Discussion of Efficacy Findings

The Applicant's analysis of the primary endpoint (SPID 30) for Study FEN-201 as confirmed by Dr. Joan Buenconsejo, supports the finding of efficacy for BEMA fentanyl compared to placebo (p=0.004) for the treatment of BTP in patients with malignancies receiving around-the-clock opioid therapy for cancer pain. In addition, although the analyses of secondary endpoints were not adjusted for multiplicity, due of their consistent trends in favor of BEMA Fentanyl compared to placebo, they support the conclusion that patients receiving BEMA Fentanyl experienced greater pain relief and less pain intensity than those who received placebo.

The Applicant also performed a cumulative responder analysis as a function of the percent pain intensity difference as described by Farrar et al. **It showed that BEMA™ Fentanyl has a higher** number of responders at all response levels than placebo. The largest efficacy advantages over placebo occurred when a responder is defined as 20% to 50% PID improvement.

The analysis of safety is presented in section 7.

10.2 Deaths During Development Program

Deaths listed in italics are those reported in the 120-day safety update

Table 57: Deaths Due to Underlying Disease or Progression

Site-PID	Cause of Death	Timing of study drug discontinuation
001-2001	disease progression	9 days before death
001-2003	*Disease progression*	*day of death*
001-2004	disease progression	49 days before death
001-2006	disease progression	day of death
001-2007	disease progression	13 days before death
001-2008	disease progression	8 days before death
004-1004	disease progression	16 days before death
004-1005	neoplasm recurrence	day of death
004-1011	disease progression	2 days before death
004-1027	*Disease progression*	*1 day before death*
004-2010	*Disease progression*	*22 days before death*
005-2002	disease progression	13 days before death
011-2004	disease progression	10 days before death
017-1008	disease progression	4 days before death
018-1004	disease progression	5 days before death
018-1008	neoplasm recurrence	9 days before death
018-1011	disease progression	15 days before death
023-1003	neoplasm recurrence	day of death
023-1006	disease progression	39 days before death
028-2005	disease progression	20 days before death
028-2006	disease progression	15 days before death

028-2014	disease progression	29 days before death
038-1001	disease progression	32 days before death
038-2001	*Disease progression*	*16 days before death*
038-2003	disease progression	day of death
038-2004	disease progression	44 days before death
038-2008	disease progression	5 days before death
043-2005	disease progression	3 days before death
044-2001	neoplasm recurrence	12 days before death
044-2002	*Disease progression*	*13 days before death*
047-2005	disease progression	7 days before death
052-2003	neoplasm recurrence	12 days before death
052-2005	disease progression	8 days before death
052-2007	*Disease progression*	*2 days before death*
052-2009	disease progression	7 days before death
052-2010	*Disease progression*	*22 days before death*
052-2011	*Disease progression*	*9 days before death*
052-2012	*Disease progression*	*43 days before death*
052-2013	*Disease progression*	*7 days before death*
052-2015	*disease progression*	*28 days before death*
052-2017	*disease progression*	*2 days before death*
052-2019	*disease progression*	*day of death*
052-2022	*disease progression*	*3 days before death*
063-1005	disease progression	7 days before death
063-1010	disease progression	1 day before death
063-2001	disease progression	5 days before death
063-2003	disease progression	11 days before death
063-2004	neoplasm recurrence	12 days before death
063-2008	neoplasm recurrence	18 days before death
063-2009	neoplasm recurrence	10 days before death
063-2010	disease progression	2 days before death
082-2007	*disease progression*	*16 days before death*

Table 58: Deaths Due to Complications of Disease (chemo related, sepsis)

Site-PID	**Cause of Death**	**Timing of Study Drug Discontinuation**
004-1006	malignant pleural effusion	day of death
004-1008	acute renal failure	day of death
004-1015	pneumonia	9 days before death
004-1018	Sepsis	2 days before death
004-1022	pneumonia	8 days before death
004-2001	pseudomonas bacteremia	5 days before death
004-2003	pneumonia	15 days before death
004-2004	UGI bleed	day of death
004-2007	GI hemorrhage	4 days before death

004-2011	sepsis	4days before death
006-2003	aspiration	day of death
017-1006	pneumonia	2 days before death
032-1002	sepsis	11 days before death
069-1001	hepatic failure	51 days before death
018-2002	sepsis	9 days before death
028-2015	*alpha hemolytic strep infection*	*28 days before death*

Table 59: Deaths Due to Other Reasons

Site-PID	Cause of Death	Timing of Study Drug Discontinuation
018-2001	*Unknown (pt. had colon and prostate cancer)*	*18 days before death*
020-2001	renal failure	7 days before death
031-1002	respiratory failure	1 day before death
082-2002	cardiac arrest	day of death
082-2006	*cardiac arrest*	*1 day before death*

10.3 Serious Adverse Events During Development Program

Table 60: SAEs due to Underlying Malignancy or Progression (e.g., metastases)

Pt ID	Exposure duration at AE onset*		Related to BEMA Fentanyl			SAE	Comments
	Short	Long	Definitely	Possibly	Not		
004-1021	X	X			X	Hematemesis, splenomegaly, pleural effusion	Hematemasis after short term, other after long term exposure
017-1012	X				X	Hemoptysis	
018-1001		X			X	Failure to thrive	
035-1003	X				X	Esophageal hemorrhage	
063-1003	X				X	Bone pain	
004-1015		X			X	Dysphagia	Patient later died from pneumonia
004-1019		X			X	Malignant neoplasm	
008-1002		X			X	Carcinoid syndrome Cancer pain Intestinal obstruction	
011-2004		X			X	Pathologic hip fracture	Patient later died from cancer progression
017-2003	X				X	Gastroesophageal fistula	
019-2001		X			X	Cancer pain	
023-1005		X			X	**Recurrent Hodgkin's** dis. Bile duct obstruction	
027-2007		X			X	Chest pain, hemoptysis	
028-2014		X			X	Disease progression	Patient later died from disease progression

004-2011	sepsis	4days before death
006-2003	aspiration	day of death
017-1006	pneumonia	2 days before death
032-1002	sepsis	11 days before death
069-1001	hepatic failure	51 days before death
018-2002	sepsis	9 days before death
028-2015	*alpha hemolytic strep infection*	*28 days before death*

Table 59: Deaths Due to Other Reasons

Site-PID	Cause of Death	Timing of Study Drug Discontinuation
018-2001	*Unknown (pt. had colon and prostate cancer)*	*18 days before death*
020-2001	renal failure	7 days before death
031-1002	respiratory failure	1 day before death
082-2002	cardiac arrest	day of death
082-2006	*cardiac arrest*	*1 day before death*

10.3 Serious Adverse Events During Development Program

Table 60: SAEs due to Underlying Malignancy or Progression (e.g., metastases)

Pt ID	Exposure duration at AE onset*		Related to BEMA Fentanyl			SAE	Comments
	Short	Long	Definitely	Possibly	Not		
004-1021	X	X			X	Hematemesis, splenomegaly, pleural effusion	Hematemasis after short term, other after long term exposure
017-1012	X				X	Hemoptysis	
018-1001		X			X	Failure to thrive	
035-1003	X				X	Esophageal hemorrhage	
063-1003	X				X	Bone pain	
004-1015		X			X	Dysphagia	Patient later died from pneumonia
004-1019		X			X	Malignant neoplasm	
008-1002		X			X	Carcinoid syndrome Cancer pain Intestinal obstruction	
011-2004		X			X	Pathologic hip fracture	Patient later died from cancer progression
017-2003	X				X	Gastroesophageal fistula	
019-2001		X			X	Cancer pain	
023-1005		X			X	**Recurrent Hodgkin's** dis. Bile duct obstruction	
027-2007		X			X	Chest pain, hemoptysis	
028-2014		X			X	Disease progression	Patient later died from disease progression

032-1002		X			X	dysphagia	Patient later died from sepsis
044-2001		X			X	Pleural effusion, vomiting	Pt later died of ovarian cancer
052-2006		X			X	Disease progression	
053-1001		X			X	Pneumothorax	Lung cancer
063-2008	X			X		Hypoxia	Possibly related to study drug; lung CA patient had received 5 days of study drug; had been on 1 day of maintenance dose of 1200mcg; Hypoxia resolved 1-2 days following study drug d/c.see narrative

* Short-term exposure = FEN-113, titration periods of FEN-201 or FEN-202; Long-term exposure = double-blind period of FEN 201, open-label long term treatment of FEN-202

Table 61: SAEs due to complications of underlying malignancy (e.g. sepsis, chemo)

Pt ID	Exposure duration at AE onset		Related to BEMA Fentanyl			SAE	Comment
	Short	Long	Definitely	Possibly	Not		
004-1002	X				X	DVT, Pneumonia, Acute renal failure	
004-1006		X			X	Pneumonia x 2 Malignant pleural effusion Electrolyte imbalance Cellulitis	1 episode of pneumonia occurred during study 201; Bilateral pleural effusion preceded death
004-1010		X			X	Pyrexia Pain, mental status changes	Pyrexia occurred during study 201; Mental status changes due to use of 9 fentanyl patches (100 µg each) at once rather than the 3 prescribed-see narrative
004-1014		X			X	dehydration	
004-1017		X			X	dehydration	
004-1026	X				X	pneumonia	
006-1012	X				X	Pulmonary embolism	
015-1002	X				X	GI hemorrhage	
023-1002	X				X	pneumonia	
072-1001	X				X	pneumonia	
001-2008		X		X		vomiting	Subject died 19 days later due to progression of underlying disease.-see narrative
002-2002		X			X	sepsis	
004-2001		X			X	Bacterial arthritis	Later died of pseudomonas sepsis
004-2005		X			X	Respiratory distress DVT	Respiratory distress secondary to sepsis-see narrative
004-2006	X				X	pneumonia	
004-2008		X			X	pyrexia	
006-1006		X			X	dehydration	
006-1007		X			X	pneumonia	
018-1016		X			X	Acute abdominal infection	
023-1003		X		X		mucosal inflammation	HIV+, concurrent herpes zoster, thrush; unlikely related to study drug-see narrative
023-2003		X			X	pneumonia	

Pt ID	Exposure duration at AE onset		Related to BEMA Fentanyl			SAE	Comment
	Short	Long	Definitely	Possibly	Not		
023-2005		X			X	pneumonia	
032-1004		X			X	sepsis	
047-2003		X			X	Abdominal pain, nausea, vomiting	See narrative
047-2004	X				X	Febrile neutropenia	
063-1005		X			X	DVT	Patient later died of recurrent cervical CA
063-2001		X		X		Hypoxia	Also had pneumonia; died one month later b/o progression of rectal CA-see narrative
063-2010		X			X	hemoptysis	

* Short-term exposure = FEN-113, titration periods of FEN-201 or FEN-202; Long-term exposure = double-blind period of FEN 201, open-label long term treatment of FEN-202

Table 62: SAEs due to other reasons

Pt ID	Exposure duration at AE onset		Related to BEMA Fentanyl			SAE	Comment
	Short	Long	Definitely	Possibly	Not		
006-1003	X				X	Confusional state	Event occurred 1 day after last dose of study drug; subject discontinued from study due to non-compliance and inaccuracies in recorded dosing during titration; never entered d-b portion. No explanation given for confusional state.-see narrative
017-1008		X			X	Seizure	No cause given for seizure
023-1006	X	X			X	Hypoglycemia Failure to thrive	Hypoglycemia occurred in 201, and FTT in 202 Subject had type 2 DM; patient later died as a result of BC recurrence
001-2005		X			X	gastroenteritis	
004-1004		X			X	Contusion	Patient fell-last dose of study drug was 10 days prior to event; subject died 6 days after event due to progression of cancer
004-1024		X			X	Acute renal failure	Severe intestinal obstruction also reported
004-2003		X			X	Hip fracture	Patient died 2° to pneumonia
006-1002		X			X	IV catheter- related skin infection	
018-1012		X			X	diarrhea	
023-1001		X			X	migraine	
028-2003		X			X	Respiratory distress, asthma	Patient had pulmonary sarcoidosis and pneumonia-see narrative
028-2009		X			X	LOC, hematoma, intervertebral disc protrusion, mental status changes, orbital cellulitis	It is unlikely that LOC was due to study drug since patient had been on stable dose of 600 mcg for 7 weeks, and last dose of study drug was 6 days prior to LOC.-see narrative
043-2003		X			X	Humerus fracture	Patient fell and fx humerus approx 3 months after last dose of study drug
063-2004		X			X	Agitation	

* Short-term exposure = FEN-113, titration periods of FEN-201 or FEN-202; Long-term exposure = double-blind period of FEN 201, open-label long term treatment of FEN-202

10.4 Common Adverse Events

Table 63: Adverse Events Which Occurred During Long-term Treatment at a Frequency of ≥ 1%

System Organ Class	Preferred Term	#	% (N=190)
Blood and lymphatic system disorders			
	Coagulopathy	2	1%
	Leukocytosis	3	2%
	Leukopenia	2	1%
	Lymphadenopathy	3	2%
	Neutropenia	2	1%
	Pancytopenia	7	4%
Cardiac disorders			
	Tachycardia	3	2%
Ear and labyrinth disorders			
	Deafness	2	1%
Eye disorders			
	Conjunctivitis	2	1%
	Diplopia	3	2%
	Vision blurred	4	2%
Gastrointestinal disorders			
	Abdominal distension	4	2%
	Abdominal pain	7	4%
	Dry mouth	7	4%
	Dyspepsia	4	2%
	Dysphagia	7	4%
	Flatulence	2	1%
	Gastrooesophageal reflux disease	5	3%
	Hematemesis	2	1%
	Intestinal obstruction	5	3%
	Esophagitis	2	1%
	Stomach discomfort	2	1%
	Stomatitis	7	4%
General disorders and administration site conditions			
	Chest pain	3	2%
	Chills	2	1%
	Malaise	5	3%
	Mass	2	1%
	Mucosal inflammation	2	1%
	Thirst	4	2%
Hepatobiliary disorders			
	Jaundice	3	2%
Infections and infestations			
	Bacterial infection	3	2%
	Candidiasis	4	2%
	Catheter related infection	2	1%
	Cellulitis	3	2%
	Device related infection	4	2%

	Eye infection	3	2%
	Herpes zoster	4	2%
	Influenza	3	2%
	Nasopharyngitis	5	3%
	Neutropenic sepsis	2	1%
	Oral candidiasis	3	2%
	Sepsis	5	3%
	Sinusitis	7	4%
	Wound infection	3	2%
Injury, poisoning and procedural complications			
	Contusion	2	1%
	Excoriation	2	1%
	Fall	7	4%
	Hip fracture	2	1%
	Rib fracture	2	1%
Investigations			
	Body temperature increased	2	1%
	Breath sounds abnormal	2	1%
	Weight decreased	6	3%
Metabolism and nutrition disorders			
	Anorexia	8	4%
	Electrolyte imbalance	7	4%
	Failure to thrive	4	2%
	Hypercalcaemia	2	1%
	Hypocalcaemia	2	1%
	Hypokalemia	8	4%
	Hyponatremia	3	2%
	Hypovolemia	2	1%
	Malnutrition	5	3%
Musculoskeletal and connective tissue disorders			
	Arthralgia	7	4%
	Flank pain	2	1%
	Intervertebral disc protrusion	2	1%
	Mobility decreased	3	2%
	Muscle spasms	3	2%
	Muscular weakness	5	3%
	Musculoskeletal chest pain	2	1%
	Musculoskeletal pain	6	3%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
	Cancer pain	5	3%
	Cervix carcinoma recurrent	2	1%
	Hodgkin's disease recurrent	2	1%
	Lung carcinoma cell type unspecified recurrent	2	1%
	Metastases to central nervous system	3	2%
	Neoplasm recurrence	3	2%
	Esophageal cancer metastatic	2	1%
	Ovarian cancer recurrent	3	2%
	Pancreatic carcinoma recurrent	2	1%
	Prostate cancer metastatic	2	1%

Nervous system disorders			
	Amnesia	4	2%
	Diplegia	2	1%
	Hypoesthesia	8	4%
	Lethargy	4	2%
	Migraine	3	2%
	Paresthesias	3	2%
	Restless legs syndrome	2	1%
	Sciatica	2	1%
	Sedation	2	1%
	Somnolence	8	4%
	Tremor	2	1%
	Vocal cord paralysis	2	1%
Psychiatric disorders			
	Agitation	6	3%
	Delusion	2	1%
	Hallucination	5	3%
	Mental status changes	5	3%
	Restlessness	3	2%
Renal and urinary disorders			
	Hematuria	5	3%
	Nephrolithiasis	2	1%
	Renal failure	2	1%
	Renal failure acute	2	1%
	Urinary incontinence	2	1%
	Urinary retention	3	2%
Respiratory, thoracic and mediastinal disorders			
	Atelectasis	2	1%
	Dysphonia	2	1%
	Epistaxis	3	2%
	Hemoptysis	3	2%
	Hiccups	2	1%
	Hypoxia	3	2%
	Nasal congestion	3	2%
	Pharyngolaryngeal pain	6	3%
	Pneumonitis	2	1%
	Respiratory distress	2	1%
	Rhinorrhoea	2	1%
	Sinus congestion	2	1%
	Throat irritation	2	1%
	Wheezing	2	1%
Skin and subcutaneous tissue disorders			
	Blood blister	2	1%
	Hyperhidrosis	3	2%
	Increased tendency to bruise	2	1%
	Pruritus	2	1%
	Rash	4	2%
	Skin ulcer	3	2%
Vascular disorders			
	Deep vein thrombosis	3	2%