2.6.4.2 Methods of Analysis – N/A

2.6.4.3 Absorption – The pharmacokinetics of BEMA Fentanyl [redacted] or BEMA Fentanyl free base were evaluated in three GLP (ATRS-138, ATRS-141, & ATRS-159) and 57 non-GLP formulation screening studies using the dog as a model. The studies were performed to determine the effects of formulation variables [redacted], on drug stability and pharmacokinetics. Two of the GLP studies were conducted with fentanyl citrate (the salt form investigated in clinical studies and the drug product subject of this application) and one was conducted with fentanyl free base. Thirty-three of the non-GLP formulation screening studies were conducted with fentanyl citrate, 22 were conducted with fentanyl free base, and two were conducted with a mix of fentanyl citrate/fentanyl free base.

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In summary, pharmacokinetic studies in dogs have shown that the proposed drug can be formulated to provide rapid delivery of fentanyl across the buccal mucosa. BEMA Fentanyl containing fentanyl citrate (the proposed active pharmaceutical ingredient) was shown to have high bioavailability and produce plasma fentanyl levels in dogs within the range expected to exert analgesia. Tabular results for the three studies most relevant to the proposed drug (ATRS-138, ATRS-141, & ATRS-159) and two, single dose clinical trials are contained in section 2.6.5 Pharmacokinetics tabulated summary. Doses were not comparable to the range of clinical doses and duration proposed in this submission and were, therefore, not able to be used in a nonclinical safety assessment. Single dose pharmacokinetic studies for dogs (see section 2.6.5 tables; no 28-day dog pharmacokinetic data) did not support systemic exposure levels as the highest values were a Cmax of 6.76 ng/mL and an AUC of **16.71 ng•h/mL at the maximum dose tested** while single dose human values were a Cmax of 2.19 ng/mL and an AUC of 20.43 **ng•h/mL at a 1200 µg dose, 1/4 of the proposed maximum dose. Assuming linearity, a** maximum proposed human dose of 4800 µg (1200 µg at 4 times/day) would result in human exposures in excess of those received by the dogs, resulting in inadequate human safety margins.

2.6.4.4 Distribution - no studies were conducted for the proposed drug product as for old, well-understood drugs with significant clinical experience these studies are not required (see referenced drugs for fentanyl).

The distribution profile of fentanyl has been extensively studied in animals. Fentanyl is highly lipophilic. In rats, following intravenous administration, fentanyl rapidly distributes into brain, lungs, and myocardium followed by redistribution into the liver, kidneys, and small intestine. In humans, fentanyl readily distributes into brain, heart, lungs, kidneys, and spleen with a slower distribution into muscle and fat. The plasma protein binding of fentanyl is 80 to 85%. The primary plasma binding protein is α1-acid glycoprotein, but both albumin and lipoproteins contribute to some extent. Fentanyl has been shown to accumulate in the skeletal muscle and fat and is slowly released into the blood.

2.6.4.5 Metabolism - no studies were conducted for the proposed drug product as for old, well-understood drugs with significant clinical experience these studies are not required (see referenced drugs for fentanyl)

Fentanyl is metabolized by the liver and the intestinal mucosa to norfentanyl by CYP3A4. Norfentanyl has not been shown to be pharmacologically active. Administration of fentanyl via the buccal mucosa allows distribution of fentanyl prior to metabolism by the liver.

2.6.4.6 Excretion - no studies were conducted for the proposed drug product as for old, well-understood drugs with significant clinical experience these studies are not required (see referenced drugs for fentanyl)

Following fentanyl absorption, elimination is primarily (>90%) by biotransformation to *N*-dealkylated and hydroxylated inactive metabolites. Less than 7% of the administered dose is excreted unchanged in the urine with about 1% excreted unchanged in the feces. The metabolites are mainly excreted in the urine, and fecal excretion is less important. Total plasma clearance of fentanyl was 0.5 L/h/kg. The terminal half-life after oral transmucosal fentanyl citrate administration is 3.2–6.4 hours. Fentanyl is excreted in human milk.

2.6.4.7 Pharmacokinetic drug interactions - no studies were conducted for the proposed drug product as for old, well-understood drugs with significant clinical experience these studies are not required (see referenced drugs for fentanyl).

Based on the extensive historical use of fentanyl in the United States in approved products for the treatment of pain, no new studies were conducted to further evaluate pharmacokinetic drug interactions of fentanyl. Thus, the following summary is based on previous findings of safety and efficacy for fentanyl (ACTIQ® Prescribing Information and DURAGESIC Prescribing Information). Fentanyl is metabolized in the liver and intestinal mucosa by CYP3A4; therefore, potential interactions may occur when BEMA Fentanyl is given concurrently with agents that affect CYP3A4 activity. The concomitant use of BEMA Fentanyl with strong CYP3A4 inhibitors (e.g., ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, and nefazodone) or moderate CYP3A4 inhibitors (e.g., amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, and verapamil) may result in increased fentanyl plasma concentrations, potentially causing serious adverse drug effects, including fatal respiratory depression. Patients receiving BEMA Fentanyl concomitantly with moderate or strong CYP3A4 inhibitors should be carefully monitored for an extended period of time. Dosage increase should be done conservatively.

Grapefruit and grapefruit juice decrease CYP3A4 activity, increasing blood concentrations of fentanyl, and should be avoided. Drugs that induce CYP3A4 activity may have the opposite effects. Concomitant use of fentanyl with a MAO inhibitor, or within 14 days of discontinuation, is not recommended.

2.6.4.8 Other Pharmacokinetic Studies - none

2.6.4.9 Discussion and Conclusions - none

2.6.4.10 Tables and figures to include comparative TK summary – see 2.6.5

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

Data for 57 non-GLP studies utilizing various preliminary versions of the drug product are not reported in this review as they were conducted under varying conditions in the development of the BEMA fentanyl product and resulted in the final drug product, which was tested in the listed three GLP studies below. Single dose clinical data is also reported below, but maximal human exposure values are in excess of animal values and the animal studies do not encompass dose and duration of proposed submission, thereby not allowing nonclinical safety assessment for the proposed range of clinical doses and duration proposed in this submission.

Table 2.6.5-3A. Pharmacokinetics: Absorption after a Single Dose (Fentanyl Citrate)

Absorption after a Single Dose	**Test Article: BEMA Fentanyl**			
Study No.:	ATLS-141		ATLS-159	
Species:	Dog (beagle)		Dog (beagle)	
Gender (M/F)/Number of Animals:	6 M, 6 F		5 M, 5 F	
Feeding Condition:	Fed		Fed	
Form of the Test Article:	Fentanyl citrate		Fentanyl citrate	
Vehicle/Formulation:	BEMA disc		BEMA disc	
Method of Administration:	po, buccal mucosa		po, buccal mucosa	
Dose (µg/disc):	578 (368 µg free base)		1326 (844 µg free base)	
Sample (e.g., whole blood, plasma, serum):	Plasma		Plasma	
Analyte:	Fentanyl		Fentanyl	
Assay:	GC/NPD		GC/NPD	
PK Parameters:	M	F	M	F
C_{max} (ng/mL)	2.79	1.53	6.56	6.96
T_{max} (hr)	2.3	5.3	2.95	1.10
AUC (hr·ng/mL)	11.84_{0-24hr}	9.87_{0-24hr}	19.77_{0-24hr}	13.64_{0-24hr}
Additional Information:	BEMA Fentanyl citrate disc, 1/4" diameter, pH-adjusted bioadhesive (Drug Product Lot Number ALN 967-044; AL-3701.02). Sedation was noted in all but one female generally 0.5–4 hr postdose. Salivation was observed in three dogs. One female had very slight erythema at 6 and 8 hr. No other irritation was noted at any of the test article application sites. An average Draize score of 0.0038 was achieved.		BEMA Fentanyl citrate disc. All animals survived until scheduled euthanasia (Drug Product Lot Number 1461; AL-3701.04). No gross irritation, redness, or swelling were noted in cheek mucosa. Salivation was observed in one male and two females on Day 0. Remarkable clinical signs on Day 1 were limited to salivation in one male.	

Absorption after a Single Dose	Test Article: BEMA Fentanyl	
Study No.:	ATLS-138	
Species:	Dog (beagle)	
Gender (M/F)/Number of Animals:	6 M, 6 F	
Feeding Condition:	Fed	
Form of the Test Article:	Fentanyl free base	
Vehicle/Formulation:	BEMA disc	
Method of Administration:	po, buccal mucosa	
Dose (µg/disc):	383	
Sample (e.g., whole blood, plasma, serum):	Plasma	
Analyte:	Fentanyl	
Assay:	LC/MS/MS	
PK Parameters:	M	F
C_{max} (ng/mL)	2.23	4.82
T_{max} (hr)	0.58	0.50
AUC (hr·ng/mL)	8.53_{0-24hr}	12.09_{0-24hr}
Additional Information:	BEMA Fentanyl free base disc, 5/8" diameter, pH adjusted bioadhesive (Drug Product Lot Number ALN 967-023; AL-3701.01). The bioavailability of this formulation was 60–100%. Low or no food consumption was noted on Day 0 in five dogs. Sedation was generally noted in all dogs 0.25–2 hr postdose. Salivation and emesis were observed in some dogs. One male had very slight erythema at 2 hr. No other irritation was noted. An average Draize score of 0.0019 was achieved for this study.	

Table 2.6.5-3C. Pharmacokinetics: Absorption after a Single Dose (Clinical Studies)

Absorption after a Single Dose	Test Article: BEMA Fentanyl			
Study No.:	FEN-107	FEN-110		
Species:	Human	Human		
Gender (M/F)/Number of Subjects:	12 subjects	12 subjects		
Feeding Condition:	Fed	Fed		
Form of the Test Article:	Fentanyl citrate (Lot numbers 34822, 34823, 34824)	Fentanyl free base (Lot numbers 35117, 35133, 35134)		
Vehicle/Formulation:	BEMA disc	BEMA disc		
Method of Administration:	po, buccal mucosa	po, buccal mucosa		
Dose (µg/disc):	800	200, 600, 1200		
Sample (e.g., whole blood, plasma, serum):	Plasma	Plasma		
Analyte:	Fentanyl	Fentanyl		
Assay:	LC/MS/MS	LC/MS/MS		
PK Parameters:	800 µg, pH 7.25	200 µg	600 µg	1200 µg
C_{max} (ng/mL)	1.67	0.38	1.16	2.19
T_{max} (hr)	1.00 (0.75–4.00)[a]	2.00 (1.00–4.00)[a]	2.00 (1.00–4.00)[a]	3.00 (0.75–4.00)[a]
AUC (hr·ng/mL)	14.46_{0-inf}	3.46_{0-inf}	11.72_{0-inf}	20.43_{0-inf}
Additional Information:	Single-dose, 4 way crossover PK study in healthy volunteers to compare the PK of the re-formulated BEMA Fentanyl with Actiq®.	Single dose, 3 way crossover PK study in healthy volunteers to assess absorption of transdermal application, effect of heat on absorption, and removal of buccally applied disc.		

[a] = Presented as median (range).
— = Not detailed in the report.

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology:

GLP toxicology studies were conducted to evaluate the toxicity profile of daily BEMA Fentanyl administration in the dog. A 28-day, repeat-dose toxicity study and three, single-dose local tolerance studies evaluating the test article administration site after a single dose (two with fentanyl citrate and one with fentanyl free base) were performed in dogs to evaluate the safety of BEMA Fentanyl formulations. There were no new local or systemic adverse effects observed in these studies. The 28-day study is summarized in this section and the local tolerance studies are summarized in the local tolerance section after the reproductive toxicology section below.

Table 2.4-3. Overview of Toxicology Program with BEMA Fentanyl Citrate or BEMA Fentanyl Free Base

Report Number	Study Type	Route of Administration	Species	BEMA Fentanyl Dose Administered	GLP Status
Repeat-Dose Toxicity					
0436DA76.001	28-day	po	Dog	273 µg fentanyl free base at pH 6, 7.25, or 8.5 twice daily (429 µg fentanyl citrate)	GLP
Local Tolerance Studies					
ATLS-141	Acute	po	Dog	368 µg fentanyl free base (578 µg fentanyl citrate)	GLP
ATLS-159	Acute	po	Dog	844 µg fentanyl free base (1326 µg fentanyl citrate)	GLP
ATLS-138	Acute	po	Dog	383 µg fentanyl free base	GLP

The repeat-dose toxicity of BEMA Fentanyl [redacted] was evaluated in a GLP study in beagle dogs (3/sex/group) following buccal administration of a placebo disc or a disc containing fentanyl citrate (dose expressed as 273 µg of fentanyl free base which is equivalent to 429 µg of fentanyl citrate) formulations at pH 6.0, 7.25, or 8.5 (1.1 cm diameter) twice daily, at least 6 hours apart, for 28 days (Study No. 0436DA76.001). No toxicokinetic data was collected. Twice daily doses were administered throughout the study with the first (morning) dose applied to the right buccal mucosa and the second (afternoon) dose applied to the left buccal mucosa. Mortality, clinical observations, body weights, food consumption, ophthalmoscopic examinations, electrocardiograms (ECGs), hematology, coagulation, clinical chemistry, gross pathology, organ weights, and local histopathology (buccal mucosa only) were evaluated. There were no mortalities in this study. There were no test article-related effects on ophthalmology, ECGs, coagulation,

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clinical chemistry, gross pathology, or histopathology. Clinical observations noted in all test article-treated groups included decreased activity, excessive salivation, brown mucous in feces, abnormal gait and stance, emesis, and tremors. These findings were not unexpected and were related to the known pharmacological activity of fentanyl. One male dosed with the pH 8.5 disc was prostrate approximately 1–2 hours postdose on Days 1 and 27. There were no other observed differences based on the pH of the discs. Mean male and female body weights gradually decreased during the treatment period in the fentanyl citrate-treated groups and were **9–16% lower on Day 28 as compared to the** controls. Food consumption was decreased in the treated groups as compared to the controls beginning on Day 2. Statistically significant decreases in food consumption were observed in males on Day 3 (pH 8.5 group), and Days 11 and 17 (pH 6.0 and 7.25 groups) and in females on Days 4, 5, and 8 (pH 6.5, 7.25, and 8.5 groups) and Day 11 (pH 7.25 group). Treatment produced a decrease of 27–46% and 6–19% in white blood cell (WBC) counts in males and females, respectively, on Day 29. Absolute neutrophils (males and females), lymphocytes (males), and monocytes (males) were decreased in the treatment groups. Erythrocyte morphology was unaffected. An increase of 21–37% and 31–50% in absolute and relative spleen weights, respectively, was observed in the treated males and females as compared to the controls. An increase in absolute and relative ovary weights (33-74%) was observed in fentanyl-treated females. Gross lesions were identified in three of the control animals and in one animal in each of the groups receiving test article. None of these gross lesions were considered related to treatment with the test article. Occasionally minimal, mixed inflammation or mononuclear cell infiltrates were noted in the submucosa or mucosa of the mucocutaneous junction or buccal mucosa. The lesions are not considered test article-related as the observations were noted at similar frequency and severity in both control and test article-treated animals. Test article-related histological lesions were not noted in samples of oral mucosa examined for this study, the only tissues examined histologically. No NOAEL was identified. In summary, treatment-related effects included decreased activity, abnormal gait and stance, excessive salivation, tremors, emesis, decreased body weight and weight gain, decreased food consumption, and decreased WBC parameters. There were no definitive differences in toxicity noted based on the pH of the discs.

Genetic toxicology: Based on the existing nonclinical genotoxicity data and the historical evidence of fentanyl use for the treatment of pain in humans, no new studies were conducted to further evaluate the genotoxicity of fentanyl. Thus, the following summary of genotoxicity data is based on previous studies for fentanyl (see referenced drugs for fentanyl).

Fentanyl citrate was not mutagenic *in vitro* in the Ames reverse mutation assay in *Salmonella typhimurium* or *Escherichia coli* or the mouse lymphoma mutagenesis assay, and was not clastogenic in the *in vivo* mouse micronucleus assay. There was no evidence of mutagenicity following testing of fentanyl HCl in the Ames Salmonella mutagenicity assay, the primary rat hepatocytes unscheduled DNA synthesis assay, the BALB/c 3T3 transformation test, *in vitro* human lymphocyte assay, and the *in vitro* Chinese hamster ovary (CHO) chromosomal aberration assay.

Carcinogenicity: Because of the indication and course of disease, studies to evaluate the carcinogenic potential of fentanyl have not been conducted as this evaluation is not considered necessary for approval.

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Reproductive toxicology: Based on the extensive nonclinical reproductive and developmental toxicity data available and the historical evidence of fentanyl use for the treatment of pain in humans, no new studies were conducted to further evaluate the reproductive and developmental toxicity of fentanyl. Thus, the following summary of reproductive and developmental toxicity data is based on previous studies for fentanyl as reflected on the label and based on the RLD labels for ACTIQ® and/or DURAGESIC®.

Fentanyl has been shown to impair fertility and to have an embryocidal effect, with an increase in resorptions when given during organogenesis on Gestation Days 12 through 21, in rats at doses of 30 μg/kg intravenously or 160 μg/kg subcutaneously (ACTIQ® Prescribing Information). These intravenous and subcutaneous doses are approximately 0.24- and 1.3-times the 1200-μg BEMA Fentanyl disc dose on a mg/m^2 basis, respectively. The previously approved reference drug label for ACTIQ® lists these observed effects as within the range of the human recommended dose range.

The potential effects of fentanyl on embryofetal development were studied in mouse, rat, and rabbit models. Increased frequencies of death and developmental delay were seen among fetuses of pregnant mice given single SC injections of 14,500–16,000 μg/kg of fentanyl (the low dose is approximately 62 times the 1200-μg BEMA Fentanyl disc dose on a mg/m^2 basis). Administration of fentanyl (0, 10, 100, or 500 μg/kg/day) to pregnant female Sprague-Dawley rats from Gestation Days 7 to 21 via implanted micro-osmotic minipumps did not produce any evidence of teratogenicity (ACTIQ® and DURAGESIC® Prescribing Information; the high dose is approximately 4-times the 1200-μg BEMA Fentanyl disc dose on a mg/m^2 basis). In contrast, the intravenous administration of fentanyl (0, 10, or 30 μg/kg/day) to pregnant female rats from Gestation Days 6 to 18 suggested evidence of embryotoxicity and a slight increase in mean delivery time in the 30-μg/kg/day group (ACTIQ® and DURAGESIC® Prescribing Information). There was no clear evidence of teratogenicity noted. Pregnant female New Zealand white rabbits were treated with fentanyl (0, 25, 100, or 400 μg/kg/day) via intravenous infusion from Days 6 to 18 of pregnancy. Fentanyl produced a slight decrease in the body weight of the live fetuses at the high dose, which may be attributed to maternal toxicity (ACTIQ® and DURAGESIC® Prescribing Information). Under the conditions of the assay, there was no evidence for fentanyl-induced adverse effects on embryofetal development at doses up to 400 μg/kg (approximately 7-times the 1200-μg BEMA Fentanyl disc dose on a mg/m^2 basis).

The potential effects of fentanyl on pre- and postnatal development were examined in the rat model (DURAGESIC® Prescribing Information). Female Wistar rats were treated with 0, 25, 100, or 400 μg/kg/day fentanyl via intravenous infusion from Day 6 of pregnancy through 3 weeks of lactation. Fentanyl treatment (400 μg/kg/day) significantly decreased body weight in male and female pups and also decreased survival in pups at

Day 4. Animals receiving 100 or 400 µg/kg/day fentanyl had alterations in some landmarks of physical development (delayed incisor eruption and eye opening) and transient behavioral development (decreased locomotor activity at Day 28 which recovered by Day 50). The 100 or 400 µg/kg/day doses are 0.81- and 3.2-times the 1200-µg BEMA Fentanyl disc dose on a mg/m2 basis, respectively. The previously approved reference drug label lists these observed effects as within the range of the human recommended dose range.

In humans, there are no adequate and well-controlled studies in pregnant women. No epidemiological studies of congenital anomalies in infants born to women treated with fentanyl during pregnancy have been reported (ACTIQ® Prescribing Information). Fentanyl readily passes across the placenta to the fetus and is excreted in human milk (DURAGESIC® Prescribing Information). Chronic maternal treatment with fentanyl during pregnancy has been associated with transient respiratory depression, behavioral changes, or seizures characteristic of neonatal abstinence syndrome in newborn infants (ACTIQ® and DURAGESIC ®Prescribing Information). Symptoms of neonatal respiratory or neurological depression were no more frequent than expected in most studies of infants born to women treated acutely during labor with intravenous or epidural fentanyl (ACTIQ® and DURAGESIC ®). Transient neonatal muscular rigidity has been observed in infants whose mothers were treated with intravenous fentanyl (ACTIQ® and DURAGESIC ®).

Local tolerance: Single-dose, local (buccal) tolerance studies were conducted in dogs as part of the development program for the BEMA Fentanyl. The dog model was chosen for the local tolerance studies because of the lower level of keratin in the dog buccal mucosal membrane than the human and therefore greater probability of identification of a potential mucosal irritant. Single doses were evaluated in two studies which were conducted with the proposed drug product BEMA Fentanyl ⟵ (Study No. ATLS-141 and Study No. ATLS-159) and one study was conducted with BEMA Fentanyl free base (Study ATLS-138). b(4)

Twenty-four hour Draize scores for local tolerance of the test (right) and control (left) cheek mucosa were recorded for all three studies pre-dosing, and at 0, 5, 15, & 30 minutes post-dosing, and at 1, 2, 4, 6, 8, 12, & 24 hours post-dosing. The Draize scores were obtained according to the following scoring criteria:

Erythema and eschar formation	Grade
No erythema	0
Very slight erythema (barely perceptible)	1
Well defined erythema	2
Moderate erythema	3
Severe erythema (beet redness) to slight eschar formation (injuries to depth)	4