Oral Apomorphine Film (APL-130277) Produces No Buccal Mucosal Irritation: Results from a 28-Day Toxicology Study in Hamsters

#846

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CYNAPSUS

BACKGROUND

- Apomorphine HCl is a highly acidic compound
- Previous, non-parenteral formulations have been associated with mucosal irritation
- APL-130277 is a unique, sublingually administered film containing apomorphine
- APL-130277 is designed with a buffer layer that rapidly neutralizes acid generation

OBJECTIVE

Determine the tolerance of and potential for mucosal irritation following the administration of apomorphine film (APL-130277).

METHODS

Buccal mucosal testing using Syrian hamsters is an internationally accepted model to determine potential irritation by drugs
(Gardner AF. J Dent Res. 1964;43:1211-1221).

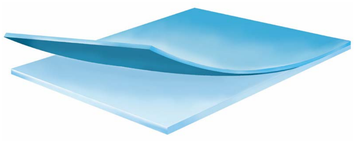
Test Articles

- **APL-130277** bilayer film, each containing 2.08 mg of apomorphine HCl.
  Note: *Dose is approximately 15 x higher than a 30 mg dose in a 60 kg human (range in clinical trials: 15-35 mg, when the doses are expressed in terms of body weight/mass and using 135 g hamsters for comparison.)*
- **Placebo** bilayer film, each containing 0 mg apomorphine HCl.
- *APL-130277 and placebo were manually sectioned into 12 strips (5.5 mm by 7.3 mm)*

Dosing

- Hamsters were administered APL-130277 or placebo three times daily for 28 d

Figure 1: Sublingual Bilayer Film



APL-130277 or Placebo Administration

Right cheek pouch.

- Test film placed onto buccal mucosa followed by 0.1 mL of water to enhance dissolution
- Successive films were applied to same area of the cheek pouch for each dose.

Left cheek pouch

- Manipulated in the same manner without the placement of a film but with the addition of water

Study Assessments (Figure 2)

Clinical Observations

- Clinical signs, body wt, food consumption
- Cheek pouches everted, cleared of food, and examined for signs of irritation
  - Prior to the first dose:
    - Days 1, 2, 3, 4, 8, 14, and 21
  - Prior to necropsy on Day 29 using
- Draize scoring system 0-4 (see details at end of poster)*

Necropsy

- Day 29, animals were necropsied

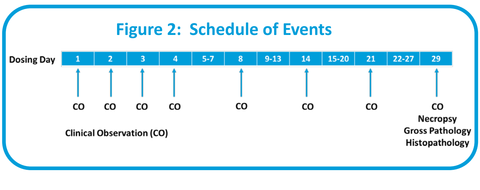
Gross Pathology

- Left and right cheek pouches from each animal were macroscopically examined

Histopathology

- Changes observed in 3 separate samples of each cheek pouch/hamster graded on scale of 0-5 (see details at end of poster)**

Figure 2: Schedule of Events



RESULTS

Treatment Group	Animals (N = 32) Mean Body Wt Change ± SD		Apomorphine Dose (mg)	Dosing Frequency
	Male	Female		
Control	N=8 +9.5 ± 4.4g	N=8 +15.2 ± 6.5g	0	*tid* x 28d
APL-130277	N=8 -3.0 ± 4.1g	N=8 -4.0 ± 8.9g	2.08	*tid* x 28d

Clinical Observations

- Post-dose hyperactivity severity in APL-130277 group decreased during study.
- Initial body wt loss (starting body wt was 134 g [males] and 143 g [females]) and reduced food consumption showed recovery as study progressed.
- No signs of irritation over the 28 days of dosing in males and females dosed either with the placebo or APL-130277

Gross Pathology and Histopathology

No gross lesions or histopathologic findings were found in any buccal mucosa of any males or females treated with no films, placebo or with APL-130277.

CONCLUSIONS

- APL-130277 produced no irritation of the cheek pouch buccal mucosa when administered at a relatively high apomorphine dose of 2.08 mg (which is ~ 15 X higher than a 30 mg film dose in a 60 kg human, when the doses are expressed in terms of body weight/mass and using 135 g hamsters for comparison).
- Additional safety data is being collected in on-going Phase 3 trials.

SCORING SYSTEMS

*** Draize**

Score	Description
0	No erythema; no edema
1	Very slight erythema (barely perceptible); very slight edema (barely perceptible)
2	Well defined erythema; slight edema (edges well defined by definite raising)
3	Moderate to severe erythema; moderate edema (raised approximately 1 mm)
4	Severe erythema (beet-redness) to slight, eschar formation (injuries in depth); severe edema (raised more than 1 mm and extending beyond the area of exposure

**** Histopathology**

Score	Description
None (0)	Tissues were considered to be normal
Minimal (1)	Lesions were detectable within reasonable viewing
Mild (2)	Lesions easily seen, but enveloped a small amount of tissue area
Moderate (3)	Lesions were prominently present, involving 10% to 50% of area
Marked (4)	Lesions were extensive and may involve 50% to 75% of area
Severe (5)	Lesions were interpreted as within the worst possible scenario

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