose and not duration dependent (response to IR, SDN 7). However, this reviewer disagrees, and believes the finding to be both dose- and duration-dependent. A dose of 30 mg/kg/day administered to male rats for 3- and 6-months is a NOEL for PLD. The same dose of 30 mg/kg/day (and slightly lower exposure) in the 2-year study resulted in widespread, multi-organ PLD, including macro- and microscopic lung findings (vacuolated macrophages) with corresponding respiratory-related clinical signs, indicating possible functional impairment. In addition, as noted in the consult review by Drs. Francke and Mog (CFSAN expert pathologists) they also disagree with the sponsor that the PLD is not duration related and support the conclusion of this reviewer (see appendix 4). They also state that in their opinion, *"multi-systemic PLD is not rat specific as it occurs in multiple species (mouse, monkey and rat). The manifestation of the type of fibrosis observed*

(secondary to inflammation) is not rat specific either but depends on the severity and the PLD and the degree of chronicity of the inflammation the PLD is associated with."

Multi-organ PLD with chronic inflammation and secondary fibrosis in the lungs and PLD-related morbidity/mortality in rats is a clinically relevant finding. If feasible, signs of inflammation should be carefully monitored in humans in any future long-term clinical trials. However, from a nonclinical standpoint, the current safety margin of 9-fold, based on AUC, for adverse PLD effects (i.e. chronic inflammation with secondary fibrosis in the lungs, and morbidity/mortality) compared to the MRHD of 34 mg/day pimavanserin is acceptable for the indication of Parkinson's disease psychosis. This is due to the fact that the average life expectancy for these patients is not more than a few years and therefore the concern for developing multi-organ PLD that may lead to chronic inflammation and possible secondary fibrosis in the lungs is reduced compared to a patient population in which the life expectancy is much longer. It is this reviewer's opinion that a 9-fold safety margin would not be acceptable for other chronic indications in which patients could potentially be treated with pimavanserin for more than a few years. In addition, this reviewer would require additional nonclinical studies with pimavanserin to further our understanding of reversibility, margin of safety, and extent of the severity of PLD-associated lung fibrosis.

Table 74: Sponsor's table of incidence of phospholipidosis in lungs of rats, mice and monkeys

Table 2.4.4-2a Incidence1 of Phospholipidosis (foamy macrophages) in the Lung in Mice and Rats

Dose (salt) mg/kg/day	14-day mouse M/F		13-week mouse M/F		2-year mouse M/F		14-day rat M[2]	28-day rat M/F		3-month rat M/F		6-month rat M/F[3]		2-year rat M/F	
0	0/5	0/5	0/15	0/15	0/120	0/120	*0/6*	0/10	0/10	0/10	0/10	1/36	0/38	42/120	39/120
2.6 (3)					0/59 (M)							0/20	0/20	21/60 (M)	
4.3 (5)														11/60 (F)	
6.0 (7)					0/60 (M)										
8.5 (10)			0/15	0/15	0/60 (F)					0/10	0/10	0/20	0/20	22/60 (M)	
12.8 (15)					0/60 (M)		*0/6*							19/60 (F)	
17 (20)								0/10	0/10						
21 (25)					0/60 (F)										
26 (30)			0/15	0/15						0/10	0/10	0/18	0/20	33/60 (M)	
38 (45)							*2/6*								
43 (50)	0/5	0/5			0/60 (F)									56/60 (F)	
51 (60)												15/20	17/17		
77 (90)										10/10	10/10	16/16	15/15[4]		
85 (100)	0/5	0/5	0/15	0/15			*6/6*	10/10	10/10						
128 (150)								10/10	10/10						
170 (200)	4/5	5/5													
255 (300)	5/5	5/5													

M= male; F= female
[1] Data expressed as number of animals with findings/total number of animals in group (at the end of the dosing period)
[2] Combination study conducted with 120 mg/kg/day levodopa and 30 mg/kg/day carbidopa (non-GLP)
[3] Includes data from two 6 month rat studies
[4] Sacrificed at 13 weeks

Table 2.4.4-2b Incidence[1] of Phospholipidosis (foamy macrophages) in the Lung in Monkeys

Dose (salt) mg/kg/day	1-month monkey M/F		3-month monkey M/F		12-month monkey M/F	
0	0/3	0/3	0/3	0/3	0/4	0/4
4.3 (5)	0/3	0/3	0/3	0/3	0/4	0/4
21 (25)	0/3	0/3	0/3[2]	0/3[2]	0/4	0/4
51 (60)	0/3	0/3	3/3	3/3	2/3	2/3

[1] Data expressed as number of animals with findings/total number of animals in group
[2] Evidence of phospholipidosis seen sporadically in other tissues; effects fully reversible

[The above two tables are excerpted from NDA 207318 SDN 8]

Table 75: Sponsor's table of Safety Margins

Table 2.4.4-3 **Systemic Exposures and Margins of Safety at Pimavanserin NOELs for any Evidence/Systemic Evidence of Phospholipidosis, Phospholipidosis Leading to Lung Fibrosis, and Morbidity/Mortality due to Phospholipidosis**

Study	Overall Study		Any Evidence/ Systemic Evidence of PLD		Lung Fibrosis		Morbidity/Mortality	
	NOAEL mg/kg/day	AUC[1] at NOAEL ng·h/mL (margin[2])	NOEL mg/kg/day[3]	AUC[1] at NOEL ng·h/mL (margin[2])	NOEL mg/kg/day	AUC[1] at NOEL ng·h/mL (margin[2])	NOEL mg/kg/day	AUC[1] at NOEL ng·h/mL (margin[2])
3-Month Mouse	10 30	M = 516 (0.3) F = 3800 (2)	100	M =21400 (13) F = 21800 (14)	100	M = 21400 (13) F = 21800 (14)	NA[4]	M = 516 (0.3) F = 3800 (2)
6-Month Rat	10	M = 1030 (0.6) F = 1570 (1)	30	M = 8670 (5) F = 14440 (9)	60 30	M = 15900 (10) F = 14440 (9)	60 30	M = 15900 (10) F = 14440 (9)
2-Year Rat	10 15	M = 1140 (0.7) F=3200 (2)	10 15	M = 1140 (0.7) F=3200 (2)	30 50	M = 6340 (4) F = 25900 (16)	30 15	M = 6340 (4) F = 3200 (2)
12-Month Monkey	25	M = 6680 (4) F = 6230 (4)	25	M = 6680 (4) F = 6230 (4)	60	M = 15000 (9) F = 15200 (10)	60	M = 15000 (9) F = 15200 (9)

NOAEL = no observable adverse effect level; NOEL = no observed effect level; PLD = phospholipidosis

1 Male (M) and female (F) end-of-study value. AUC expressed as $AUC_{0\text{-}inf}$ for mouse (Study (b) (4)616002) or $AUC_{0\text{-}24h}$ for the rat and monkey studies (Studies (b) (4)146.02, (b) (4)616007, (b) (4)616004, and (b) (4)146.01). AUC values expressed as salt.

2 Margin calculated using the end of study value and the estimated AUC for humans at the recommended 40 mg dose: 1606.6 ng·h/mL (Expert Opinion entitled "Pharmacokinetic Modeling of Pimavanserin in Healthy Subjects, Subjects with Parkinson's Disease, and Subjects with Parkinson's Disease Psychosis")

3 NOELs for "any evidence of phospholipidosis" and "systemic phospholipidosis" occur at the same dose in each species.

4 NA– not applicable. Deaths observed at ≥ 30 mg/kg/day (M) or 100 mg/kg/day (F) in mice were of undetermined cause; unrelated to phospholipidosis.

[The above table is excerpted from NDA 207318 SDN 8. Doses are expressed as tartrate salt.]

The sponsor's table above is misleading, as lung fibrosis only occurred in the 6-month rat study, therefore all other rows should be ND (not detected). Also, PLD morbidity/mortality did not occur in the 12-month monkey study, so that row should also be ND. The table implies that morbidity/mortality occurred at doses >60 mg/kg/day in the 12-month monkey study, but 60 mg/kg/day was the highest dose tested.

Table 76: Reviewer's table of Safety Margins for PLD with Chronic Inflammation in lungs or PLD-related morbidity/mortality in rats

	NOEL (mg/kg/day)	AUC at NOEL (ng.hr/ml)	Exposure Margin*
Chronic Inflammation + Fibrosis	M: 60 F: 30	M: 15,900 F: 14,400	M: 9.8 F: 8.8
Morbidity/ Mortality in 6-month study	M: NA F: 30	F: 14,400	F: 8.8
Morbidity/ Mortality in 2-year study**	M: NA F: 15	F: 3,200	F: 2.0

M: male, F: female
*MRHD: 34 mg pimavanserin, steady state predicted AUC_{0-24} in humans = 1630 ng.hr/ml
** The highest dose for females in 2-year study was 50 mg/kg/day which resulted in mortality (AUC = 25,900 ng.hr/ml, exposure margin of 16)

Table 77: Reviewer's table of Overall Safety Margins for Phospholipidosis in Lungs of animals from all Toxicology studies

	Mouse	Rat	Monkey
NOEL (mg/kg/day)	M: 100 F: 100	M: 10 F: 15	M: 25+ F: 25
NOEL AUC	M: 21400 F: 21800	M: 1140 F: 3200	M: 6680 F: 6230
Exposure Margin*	M: 13 F: 13	M: 0.7 F: 2.0	M: 4.1 F: 3.8

M: male, F: female
+: PLD was observed in other tissues of monkeys at 25 mg/kg/day and was reversible by end of a 1-month recovery period.
Animal AUC_{0-24} (ng.hr/ml)
*MRHD: 34 mg pimavanserin, steady state predicted AUC_{0-24} in humans = 1630 ng.hr/ml

Doses in the above tables are for pimavanserin tartrate.

References

Halliwell, H.W. (1997) Cationic Amphiphilic Drug-Induced Phospholipidosis. *Tox. Path.*, 25: 53-60.

McFarland, K., et al., (2011); Pimavanserin, a 5-HT_{2A} inverse agonist, reverses psychosis-like behaviors in a rodent model of Parkinson's disease. *Behavioral Pharmacology.* 22: 681-692.

Nikula, K.J. et al., (2013); STP Position Paper: Interpreting the significance of increased alveolar macrophages in rodents following inhalation of pharmaceutical materials.

Vonderfecht, S.L, et al., (2004); Myopathy related to administration of cationic amphiphilic drug and the use of multidose drug distribution analysis to predict its occurrence. *Tox. Path.* 32: 318-325.

12 Appendix/Attachments

12.1 Meeting minutes from ECAC for rat SPA

Executive CAC
Date of Meeting: October 16, 2007

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Joseph Contrera, Ph.D., OPS, Member
Abby Jacobs, Ph.D., OND IO, Member
Karen Davis Bruno, Ph.D., DMEP, Alternate Member
Barry Rosloff, Ph.D., DPP, Team Leader
Violetta Klimek, Ph.D., DPP, Presenting Reviewer

Author of Draft: Violetta Klimek

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

The committee did not address the sponsor's proposed statistical evaluation for the 2-yr carcinogen bioassay, as this does not affect the sponsor's ability to initiate the bioassay. The sponsor may seek guidance on the statistical evaluation of bioassay results from agency staff separately. Data files should be submitted electronically following the CDER/CBER Guidance for Industry, Providing Regulatory Submission in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (April 2006).

IND # 68,384
Drug Name: Pimavanserin (ACP-103)
Sponsor: ACADIA Pharmaceuticals

Background:

Pimavanserin is an inverse agonist and competitive antagonist at the 5-HT_{2A} receptor with some activity at 5-HT_{2C} being developed for the treatment of psychosis.
The sponsor submitted a request for Special Protocol Assessment: Rat Carcinogenicity Protocol.

Rat Carcinogenicity Study Protocol and Dose Selection

The results of 3-month and 6-month oral toxicity studies in rats were evaluated for the dose selection. The toxicity findings from the 3-month study indicate that pimavanserin at 90 mg/kg/day would likely limit survivability of the animals over a 2-year dosing period. The doses proposed by the sponsor to be evaluated in the 2-year carcinogenicity study are 0, 3, 10, and 30 mg/kg administered once per day by oral gavage.
Body weight reductions were used as the toxicity-based endpoint for high dose selection. The data indicated that there was a mild reduction in body weight at 30 mg/kg/day in both genders in the 6-month study, although it was not dose related in females. In the 3-month study body weight reduction was observed only in males at 30 mg/kg/day.
Executive CAC Recommendations and Conclusions:

The Executive CAC concurred with the sponsor's doses of 0, 3, 10 and 30 mg/kg/day in males, based on body weight effects, and recommended doses of 0, 5, 15, and 50 mg/kg/day in females by oral gavage for the 2-year carcinogenicity study. In the female rats the recommended high dose is one-third the lethal dose (200/150 mg/kg/day) as determined in a 28-day study.

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

cc:\
/Division File, DPP
/Barry Rosloff, DPP
/Violetta Klimek, DPP
/ Keith Kiedrow, DPP
/ASeifried, OND IO

12.2 Meeting minutes from ECAC for mouse SPA

Executive CAC
Date of Meeting: December 11, 2007

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Tim McGovern, Ph.D., DPAP, Alternate Member
Barry Rosloff, Ph.D., DPP, Team Leader
Violetta Klimek, Ph.D., DPP, Presenting Reviewer

Author of Draft: Violetta Klimek

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

The committee did not address the sponsor's proposed statistical evaluation for the 2-yr carcinogen bioassay, as this does not affect the sponsor's ability to initiate the bioassay. The sponsor may seek guidance on the statistical evaluation of bioassay results from agency staff separately. Data files should be submitted electronically following the CDER/CBER Guidance for Industry, Providing Regulatory Submission in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (April 2006).

IND # 68,384
Drug Name: Pimavanserin (ACP-103)
Sponsor: ACADIA Pharmaceuticals

Background:

Pimavanserin is an inverse agonist and competitive antagonist at the 5-HT_{2A} receptor,with some activity at 5-$HT_{2C,}$ being developed for the treatment of psychosis. Pimavanserin has the physical-chemical property of a cationic amphiphilic drug. This class of drugs has been associated with the development of phospholipidosis. Seven pimavanserin metabolites were identified of which 5 were common between mice and human. Pimavanserin was tested negative in an adequate battery of genotoxicity studies.

Mouse Carcinogenicity Study Protocol and Dose Selection were evaluated at the meeting:

For dose selection for the 2-Year Carcinogenicity Study of Pimavanserin in Mice, the results of the 14-day and 3-month oral toxicity studies in mice have been considered.
Doses of pimavanserin of 50, 100, 200, and 300 mg/kg/day were used in the 14-day study and 10, 30 and 100 mg/kg/day were used in the 3-month study.

The lethality in the 13-week study was used as the toxicity-based endpoint for high dose selection. In the main study groups (15 mice/sex/group), 2 males died at 30 mg/kg and 5 mice (3 males and 2 females) died at 100 mg/kg. In the TK groups (39/sex/group) of this study, 1 male at

30 mg/kg and 2 males and 1 female at 100 mg/kg died. Although the cause of death for all test article-treated animals was undetermined (other than those attributable to gavage errors) it was considered to be likely related to pimavanserin treatment.

Executive CAC Recommendations and Conclusions:

The Executive CAC concurred with the sponsor's doses of 0, 10, 25 and 50 mg/kg/day for females but recommended doses of 0, 3, 7, and 15 mg/kg/day for the males. In both genders the recommended high dose is half of the lethal dose (100 and 30 mg/kg/day, females and males, respectively) as determined in the 13-week study.

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

cc:\
/Division File, DPP
/Barry Rosloff, DPP
/Violetta Klimek, DPP
/ Keith Kiedrow, DPP
/ASeifried, OND IO

12.3 Meeting minutes from ECAC for review of rat and mouse carcinogenicity study results

Executive CAC

Date of Meeting: January 12, 2016

Committee: Karen Davis Bruno, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
Tim McGovern, Ph.D., OND IO, Member
Lois Freed, Ph.D., DNP, Alternate Member
Aisar Atrakchi, Ph.D., DPP, Pharm Tox Supervisor
Amy Avila, Ph.D., DPP, Presenting Reviewer

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

NDA # 207318

Drug Name: Pimavanserin (NUPLAZID)

Sponsor: Acadia Pharmaceuticals

NDA 207318 was submitted on September 1, 2015 to pursue marketing approval of pimavanserin for the treatment of psychosis associated with Parkinson's disease. 2-year mouse and rat carcinogenicity study results were submitted with the NDA.

Mouse Carcinogenicity Study

CD-1 mice (60/sex/group) were administered pimavanserin tartrate by oral gavage in a vehicle of deionized water for 104 consecutive weeks. Doses of 3, 7, and 15 mg/kg/day were used for males and 10, 25, and 50 mg/kg/day for females. Two identical control groups were administered the vehicle. Dosing was terminated during study week 101 for high dose males due to the number of surviving animals reaching 20. The sponsor received agreement from the division and the ECAC prior to the cessation of dosing for this group. There was a statistically significant decrease in survival rates for high dose males (15 mg/kg/day) compared to controls. There were no statistically significant drug-related neoplastic findings in either males or females.

Rat Carcinogenicity Study

Sprague Dawley rats (60/sex/group) were administered pimavanserin tartrate by oral gavage in a vehicle of deionized water for 104 consecutive weeks. Doses of 3, 10, and 30 mg/kg/day were used for males and 5, 15, and 50 mg/kg/day for females. Two identical control groups were administered the vehicle. Dosing was terminated during study week 96 for high dose males due to surviving animals reaching 20. Subsequently,

this group was euthanized during study week 101 due to the number of surviving animals reaching 15. Dosing was terminated during study week 103 for low dose males due to surviving animals reaching 20. The sponsor received agreement from the division and the ECAC prior to the cessation of dosing and/or premature sacrifice for these groups. There were no statistically significant drug-related neoplastic findings in either males or females.

Executive CAC Recommendations and Conclusions

Mouse

- The Committee agreed that the study was acceptable, noting prior approval of the protocol.
- The Committee concurred that there were no drug-related neoplasms in the study.

Rat

- The Committee agreed that the study was acceptable, noting prior approval of the protocol.
- The Committee concurred that there were no drug-related neoplasms in the study.

Karen Davis Bruno, Ph.D.

Chair, Executive CAC

cc:\

/Division File, DPP
/AAisar, DPP
/AAvila, DPP
/BMuoio, CSO/PM, DPP
/ASeifried, OND IO

16 Page have been withheld in full as duplicate copy of consult review dated January 13, 2016 immediately following this page

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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.

/s/

AMY M AVILA
02/12/2016

AISAR H ATRAKCHI
02/12/2016

Memorandum

Date: January 13, 2016

From: Sabine Francke, D.V.M., Ph.D., FIATP and Steven Mog, D.V.M., DACVP, Senior Science and Policy Staff, Office of Food Additive Safety, CFSAN (HFS-205)

Subject: Division of Psychiatry Products - NDA 207318 (Pimavanserin): Request for nonclinical histopathology consult

To: Amy Avila, Ph.D., Pharmacology/Toxicology Reviewer, Division of Psychiatry Products FDA/CDER/OND, HFD-130

References:

1. E-mail from Avila to Francke dated December 4, 2015 subject: Pathology consult for pimavanserin (new NDA in OND/Division of Psychiatry Products); with the following attachments:
    a. Pimavanserin NDA 207318 histopath Consult
    b. Path report 24-month rat study ((b) (4)-616004)
    c. Micro summary tables males 24-month rat study ((b) (4)-616004)
    d. Micro summary tables females 24-month rat study ((b) (4)-616004)
    e. Path report 6-month rat study ((b) (4)-616007)
    f. 14 OCT 2015-Responses to Non-Clinical Information
2. E-mail requests by Pathology for the following reports:
    a. December 7, 2015
        i. individual animal histopath data from 6-month study ((b) (4)-616007)
        ii. 24-month rat study report ((b) (4)-616004)
        iii. Monkey 3-month path report
        iv. 14-day mouse path report
        v. 12-month monkey path report
        vi. 3-month mouse path report
        vii. (b) (4)-616007 – A 6-Month Oral (Gavage) Toxicity Study of ACP-103 in Sprague Dawley Rats Followed with a 6-Month Recovery Period
    b. December 18, 2015
        i. 03-S12-UK – A Subchronic Toxicity Study of ACP-103 in the Rat Administered Daily for 3 Month by Oral Gavage with Toxicokinetic Sampling
        ii. (b) (4)-146-02 – A 6 Month Oral Administration Repeat Dosing Toxicity Study of ACP-103 in Sprague-Dawley Rats Followed by a 3-Monthy Recovery Period
        iii. 03-S12-UK – Supplemental Data – Description of Kidney Lesions included in Pathology Report for 03-S12-UK
        iv. 28-day rat study HTI1002
    c. January 8, 2016
        i. (b) (4)-616002 – A 13 Week Oral (Gavage) Toxicity Study of ACP-103 in Mice with a 28-Day Recovery Period
        ii. (b) (4)-146-01 – A 12 Month Nasogastric Gavage Toxicity Study of ACP-103 in Cynomolgus Monkeys Followed by a 4-Month Recovery

Based on your request (reference 1) we both have reviewed the materials that were provided to us; we have focused our evaluation on documents listed above, relevant to answering your specific questions (reference 1a) which we addressed below in this memorandum.

Background:
Pimavanserin (ACP-103; Nuplazid) is an oral cationic amphiphilic drug (CAD) used as a serotonin 5-hydroxytryptamine (5-HT) receptor inverse agonist for chronic treatment of psychosis occurring with Parkinson's disease. The sponsor, ACADIA Pharmaceuticals, Inc. (San Diego, CA) tested the compound over a 12 year period (2002-14) pre-clinically in multiple laboratories and test species (mouse, rat, monkey) as well as clinically (open labeled trial; reference 1f, Appendix 1 pg. 14). Consistent with other CADs, in all three non-human species tested, Pimavanserin was reported to cause **multi-systemic phospholipidosis**. In addition, the findings of "**chronic inflammation**" and "**fibrosis**" were reported mainly in recovery animals of two rat studies. The sponsor was asked to provide more detailed information concerning these findings and provided comments (#2, #3, and #4) to answer FDA's specific questions (reference 1 f).

What follows is a **brief chronological summary** of study results from relevant studies in laboratory animals you provided for our review (referenced above), focusing specifically on histopathological findings reported in the lungs, as your questions below center mainly around pulmonary Pimavanserin induced phospholipidosis.

1. June 2002 – September 2003: HTI 1002, 1 month Rat study with 1 month recovery: (R 1/1)
The study was conducted (b) (4) (reference 2 b iv pg. 1) administering Pimavanserin by **oral gavage** to 10 Sprague-Dawley rats per sex per group with an additional 5 recovery animals in the control and high dose groups only. The dose groups were **0, 17, 85, 169 mg/kg/day** (high dose reduced to 127 at day 12 (recovery group) -13 (main study animals) due to severity of clinical effects; reference 2 b iv pg. 16).

Results
General results: treatment with Pimavanserin for 1 month in rats was reported to result in noisy breathing, post dose salivation and fur staining around the mouth, reduced food consumption and weight loss and/or reduced bodyweight gain and marked multi-systemic phospholipidosis (PLD) at the two high doses of 85 and 169/127 mg/kg/day (reference 2 b iv pg. 28, 29). The study authors described the incidences of PLD to occur in a dose related pattern and noted that in general, females showed more severe signs than males. Two unscheduled deaths in the high dose (127 mg/kg) were reported (reference 2 b iv pg. 16, 18).
Lung results: The authors described the manifestation of treatment related PLD in the lung as "multifocal alveolar foamy macrophage aggregate(s)" and extracellular eosinophilic material as "diffuse eosinophilic alveolar foci" at the following incidence: M/F (for each sex): 0, 0, 10, 10. A different diagnosis was made for non-treatment related alveolar macrophages which were not associated with eosinophilic material and termed "focal alveolar, foamy macrophage aggregate(s)" at incidences of M: 1, 1, 0, 0; F: 0, 0, 0, 0 (reference 2 b iv pg. 27). Occurrence of "inflammatory cell infiltrates" were recorded only in the summary tables (M: 7, 5, 10, 10; F: 4, 3, 6, 8; reference 2 b iv pg. 99) but not brought forward in the pathology report narrative.

Pathology comment: In the summary table reference 2 b iv pg. 99; the inflammatory response diagnoses were differentiated by location within the pulmonary tissue into "perivascular, alveolar and interstitial" some with incidences indicative of a dose related trend. Combining all inflammatory response diagnoses, however, resulted in incidences not indicative of a treatment effect which was likely the reason why this observation was not mentioned in the study report narrative as a component of PLD.

2. August 2004 – Path report completion: (b) (4) 177.01, 3 Month Monkey study with 1 month recovery: MK 3/1

This study was conducted (b) (4) administering Pimavanserin by **oral gavage** to 3 cynomolgus monkeys per sex per group with an additional 2 recovery animals in all dose groups. The dose groups were **0, 5, 25, 60 mg/kg/day** (reference 2a iii pg. 2).

Results:

General results: The treatment with Pimavanserin for 3 months in monkeys was reported to result in increased lung weights of high dose males (2/3 main study and 1/2 recovery).

Multi-systemic PLD was described at 60 and to a lesser extent at 25 mg/kg in both sexes characterized by macrophages with fine vacuolated foamy cytoplasm (reference 2 a iii pg. 4). Complete recovery was reported at the 25 and partial recovery for the 60 mg/kg dose after one month. No treatment related changes were reported throughout the study at the 5 mg/kg dose level.

Lung results: The authors described the manifestation of treatment related PLD in the lung as "lung alveolar foamy macrophage accumulation was minimal to moderate with a tendency to orient somewhat about vessels and small to mid-sized airways" (reference 2 a iii pg. 4).

Pathology comment: The authors specifically stated that "In all of the tissues with either foamy macrophage accumulation or accentuated cytoplasmic vacuolation, there was no associated degenerative, necrotic, proliferative, or inflammatory changes related to the [PLD] affected cells" (reference 2 a iii pg. 5).

As a background finding, the authors noted that "In the lungs, pigment (generally in peribronchial and peribronchiolar location) and minimal chronic pleural inflammation (tags) at the lobe margins were noted" (reference 2 a iii pg. 5). We agree that few pleural tags (pleural adhesions) in monkeys are common background findings.

The overall pathology report (gross and organ weight evaluations) was issued by (b) (4) study pathologist (b) (4) The histopathology report (tissue slide evaluation), however, was issued by (b) (4) of (b) (4) ; reference 2 a iii pg 2). We did not find a signature page for the histopathology data read (b) (4) It is unusual to have a pathologist read the slides, who does not also sign off on the pathology report with which the pathological slide diagnoses and incidence tables become raw data.

3. January 2004 – January 2005: 03-S12-UK, 3 Month Rat study with 1 month recovery: R 3/1

The study was conducted at (b) (4) (test site) **and** (b) (4) (testing facility; reference 2 b i, pg. 15-16) administering Pimavanserin by **oral gavage** to 10 Sprague-Dawley rats per sex per group with an additional 5 recovery animals for all dose groups. The dose groups were **0, 10, 30, 90 mg/kg/day**, (reference 2 b i, pg. 19).

Results

General results: Treatment with Pimavanserin for 3 month in rats was reported to result in decreased body weights for both sexes at 90 mg/kg and for males at 30 mg/kg as well as fur staining at 90 and 30 mg/kg in both sexes (reference 2 b i, pg. 27). Test article related mortality, reduced food consumption and respiratory signs were not recorded.

Clinical Chemistry: Creatinine, Blood Urea Nitrogen (BUN) and Aspartate Aminotransferase (AST) were elevated at 90 mg/kg in both sexes (reference 2 b i, pg. 28-29).

Gross: An increased incidence of abnormal discoloration and/or consistency of the lungs in 90 mg/kg females was reported (reference 2 b i, pg. 30).

Organ weights: Several organ weight changes were reported to be increased at the 90 mg/kg dose level for both sexes including lungs and kidneys.

Microscopic changes:

Treatment related **multi-systemic PLD** (consistent with findings noted in the 28-day rat study) was reported only at 90 mg/kg for both sexes with partial reversibility noted during the 1 month recovery period (reference 2 b i, pg. 39-41).

In addition, **renal nephrosis** (M/F: 0, 0, 0, 10; which consisted of one or more of the following lesions: a segmental cortical tubular vacuolation, cortical tubular degeneration, tubular casts, and medullary tubular dilatation) and individual **myofiber degeneration** of skeletal muscles (M: 0, 0, 0, 3 ; F: 1, 0, 0, 7) at the 90 mg/kg dose were noted to be different from changes consistent with PLD (reference 2 b i, pg. 39). During the 1 month recovery phase the incidence of renal nephrosis in males was reported to be partially reduced (M: 0, /, /, 3/5) while the severity slightly increased from 2.1 to 2.3. For females, renal nephrosis incidences were not reported lower after the recovery phase (F: 0, /, /, 5/5) however the severity was slightly reduced (2.0 vs. 1.6; reference 2 b i, pg. 302, 317). Skeletal muscle myofiber degeneration was not reported at the end of the 1 month recovery phase.

Lung results: The authors described the manifestation of treatment related PLD in the lung as "foamy macrophage(s)" at the following incidence: M/F: 0, 0, 0, 10. This treatment related observation was differentiated from a background observation of "Macrophages, alveolar", a non-treatment related finding at incidences of M: 2, 2, 6, 0; F: 0, 1, 1, 0 (reference 2 b i, pg. 304). Treatment related inflammation associated with PLD was not reported in the main study. However, a finding of "chronic inflammation" (M: 0, /, / , 3/5; F: 0, /, / , 4/5; reference 2 b i, pg. 319) labeled as "a new finding consistent with a chronic inflammatory response, associated with the foamy macrophage accumulations, attributed to the body's attempt at removing the alveolar luminal material" was reported (reference 2 b i, pg. 40).

Pathology comment: It should be noted that the incidences of "chronic inflammation" reported to affect 3/5 high dose males in the Recovery Summary Table (reference 2 b i, pg. 319) could not be correlated as a diagnostic entry in the individual animal table of recovery males. Instead 3/5 males had a diagnosis of pulmonary "adenomatous hyperplasia" surrounding foci of foamy alveolar macrophages characterized by hyperplasia of the type 2 pneumocytes, in the individual animal tables. Therefore, it appears that a table compilation error occurred regarding the population of the summary table because, "adenomatous hyperplasia" reported in the individual animal data for these 3 high dose males (UK7001, 7004, 7005), became an incidence of 3 high dose males with "chronic inflammation" in the summary tables. "Chronic inflammation" was not an entry for any recovery male in the individual animal tables (reference 2 b i, pg. 851, 854, 860, 861); in females, however, the entries for "chronic inflammation" correlated correctly between the individual animal data and the summary data

tables. Therefore the **correct summary incidences** based on the individual animal entries for treatment related cellular responses to pulmonary PLD in the recovery phase of this study would be:

1. chronic inflammation M: 0, /, /, 0; F: 0, /, /, 4
2. adenomatous hyperplasia M: 1, /, /, 3; F: 0, /, /, 0

4. November 2007, completion – Pathology Report: (b) (4) 616001, 14 day Mouse study, no recovery: MS 14D/0

The study was conducted (b) (4) administering Pimavanserin by **oral gavage** to 5 CD-1 mice per sex per group. The dose groups were **0, 50, 100, 200, 300 mg/kg/day** (reference 2 a iv, pg. 1-3).

Results

General results: Treatment with Pimavanserin for 14 days in mice was reported to result in 3 treatment related deaths (0, 0, 0, 1 F, 1F/1M; and one non-treatment related death (F: 200 mg/kg interpreted as gavage accident; reference 2 a iv, pg. 8). Body weight was reported to be reduced in both sexes of the 300 mg/kg dose group. Organ weights of the lung was increased in males of the 300 mg/kg dose group; lung and liver weights were reported to be increased in the females of the 200 and 300 mg/kg dose groups. The study pathologist reported systemic cytoplasmic vacuolation or alteration in the lung, spleen, pituitary gland, kidney, and liver (several body tissues were not examined).

Lung results: The authors described treatment related vacuolated alveolar macrophages in the lungs as "enlarged macrophages due to abundant amounts of lightly basophilic foamy to microvacuolated cytoplasm" at incidences of M: 0, 0, 0, 4, 5; F: 0, 0, 0, 5, 5 with mild to moderate severity (reference 2 a iv, pg. 15). An inflammatory response in the lung to this change was not reported.

Pathology comment: This is the first Pimavanserin study conducted (b) (4) while previous studies (2 rat and 1 monkey study), performed at different laboratories were completed at the time this mouse study was reported. It appears based on the careful phrasing of the study finding-interpretation as being consistent with PLD (mainly based on comparison of the observed study findings to a publication by Rudman et al., 2004; reference 2 a iv, pg. 16), that the pathologist reading this mouse study had no knowledge of the Pimavanserin study results of studies previously conducted in other species by other laboratories.

5. December 2007, completion – Pathology Report: (b) (4) 616002, 3 month Mouse study, with 1 month recovery: MS 3/1

The study was conducted (b) (4) administering Pimavanserin by **oral gavage** to 10 CD-1 mice per sex per group with an additional 5 recovery animals for the all dose groups. The dose groups were **0, 10, 30, 100 mg/kg/day** (reference 2 a vi, pg. 1-3).

Results

General results: Treatment of mice with Pimavanserin for 3 months was reported to result in deaths of treated mice as well as one control animal at the following incidences M: 1, 0, 2, 3; F: 0, 0, 0, 2. Because of these deaths, reduced numbers of recovery animals were allocated for the higher dose

groups to the 3 month recovery phase resulting in an N of M: 4, 5, 3, 2; F: 5, 5, 5, 3 (reference 2 a vi, pg. 193).
Gross observations were not reported for this study while male body weights were reported to be significantly decreased in high dose males (9.7%) but not in females. The study authors interpreted this change, however, as being spurious (reference 2 a vi, pg. 10). Body weight changes were not reported following a 1 month recovery phase. Treatment related organ weight changes reported by the study authors were restricted to the thyroid and parathyroid gland.
Multisystemic phospholipidosis (PLD) was not diagnosed in this study. Test article related effects were reported to be restricted to the **liver** of all treated males and females characterized by homogeneous, granular, eosinophilic cytoplasm, giving a "ground glass" appearance to the hepatocytes (reference 2 a vi, pg. 13).
Lung results: Lung weight increases were not reported for the main study but were reported for the recovery 100 mg/kg male dose group (15%). The study pathologist attributed this difference to be driven by one of only 2 recovery animals and therefore being spurious and unrelated to treatment. Treatment related histopathological lung changes were not reported.

Pathology comment:
The liver change was first described in this 3 month study by the study pathologist as "ground glass" appearance and was later termed "cytoplasmic homogeneity" by this pathologist to **specifically differentiate this observation** from cytoplasmic alterations previously reported in the liver of the 14 day mouse study (read by a different pathologist and there interpreted to be consistent with PLD). The pathologist of this 3 month study contemplated mechanism other than PLD to be underlying the observed liver change such as "glycogen depletion", "metabolic adaptation", or "degenerative processes" (reference 2 a vi, pg. 13).

We verified the individual recovery lung weight data and concur with the study pathologist's conclusion that the lung weight variation in the recovery high dose was likely spurious because there were no weight changes in the main study and no histopathological correlates in the recovery animal driving this observation. Therefore we conclude that this study is overall negative of treatment related PLD changes.

6. June 2006 – December 2007: (b) (4) 146.02, 6 Month Rat study with 3 month recovery: R6/3
The study was conducted (b) (4) administering Pimavanserin by **oral gavage** to 18-20 Sprague-Dawley rats per sex per group with additional 4-5 recovery animals at each dose group. The dose groups were **0, 3, 10, 30 mg/kg/day**; reference 2 b ii, pg. 1-2).

Results
General results: Treatment with Pimavanserin for 6 months in rats was reported to result in 7 unscheduled deaths at the following incidences M: 2, 1, 0, 2; F: 1, 0, 0, 1 which the study authors interpreted "unlikely to be treatment related" (reference 2 b ii, pg. 4 of final report). Clinically treatment related changes consisting of hunched posture, lethargy and sedation were reported observations most prominent at the highest dose of 30 mg/kg. The study authors judged a reported body weight gain reduction in male and females to be marginally adverse (reference 2 b ii, pg. 6, 42). Food consumption was not reported to be altered in this study. Gross lesions were not reported.
Multi-systemic PLD was not reported in this study.

Lung results: The authors did not describe changes consistent with PLD in the lung but reported **increased "macrophage infiltration, alveoli" as a "weak" test article related change** in high dose females at 30 mg/kg only (F: 2, 2, 2, 9). The finding was also described in treated males but incidences (M: 8, 4, 4, 6) were interpreted to not be elevated over control animals (reference 2 b ii, pg. 2, 12 of 13 of the pathology report). The change was not reported in recovery animals of either sex.

Pathology comment:
We analyzed the high dose female incidence of "**macrophage infiltration, alveoli**" further by evaluating the individual animal data (reference 2 b ii, pg. table 3.1) which revealed that the finding at the 30 mg/kg dose, was not only increased over controls with regard to incidence and severity but also by distribution (diffuse and multifocal in treated animals vs. focal in the controls).
As this study was conducted by (b) (4), one would assume that the study authors were aware of results reported in the 3 month Monkey study (MK 3/1) including multi-systemic PLD. Furthermore, we would expect a more detailed morphological description of the "macrophage infiltration, alveoli" finding, to specifically rule out a possible PLD manifestation. Unless EM was conducted, it is not certain that these macrophage infiltrations may not have been consistent with a mild form of PLD at the 30 mg/kg dose. In addition, an alternative explanation concerning the cause of these infiltrates termed "treatment related" in females but not males was not provided by the study authors.

7. March 2008 – Path report completion, (b) (4) 146.01, 12 Month Monkey study with 4 month recovery: MK 12/4
This study was conducted (b) (4) administering Pimavanserin by **oral gavage** to 4 cynomolgus monkeys per sex per group with an additional 2 recovery animals in all dose groups. The dose groups were **0, 1 (= starting dose) /5 (= escalated dose), 5/25, 25/60 mg/kg/day**. Animals were on the starting dose until day 43 and continued from then on with the escalated dose until study completion (reference 2 a v pg. 1, 5).

Results
General results: Treatment with Pimavanserin for 12 months in monkeys was reported to result in 2 deaths unrelated to treatment, one high dose male (60 mg/kg, day 54, interpreted to be a dosing accident) and one high dose female (60 mg/kg, day 149, interpreted to be due to colitis). Changes concerning clinical signs, clinical pathology, body weight/or body weight gain, and food consumption was not addressed in the pathology report.
Changes consistent with **multi-systemic PLD** were reported but the specific term of PLD was not used by the study authors in the report. The authors referred to these changes by using the term "foamy macrophages" (lung, stomach and small intestine) as well as "foamy cytoplasm" (adrenal and submandibular salivary glands (reference 2 a v pg.10).
Lung results: A pulmonary pleural adhesion (**fibrous thickening, pleura**) was a reported gross necropsy finding in one high dose male (60 mg/kg) and one low dose male (5 mg/kg) interpreted to be a common background finding in monkeys by the study authors (reference 2 a v pg.10, 404 and reference 2 c ii pg. 1764).
The authors reported mild treatment related "perivascular and alveolar foamy macrophages" in the lung at the following incidences: M/F: 0, 0, 0, 2. These observations were distinguished from a background finding of "alveolar foamy macrophages" without perivascular foamy macrophages at incidences of M: 1, 0, 2, 0; F: 2, 1, 1, 0.

Pathology comment:
It was unclear to us why the [redacted] study pathologist would not interpret the observed treatment related alveolar foamy macrophage changes in the lung and other organs as PLD, consistent with the previous 3 month Pimavanserin monkey study (MK 3/1) that had been conducted in the same laboratory. Exploring this further, it appears that in the MK 3/1 study only the [redacted] contracted "histo-pathologist" diagnosed PLD while the [redacted] Study pathologist of did not.

8. October 2007 – September 2011: [redacted] 616004, 24 Month Rat study with no recovery: R24/0
The study was conducted [redacted] administering Pimavanserin by **oral gavage** to 60 Sprague-Dawley rats per sex per group. The dose groups were **M: 0, 0, 3, 10, 30; F 0, 0, 5, 15, 50 mg/kg/day** (reference 2 a ii, pg. 1350-2).

Results
General results: This 24 month rats study was reported to result in early deaths along all dose groups. Only the deaths of the high dose females were attributed to a treatment related finding consisting of presence of vacuolated macrophages (severe form) in the lung (reference 2 a ii, pg. 1357, 1358 text table 1).
Clinical signs: Treatment related clinical signs of "**rales**" (noisy breathing) was reported in both high dose groups of males (30 mg/kg) and females (50 mg/kg) throughout the study with slightly increased incidences in females (reference 2 a ii, pg. 16 of the final study report).

Pathology comment: Verifying specifically the reported clinical observations of "rales" in the summary tables (reference 2 a ii, pg. 1403), we noted the following incidences for rales at 1-2 hrs post dosing as M: 3, 0, 2, 7, 46; F: 3, 4, 5, 40, 58. Therefore we consider the effect of rales at the female mid dose (15 mg/kg) also treatment related in addition to high dose effects in both sexes reported by the pathologist. However, since PLD incidences at this dose group did not correlate to the clinical signs of rales at this dose group (see lung changes below), further comparisons would be required. The body weight was reported to be reduced throughout the study in all treatment groups for both sexes. The study authors interpreted weight effects of only the high dose in males and females as toxicity related (reference 2 a ii, pg. 16-18 of the final study report).

Gross: Test article related gross observations for the 50 mg/kg females, affecting the lungs, paws and tails were reported in text table 2 (reference 2 a ii, pg. 1358).
An increased incidence of **cardiomyopathy** (M: 51, 52, 51, 46, 49; F: 31, 41, 37, 40, 52), was reported to be treatment related for high dose females (50 mg/kg; (reference 2 a ii, pg. 1361-63).
Multi-systemic phospholipidosis (PLD) was reported for the 30 mg/kg male (10/60) and 50 mg/kg female (45/60) dose groups and described as cytoplasmic vacuolation of many cell types and tissues. The lung was reported to be the most commonly affected tissue in both sexes and incidences were summarized in text table 4 (reference 2 a ii, pg. 1360-64).
Lung results: Gross lung findings of high dose females were reported to be "not fully collapsed, pale, mottled, white areas and/or firm" (reference 2 a ii, pg. 1361). Vacuolated macrophages within the lungs were reported to be common microscopic observations across all control and test groups with a test article-related increase in severity and/or incidence in the 30 mg/kg/day male and 50 mg/kg/day

female group (reference 2 a ii, pg. 1357 pathology report).
The authors described the manifestation of treatment related PLD in the lung as well as background finings as "macrophages, vacuolated" at the following incidence and severity: M: 20 (1.1), 22 (1.1), 21 (1.0), 22 (1.0), 33 (1.2) F: 20 (1.0), 19 (1.0), 11(1.0), 19 (1.0), 56 (2.6) (extrapolated from reference 2 a ii, pg. text table 4 pg. 1363). Distinguishing features between control and treatment related vacuolated macrophages were reported to be **abundant extracellular material**, that filled alveolar spaces and occurred only in the high dose group (30 and 50 mg/kg) of males and females and only with moderate to severe involvement of the lung but not in the controls (reference 2 a ii, pg. text table 4 pg. 1363). The study authors described the extracellular material in the individual animal tables further as "most of the vacuolated material appears to be free in the alveoli; possible lysis of macrophages" (reference 2 a ii, pg. 19330). The study authors described higher incidences of **"mixed inflammatory cell infiltrates"** (M: 2, 0, 4, 4, 8; F: 5, 5, 2, 1, 15) and "**inflammation**" (M: 10, 2, 5, 4, 9; F: 5, 5, 3, 4, 14) to be treatment related only at the female high dose (50 mg/kg). Furthermore, the study authors stated that both of these inflammatory changes were "associated with many cases of moderate to severe infiltrates of vacuolated macrophages" (reference 2 a ii, pg. 1362-63).

Pathology comment:
The extracellular material was not separately scored in the summary or individual animal tables (reference 2 a ii, pg. text table 4 pg. 12-13, 19412). The study authors speculated that "the accumulation of this extracellular material in the lungs likely would have created an increased workload on the heart" and was considered to be the most likely explanation for the increased incidence and severity of cardiomyopathy seen in the 50 mg/kg/day group females (reference 2 a ii, pg. text table 4 pg. 12). We verified a correlation of moderate and severe cardiomyopathy to the occurrence of moderate to severe vacuolated macrophages of the lung with vacuolated material free in the alveoli (reference 2 a ii, pg. text table 4 pg. 9290/19317, 9351/19330, 9515/19298, 9641/19413) and therefore agree with the pathologist's reasoning regarding the finding of cardiomyopathy.

9. January 2011 – March 2014: (b) (4) 616007, 6 month Rat study, with 6 month recovery: R6/6
The study was conducted (b) (4) (reference 2 a vii, pg. 1), administering Pimavanserin by **oral gavage** to 20 Sprague Dawley rats per sex per group with an additional 10 recovery animals for the all dose groups. The dose groups were **0, 60, 90 mg/kg/day** (reference 2 a vii, pg. 18). The original pathology report was signed (b) (4) October 2012; Amendment 1 was signed (b) (4) January 2014 (reference 2 a vii, pg. 738).

Pathology comment:
It is unclear to us why, based on previous study results, a 30 mg/kg dose group was not included in the study design of this 6 month rat study (b) (4) The results of the R 24/0 study, conducted at (b) (4) should have been available at the time the R 6/6 study was designed, warranting an inclusion of the 30 mg/kg dose based on positive PLD findings at the 30 mg/kg dose level for males in the R 24/0 study. In addition, the previous R 6/3 study was conducted in a different laboratory (b) (4) with an unexplained treatment related increase in alveolar macrophage in females at the 30 mg/kg dose group.

Results
General results: treatment with Pimavanserin for 6 month in rats was reported to result in several unscheduled deaths (M: 3, 1, 4; F: 1, 4, 5); the early deaths in the high dose females (90 mg/kg) was

interpreted as “poor tolerability” leading to early termination of this dose group (90 mg/kg) at study week 13 (reference 2 a vii, pg. 48).

Pathology comment:
*The reported early termination of the female high dose group (90 mg/kg) at study week 13 resulted in only about half of the intended exposure of 6 month, which needs to be taken into consideration when comparing study findings among all dose groups as they consequently have different exposure periods.
Several **clinical observations** were recorded including “respiration labored” and “**rales**” (M: 0, 23, 28; F: 0, 25, 28 at 1-2 hrs post dosing; reference 2 a vii, pg. 50). Body weight reduction and lower food consumption was reported for male and female high dose groups; reduced body weight was also reported for females at 60 mg/kg (reference 2 a vii, pg. 52-53).
Clinical pathology: Several clinical parameter changes were reported including an increase in absolute neutrophil counts (F: 60 mg/kg, M/F: 90 mg/kg) and monocyte counts (M/F: 60, 90 mg/kg) (reference 2 a vii, pg. 54-55).
Serum chemistry: BUN increases were reported for males and female at 90 mg/kg; increased creatinine values were reported in females at 60 mg/kg and males at 90 mg/kg. Elevated phosphorus levels were increased in 60 and 90 mg/kg males. The urinalysis specific gravity was reported to be lower for males at 60, 90 mg/kg; (reference 2 a vii, pg. 56).
Gross findings: The study authors reported an extensive list of organs to be discolored (pale, mottled, white / yellow areas) including lungs and kidneys in males at 90 mg/kg and females at 60 and 90 mg/kg. All but the lung discolorations (white areas) were reported to resolve in the recovery phase of 6 months (reference 2 a vii, pg. 58-59).
Organ weights: Organ weight changes were reported for both treatment groups (60 and 90 mg/kg) and both sexes for many organ tissues including lung and kidney; higher absolute lung weights were reported to remain increased in recovery animals over controls in both sexes of the high dose group (90 mg/kg; reference 2 a vii, pg. 59-60).
Microscopic evaluation: **Multi-systemic phospholipidosis (PLD)** was reported for a long list of body tissues including lungs and kidney for both sexes at both doses (60 and 90 mg/kg).
Lung results: The study authors described “minimal to severe vacuolated macrophages in all dose groups at the primary and recovery necropsies”. Specifically, the study authors described the incidences of PLD to occur in the lung of treated animals as “macrophages, vacuolated” at the following incidences (M: 1/N=17, 15/20, 16/16; F: 0/19, 17/17, 15/15) and to be characterized by “collections of large foamy macrophages and **multinucleated giant cells** with lightly eosinophilic cytoplasm filling the alveoli. Macrophages were accompanied by **cholesterol clefts** and variable amounts of **extracellular eosinophilic proteinaceous material**”. The authors described the extracellular material to be similar to the macrophage cytoplasm and interpreted the material to likely result from “macrophage lysis and release of contents”. In addition the authors describe “pneumocytes lining the alveoli protruded into the lumen and contained numerous cytoplasmic vacuoles as did the respiratory epithelium of the larger airways and the trachea (minimal to mild vacuolated epithelium” in the 60 and 90 mg/kg/ group for males and females, (reference 2 a vii, pg. 62). The study authors reported that by “the recovery necropsies, the incidence and severity of vacuolated macrophages and vacuolated epithelium was lower (M: 2/10, 2/9, 8/10; F: 2/10, 8/9, 9/10); however, **minimal to mild interstitial and pleural fibrosis** was observed in the 90 mg/kg males and females and the 60 mg/kg females in addition to vacuolated epithelial cells and macrophages” (reference 2 a vii, pg. 62- 63). One main study high dose female (90 mg/kg) was also recorded with

fibrosis in the lung (mild) in text table 3 but not mentioned in the report narrative (reference 2 a vii, pg. 62).
The study authors stated that the "fibrosis and macrophages correlated to the white areas observed at the recovery necropsies and to the higher absolute and relative lung weights that persisted at the recovery necropsies". The observed fibrosis (interstitial and pleural) was reported for the recovery animals at the following incidences (M: 0, 0, 5: F: 0, 7, 5*). The study authors offered the following interpretation for the fibrosis finding: "Although the incidence and/or severity of vacuolation (epithelial and macrophage) was reduced following the non-dosing (recovery) period and would have likely completely resolved with additional time, the **fibrosis was considered a permanent** change" (reference 2 a vii, pg. 62, 63).
Transmission Electron Microscopy (TEM): TEM was conducted on lung tissue only, resulting in the authors confirming that "the accumulation of the concentric lamellar inclusions in the alveolar macrophages was considered consistent with drug-induced phospholipidosis" reference (reference 2 a vii, pg. 76).

Pathology comment: Base on the records available, this appears to be the only study for which PLD was confirmed by TEM.

Kidney: The study authors attributed several of these unscheduled deaths to vacuolation of the renal tubular epithelium with subsequent tubular degeneration (4/30 males and 3/30 females in the 90 mg/kg/day group; reference 2 a vii, pg. 80). **Renal tubular degeneration** secondary to multi-systemic PLD was not only reported in early death animals but also in main study animals at the following incidences M: 0/N=17, 1/20, 12/16; F: 0/19, 5/17, 8/15. In the kidneys of the main study, the authors described "minimal to severe cytoplasmic vacuolation with minimal to moderate tubular degeneration characterized by tubules devoid of epithelium or with flattened epithelium (restitution) and increased incidence of mononuclear infiltrates occurring at primary necropsies in the 60 and 90 mg/kg/day males and females".
At the recovery necropsies, the majority of findings in the kidneys were reported to have "largely resolved" (tubular degeneration, M: 0, 0, 0; F: 0, 0, 0; reference 2 a vii, pg. 61, 63-64).
The original study pathologist [redacted] (b) (4) stated in the final pathology report (10/03/2012) that the "histopathologic changes in the kidneys were considered to be the basis of the higher serum urea nitrogen level in the 90 mg/kg/day group and higher creatinine level in males in the 90 mg/kg/day group" (reference 2 a vii, pg. 769). However, this sentence was removed in "Amendment 1 to the final pathology report" (01/29/2014; reference 2 a vii, pg. 736). Instead these study authors ("new study pathologist of record, [redacted] (b) (4)) offered the following interpretation of these changes being consistent with a "pre-renal (non-renal) cause, most likely increased protein catabolism secondary to the lower food consumption and lower body weights seen in this group" (90 mg/kg).

Pathology comment:
We correlated all rats with moderate renal tubular degeneration to BUN, Cr and phosphorus levels and found good correlation. Therefore, we agree with the original interpretation by the first pathologist that renal (tubular degeneration) and not pre-renal changes (Amendment 1) are the underlying cause for the clinical chemistry alterations observed.

Summary Pathology Comments:

The 9 laboratory animal studies (5 rat, 2 mouse, 2 monkey) listed above were conducted over a period of 12 years (2002-2014) at 4 different laboratories/locations (b) (4) and read by different pathologists. Most study narratives read as though the study pathologists / authors were not familiar with study findings recorded in studies conducted earlier. This was evidenced by variation in terminology and interpretation of treatment related changes.
Our evaluation revealed diagnoses compatible with or implying **multi-systemic PLD** in 7/9 studies (R1/1, MK 3/1, R3/1, MS14D/0, MK12/4, R24/0, R6/6). Studies negative for PLD were the MS 3/1 study (which resulted in non-PLD induced liver toxicity at ≥10 mg) and the R6/3 study for which a treatment related increase in alveolar macrophages was reported in females at the 30 mg/kg level. TEM is in our opinion necessary to unequivocally rule out a low grade PLD manifestation at this level for this study. TEM confirming PLD was conducted only for tissues from one (R6/6) of the 7 PLD positive studies. In one of the 7 studies positive for PLD (MK12/4), the term PLD was never specifically stated. To us, however, the description of foamy macrophage / cytoplasm of this study was compatible with multi-systemic PLD.

Female rats appeared to be more sensitive than males when comparing overall incidence tables for PLD related changes. 2 of the 7 PLD positive studies specifically stated that rat lung and kidneys were generally more severely affected, when multiple organs were reported with PLD. In all PLD positive studies, macrophages were characterized by some form of dose dependent increases in cytoplasmic vacuolation (**foamy macrophages**). In 4 (R1/1, R3/1, R24/0, R6/6) of 7 PLD positive studies, **eosinophilic material** (generally interpreted to be phospholipid) was observed inside vacuolated macrophage as well as extracellularly within the alveolar lumen (interpreted to be a consequence of macrophage lysis). Only in the R6/6 study, macrophages were further described to also include multinucleated giant cells and cholesterol clefts. Multinucleated giant cells generally result from macrophage fusion secondary to an inability of the macrophage to digest phagocytosed material; intracellular cholesterol clefts in macrophages are indicative of lipid rich materials stored within the macrophages. The manifestation of both of these features is theoretically conceivable considering the drug-class context of phospholipidosis. Multinucleated giant cells as well as cholesterol clefts are, however, not a typical feature of phospholipidosis; therefore these observations may warrant further investigation and safety consideration.

In the rat study of the longest duration (R24/0) **inflammatory cell infiltrates and inflammation** were described to be **associated** with the vacuolated macrophages and the extracellular material. In addition the R1/1 and the R3/1 also recorded inflammatory cell responses although the combined inflammatory response of the R1/1 study did not necessarily show incidences indicating a treatment relationship. Nevertheless, overall it appears that with PLD at higher doses, alveolar macrophages and extracellular material elicit a low grade inflammatory response in the pulmonary parenchyma. The incidences of inflammatory responses generally correlated to the higher PLD severity scores and treatment doses of Pimavanserin. In one of these rat studies (R3/1 – following the correction of an assumed summary table compilation error (see pathology comment for study R3/1 for details), the recorded inflammatory response was restricted to the 1 month recovery group and consisted of "adenomatous [type 2 pneumocyte] hyperplasia in males and **chronic inflammation** in females". Chronic inflammation by definition implies low degrees of interstitial **collagen deposition which is consistent with fibrosis**, resulting from long standing (weeks to months) inflammatory processes. In the recovery group of the R6/6 study, minimal to mild **interstitial and pleural fibrosis** was diagnosed which was identified by the study authors as a permanent change. Resolution of chronic

inflammation with low grade collagen deposition, as a component of chronic inflammation, will result in small areas of focal to multifocal fibrosis which persists while the inflammatory cellular components subside over time.

Fibrosis:
Optimally a slide review would have been conducted by CFSAN Pathology to assess the quality and quantity of the specific histological changes associated with the reported PLD. However, in lieu of slides, we concluded based on the overall information provided in the studies above, that the described '**fibrosis**' appears different from primary pulmonary fibrosis and is not compatible with "human pulmonary fibrosis".
The described changes are not suggestive of the spectrum of pathologic changes usually associated with the group of chronic diffuse lung disorders or acute lung injury associated with adverse drug reactions in humans. We propose a PLD process with an associated low grade ongoing inflammatory cell response which organizes over time (chronicity) resulting in collagen deposits manifesting as fibrosis". This "fibrosis" is a minor component of the lesions and is interpreted as being a secondary consequence of the inflammatory reaction. Fibrosis (newly produced collagen) at very small amounts is difficult to discern histologically in an H&E stained slide from preexisting collagen as both stain eosinophilic (pink). To more readily identify and visualize the degree of fibrosis, a special stain (Masson's trichrome) for collagen is generally used.

Your specific Questions: reference 1 a

1. *The sponsor acknowledges that pimavanserin causes widespread "systemic" phospholipidosis in mice, rats and monkeys. They also stated in their toxicology summary section that fibrosis occurred in the lungs of rats and that the finding was considered a permanent change that is toxicologically relevant to humans. However, the sponsor suggests that the finding is rat-specific, only dose- and not duration-dependent and there is an adequate safety margin compared to human exposures (9-fold). Do you agree with the sponsor's conclusions that the lung fibrosis is not a relevant risk to humans?*

Pathology comment: With regard to PLD and fibrosis observed in the lungs of rats the sponsor states the following (reference 1 f comment #2):

> "In the rat study (Study (b) (4)-616007), putative events leading to the observed lung fibrosis, i.e., collections of large foamy macrophages and the presence of extracellular material with or without chronic inflammation and eventual fibrosis [ ], reflect a known path in fibrogenesis.

We agree with the sponsor's assessment regarding the underlying pathomechanism leading to the fibrosis described in these studies (secondary to chronic inflammation which in turn is a response to PLD).

The sponsor proceeds (comment #2):

> "It is important to note that the moderate to severe phospholipidosis, the putative initiating factor for the lesion, is dose related but not duration related."

We agree with the sponsor that the PLD appears to be dose dependent, evidenced by e.g. the R6/6 study showing reduced incidences and severities of the PLD in the 60 mg/kg dose compared to the 90 mg/kg group of both sexes. However, we disagree with the sponsor that the PLD is not duration related. While PLD changes are not reported for males at the 30 mg/kg dose in the R3/1 and R6/3 studies, this dose level is affected by PLD after prolonged treatment with Pimavanserin in males of the R24/0 study. In addition in our opinion, multi-systemic PLD is not rat specific as it occurs in multiple species (mouse, monkey and rat). The manifestation of the type of fibrosis observed (secondary to inflammation) is not rat specific either but depends on the severity of the PLD and the degree and chronicity of the inflammation the PLD is associated with.

With regard to relevant risk, the sponsor stated (comment #2):

> "The observation of fibrosis is toxicologically relevant to humans; however, the finding in rats occurred only at a high dose (a dose causing lethality), and at ~18-fold human exposure"…[…….] Fibrosis in rats occurred only in animals that had moderate to severe phospholipidosis that was slow to resolve and only at high doses. With a high margin (>15 fold) for the fibrotic finding in rat, this is not considered to be a concern for patients".

We do not see that the sponsor specifically states that "*the lung fibrosis is not a relevant risk to humans?"* We do agree with the sponsor, that the observed minimal multifocal fibrosis that resides following longstanding low grade inflammation in response to PLD at high doses is

relevant to humans. The exposure margins and resulting concern for patients, are depending on the assessment of the adverse effect levels and are beyond the scope of this evaluation. Events considered adverse secondary to PLD reported in some of the 9 studies evaluated are inflammation (including chronic inflammation with fibrosis) and type 2-pneumocyte hyperplasia (Nikula et al., 2013; STP Position Paper: Interpreting the significance of increased alveolar macrophages in rodents following inhalation of pharmaceutical materials).

2. *In your expert opinion, do you have a hypothesis for why the lung fibrosis was primarily observed at the end of the 6-month recovery period and not in main study animals?*

Pathology comment: as outlined above under the Pathology summary comments we agree with the sponsors scenario outlined in reference 1 f comment #3, that a continuum underlies the development of the minimal-mild, multifocal fibrosis observed in the R6/6 study consisting of PLD (at high doses with multinucleated giant cells and cholesterol clefts), extracellular material, inflammation, and chronic inflammation (with fibrosis). The fibrosis reported in the R6/6 study represents a "point in time" observation which after cessation of treatment at which the resolution process resulted in remnant minimal-mild, multifocal foci of fibrosis while the originally associated inflammation had resolved.

3. *In your expert opinion, is it accurate to conclude that lung fibrosis is progression of persistent inflammation which in turn is a result of PLD? If so, is it reasonable to conclude that lung fibrosis is a clinically relevant outcome if pimavanserin is to be administered over a long period of time?*

Pathology comment: The fibrosis findings presented in the studies evaluated are in our opinion not consistent with the term "lung fibrosis" which implies a primary fibrotic process. We prefer the term "chronic inflammation" which implies some degree of organizing fibrosis or "fibrosis secondary to chronic inflammation". The level of secondary inflammatory fibrosis reported in the rat were described as of minimal to mild severity and being focal to multifocal in distribution; therefore, the clinical relevance of this finding depends on dose and duration. The relevant clinical parameter to monitor for is inflammation. We do consider any PLD **with** inflammation (including chronic inflammation) a clinically relevant outcome.

4. *Although the sponsor did not conduct any specific pulmonary function tests in animals, do the clinical respiratory-related findings in rats, along with the macro- and microscopic findings in the lungs suggest that pimavanserin may adversely affect lung function? If so, would this be a clinically relevant finding that can be monitorable?*

Pathology comment: The studies evaluated reported in 3/5 rat studies respiratory related findings of "noisy breathing" (R1/1) or "rales" (R24/0, R6/6) which correlated to pulmonary PLD **and** the amount of extracellular eosinophilic material. Auscultation of rales would be a clinically monitorable parameter. Monkeys and mice were not reported to show rales or noisy

breathing. The clinical relevance of this observation would, however, better be answered by a clinician.

5. Please provide any additional comments/recommendations you may have regarding the significance of the histopathological findings of pimavanserin in animals.

Pathology comment:
The lung and kidney appeared to be the most sensitive organs in the rat. In 2/5 rat studies (R3/1, R6/6), renal changes were reported consistent with "renal nephrosis" (tubular degeneration) in response to PLD with renal tubular vacuolation. For the R6/6 study we concurred with the original study pathologist, that the treatment related renal findings described are consistent with a renal manifestation, but not a pre-renal manifestation, as amended in the overall study report.

Please let us know if you have any questions.

Sabine Francke-carroll -S
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Sabine Francke, D.V.M., Ph.D., FIATP and Steven Mog D.V.M., DACVP

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BRENDAN MUOIO
01/29/2016
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