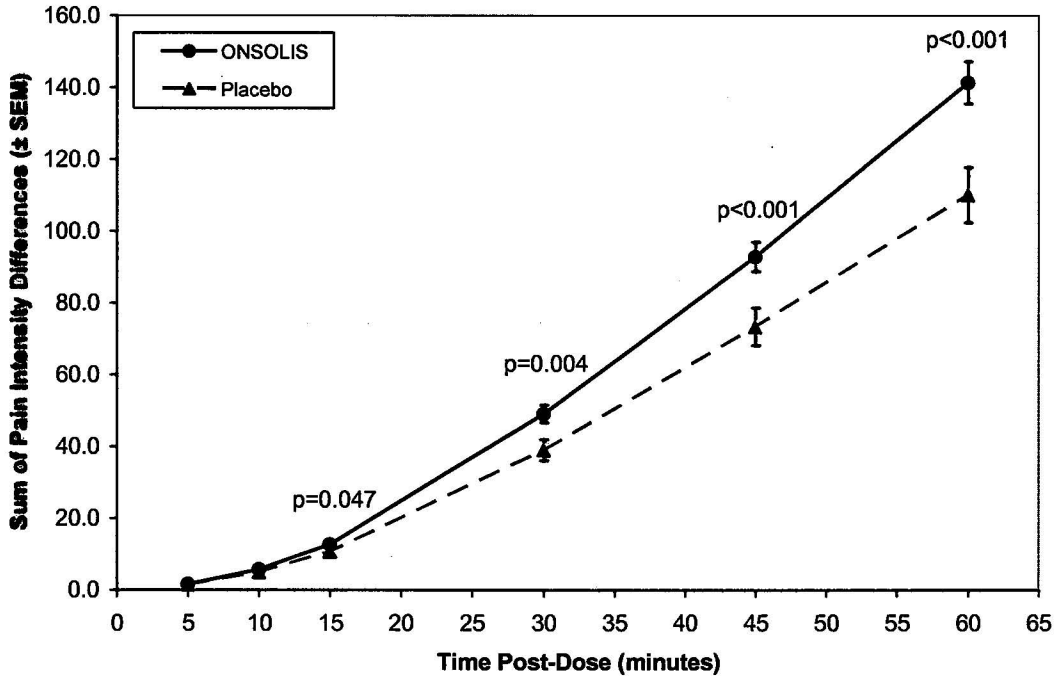
Figure 1

Sum of Pain Intensity Differences (SPID) Following ONSOLIS * or Placebo in Adult Patients with Breakthrough Cancer Pain



ONSOLIS dose identified during titration as 'successful', i.e., patient obtained adequate analgesia with tolerable side effects

Additional secondary endpoints included the pain relief at each time point, the pain intensity difference (PID) and the total pain relief calculated for each time point and a patient global evaluation. There was no planned correction for multiplicity for these secondary analyses. Most of these secondary endpoints favored the active treatment over placebo. The global satisfaction rating is shown in the table below **taken from Dr. Buenconsejo's review. There** were a greater number of the more favorable ratings and fewer of the unfavorable ratings for the active treatment compared to placebo, although the differences are not dramatic.

Table 7 Subject Overall Satisfaction with the Study Drug: ITT Population

	Placebo	BEMA Fentanyl	Mean Difference (SD) †
Mean Evaluation Score			
# of episodes Mean (SD)	174 1.5 (0.1)	359 2.0 (0.1)	N=72 pairs 0.5 (1.0)
	Number of Episodes		
Evaluation			
Poor	50 (29%)	52 (15%)	
Fair	42 (24%)	66 (18%)	
Good	40 (23%)	103 (29%)	
Very Good	29 (17%)	96 (27%)	
Excellent	13 (8%)	42 (12%)	
Source: Clinical Study Report, page 70 †Reviewer's using Paired Difference			

As the third oral transmucosal fentanyl product to undergo NDA review, it is interesting to see how the data available for BEMA Fentanyl compare with the data from Actiq and Fentora. No within-study comparisons were conducted, so the cross-study comparisons presented below must be interpreted cautiously. The following **table from Dr. Fields' review shows the number** of subjects who dropped out of studies for Actiq, Fentora and BEMA Fentanyl. There were more subjects who failed titration in BEMA Fentanyl Study FEN-201 and no apparent reason why. However, Study FEN-202, an open-label safety study with a titration period that similar to Study FEN-201, had fewer titration failures, and taken together, the numbers are similar to the experiences with Actiq and Fentora.

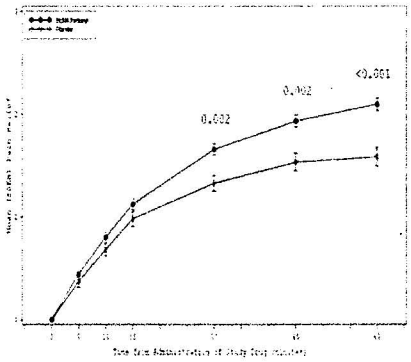
Table 8 Percentage of drop-outs during titration period for Actiq, Fentora, and BEMA Fentanyl

Drug	Number enrolled in titration period	Dropouts during titration	
		Number	Percent
Actiq	130	38	29.2
Fentora	123	46	37.3
BEMA Fentanyl FEN-201[1]	151	69	45.6
BEMA Fentanyl FEN-202[2]	146	37	25

[1]Doses in FEN-201: 200µg-1200µg
[2]Doses in FEN-202: 200µg-2400µg

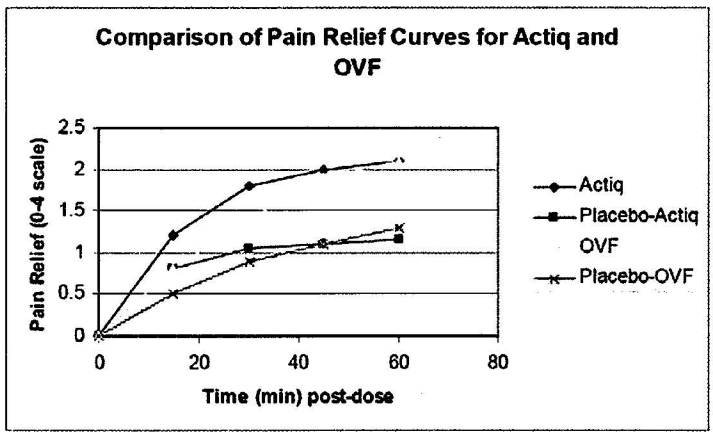
The following figures from Dr. Fields' review represent the efficacy results, specifically pain relief for the three products. Again, a note of caution as these are cross-study comparisons. The response in the placebo arm appears somewhat larger in the BEMA Fentanyl figure, but the response in the active arm appears comparable across studies.

Figure 2
BEMA Fentanyl Pain Relief Curve



The Y-axis is mean pain relief on a 0-4 scale, the tick marks are at 1 and 2. The X-axis is time is marked at 0, 5, 10, 15, 30, 45 and 60 minutes. The solid circles are BEMA Fentanyl and the open circles are placebo.

Figure 3
Actiq and Fentora Pain Relief Curves



Dosing and titration were evaluated during the studies. Patients were given a titration package that contained five doses of each of the five BEMA Fentanyl strengths. Titration began with the 200 mcg dose and subjects were instructed how to titrate to an effective dose. During the studies, patients titrated to the full range of available doses as shown in the following table **from Dr. Fields' review. Most patients titrated** to a dose between 400 mcg and 1200 mcg.

Table 9 Comparison of Effective Doses Across Studies

Dose (µg)	FEN-201 N (%) Dose Distribution in Double-blind Period	FEN-202 N (%) Initial Effective Dose	FEN-202 N (%) Effective Dose at Interim Cutoff
200	4 (5%)	14 (8%)	13 (8%)
400	15 (18%)	35 (20%)	29 (17%)
600	23 (28%)	40 (23%)	29 (17%)
800	19 (23%)	43 (25%)	41 (24%)
1200	20 (25%)	30 (17%)	43 (25%)
1600	NA	6 (3.5%)	11 (6%)
2400	NA	4 (2%)	3 (3%)
Total	81 (100%)	172 (100%)	172 (100%)

Source: BEMA Fentanyl ISS, p. 16

The applicant proposes

b(4)

The applicant was advised that the was not acceptable and that we recommend patients be titrated using 200 mcg units. The following titration algorithm is acceptable using the 200 mcg units.

b(4)

Figure 3 Dose Titration Scheme

b(4)

7. Safety

Dr. Fields reviewed the safety of BEMA Fentanyl. Sections of her review may be included below in whole or in part. Safety data came primarily from three studies. FEN-201 was the efficacy study described above. FEN-202 is an open-label study of patients electing to continue receiving BEMA Fentanyl from FEN-201, or novel patients who met the same entry criteria as FEN-201, and was ongoing at the time this application was submitted. Subjects entering directly were titrated to an effective dose (200 µg to 2400 mcg) in a manner similar to the one used in FEN-201. Once a dose was identified, subjects were permitted to continue at that dose for an unlimited period, with dosage adjustments allowed as required to control breakthrough pain. Throughout the study, all subjects returned to the clinic monthly for safety assessments, dosage adjustment, and dispensing of additional study medication. FEN-113 was an open-label, single-dose, pharmacokinetic study in 14 cancer patients with Grade 1 mucositis and without mucositis. All subjects received a single 200 mcg BEMA Fentanyl unit applied to the buccal mucosa by study personnel. Oral examinations for mucosal irritation were performed regularly in each of the studies. No laboratory safety data were collected. The remainder of the PK studies are not informative for safety as subjects received naltrexone to block the effects of the fentanyl.

The ISS is based on the 301 cancer patients who received at least one dose of BEMA Fentanyl, and the dose and duration of exposure is presented in the following table from Dr. Fields' review. The demographics are described in depth in Dr. Fields' review.

Table 10 Exposure Data by Dose and Duration for ISS Population

	BEMA Fentanyl Dose (µg)						Total
	200	400	600	800	1200	>1200	
Number of subjects	297	239	199	150	100	24	301
Number (%) of doses	2616 (4.3)	7871 (13.1)	9094 (15.1)	15161 (25.2)	18990 (31.6)	6366 (10.6)	60098
Number of subject days in study	1449	3229	3486	5684	5954	1796	21211
Mean number of doses/ subject day	2	2	3	3	3	4	3
Total exposure							
Mean days							82.2
≥60 days							112
≥90 days							91

Source: BEMA Fentanyl ISS, p. 17

There were 72 deaths during the development program including an additional 12 reported in the 120-day safety update. Dr. Fields reviewed the deaths in detail. Based on her review it appears that 52 deaths were due to progression or recurrence of disease, 14 due to complications of the underlying disease, and six due to reasons unrelated to the underlying malignancy including the two deaths she describes as "other" reasons. Many of the deaths occurred without evidence that study drug was administered in close proximity to the event. None of the narratives suggest a direct involvement of study drug although some had too few details to draw a conclusion. As noted by Dr. Fields, the population described by the study criteria was opioid tolerant and underwent dose titration, so it is unlikely that there would be a fatality associated with a single dose of BEMA Fentanyl. None of the deaths followed the first dose of study drug.

There was a total of 108 SAEs occurring in 74 patients that did not result in death during the BEMA Fentanyl development program. Dr. Fields reviewed these narratives in detail and determined that none of the SAEs were definitely due to the administration of study drug. As she notes, there were four cases possibly related to study drug, two cases of hypoxia, one mucosal inflammation, and one case of vomiting, but even these appeared to be more likely associated with the patients' underlying disease.

There were many early discontinuations from the clinical studies, FEN-201 and FEN-202. As noted, there were many patients who failed titration, 46% in FEN-201 and 25% in FEN-202. After reviewing the CRFs and patient narratives, Dr. Fields determined there were 17 discontinuations due to adverse events from FEN-201 and six in FEN-202. During the double-

blind period of FEN-201, there were five additional discontinuations due to adverse events, and another 17 from the open-label period in FEN-202. The most common adverse events leading to discontinuation were nausea, vomiting, dizziness, and sedation which are consistent with the known effects of an opioid, followed by disease progression and pneumonia. During longer-term exposure in FEN-202, there were another 54 discontinuations due to adverse events, the most common being related to the underlying disease. Nausea, dizziness, agitation and hallucinations were present in one to two percent of patients dropping out due to adverse events.

The common adverse events of greatest frequency were mostly not related to opioid use. As shown in the following table from **Dr. Fields' review, during short**-term use, anemia, diarrhea, pain, pneumonia and dehydration were more likely due to the underlying disease along with several of the remaining adverse events.

Table 11 Adverse Events during Short-Term Administration at a Frequency of ≥ 1%

Adverse Event (PT)	#	%
Headache	10	3%
Anemia	8	3%
Constipation	7	2%
Diarrhea	6	2%
Pain	6	2%
Pneumonia	6	2%
Dehydration	5	2%
Anxiety	4	1%
Dry mouth	4	1%
Hypokalemia	4	1%
Confusional state	3	1%
Dysgeusia	3	1%
Dyspnea	3	1%
Fatigue	3	1%
Gastrointestinal hemorrhage	3	1%
Pyrexia	3	1%
Sedation	3	1%
Thrombocytopenia	3	1%

In the next table, also from Dr. **Fields' review, many of the t**reatment-emergent adverse events during long-term treatment to BEMA Fentanyl were mostly likely due to the underlying disease. It is unclear if the higher incidence of nausea and vomiting in the 1200 mcg group represents a response to the medication or worse underlying disease and pain.

Table 12 Adverse Events Which Occurred During Long-Term Treatment at a Frequency of ≥ 5%

System Organ Class, Preferred Term, n (%)	BEMA Fentanyl Dose (µg)						Total (N=190)
	200 (N=19)	400 (N=51)	600 (N=67)	800 (N=74)	1200 (N=66)	>1200 (N=24)	
Number of subjects with ≥1 treatment-emergent adverse event	11 (57.9)	33 (64.7)	42 (62.7)	52 (70.3)	44 (66.7)	17 (70.8)	148 (77.9)
Blood and lymphatic							
Anemia	0	3 (5.9)	4 (6.0)	11 (14.9)	1 (1.5)	0	18 (9.5)
Gastrointestinal							
Ascites	0	3 (5.9)	3 (4.5)	3 (4.1)	1 (1.5)	1 (4.2)	11 (5.8)
Constipation	1 (5.3)	1 (2.0)	4 (6.0)	2 (2.7)	3 (4.5)	2 (8.3)	13 (6.8)
Diarrhoea	1 (5.3)	2 (3.9)	3 (4.5)	5 (6.8)	7 (10.6)	0	18 (9.5)
Nausea	2 (10.5)	5 (9.8)	6 (9.0)	8 (10.8)	17 (25.8)	4 (16.7)	39 (20.5)
Vomiting	0	3 (5.9)	6 (9.0	7 (9.5)	15 (22.7)	3 (12.5)	31 (16.3)
General/Administration Site							
Asthenia	0	5 (9.8)	2 (3.0)	7 (9.5)	4 (6.1)	3 (12.5)	21 (11.1)
Fatigue	2 (10.5)	4 (7.8)	2 (3.0)	4 (5.4)	6 (9.1)	1 (4.2)	19 (10.0)
Oedema peripheral	1 (5.3)	6 (11.8)	5 (7.5)	5 (6.8)	5 (7.6)	2 (8.3)	24 (12.6)
Pain	1 (5.3)	3 (5.9)	4 (6.0)	5 (6.8)	6 (9.1)	0	18 (9.5)
Infections							
Pneumonia	0	1 (2.0)	2 (3.0)	6 (8.1)	5 (7.6)	1 (4.2)	15 (7.9)
Urinary tract infections	0	3 (5.9)	5 (7.5)	3 (4.1)	2 (3.0)	0	12 (6.3)
Metabolism/Nutrition							
Decreased appetite	0	4 (7.8)	3 (4.5)	4 (5.4)	1 (1.5)	2 (8.3)	14 (7.4)
Dehydration	1 (5.3)	3 (5.9)	5 (7.5)	5 (6.8)	8 (12.1)	1 (4.2)	22 (11.6)
Musculoskeletal							
Back pain	2 (10.5)	1 (2.0)	1 (1.5)	6 (8.1)	2 (3.0)	0	12 (6.3)
Nervous system							
Dizziness	1 (5.3)	3 (5.9)	2 (3.0)	2 (2.7)	2 (3.0)	2 (8.3)	12 (6.3)
Headache	2 (10.5)	1 (2.0)	2 (3.0)	6 (8.1)	2 (3.0)	0	12 (6.3)
Psychiatric							
Confusional state	0	0	4 (6.0)	2 (2.7)	5 (7.6)	3 (12.5)	14 (7.4)
Respiratory							
Dyspnoea	2 (10.5)	4 (7.8)	2 (3.0)	6 (8.1)	3 (4.5)	0	17 (8.9)

Overall, there were no adverse events that were unexpected for the patient population, the concomitant medications they received and the study medication.

There were no consistent effects of gender. There was too little racial diversity in the patient population to adequately assess subpopulations. There was some evidence of greater adverse event frequency in patients over 65 years of age, however, it cannot be determined if this was drug related or due to overall greater disease burden.