



#6804: A pilot study evaluating cannabidiol oral solution in bilateral total knee arthroplasty

Sideris A^{1,2,5}, Chan W^{1,5}, Liu J^{1,2,5}, Gonzalez Della Valle A^{3,4}, Illescas A⁵, Baaklini L^{1,2,5}, Rodriguez J^{3,4}, Kirksey M^{1,2,5}, Chalmers B^{3,4}, Mayman D^{3,4}, Soffin E^{1,2,5}, Maalouf D^{2,5}, Long W^{3,4}, Haas S^{3,4}, Boettner F^{3,4}, Alexiades M^{3,4}, Saleh J⁶, Waldman S^{2,5}, Sculco P^{3,4}, Jules-Elysee K^{2,5}

¹ Pain Prevention Research Center, Department of Anesthesiology, Critical Care & Pain Management, Hospital for Special Surgery, New York, New York, USA; ² Department of Anesthesiology, Weill Cornell Medicine, New York, New York, USA; ³ Department of Orthopedic Surgery, Hospital for Special Surgery, New York, New York, USA; ⁴ Department of Orthopedic Surgery, Weill Cornell Medicine, New York, New York, USA; ⁵ Department of Anesthesiology, Critical Care & Pain Management, Hospital for Special Surgery, New York, New York, USA; ⁶ Department of Nursing Administration, Hospital for Special Surgery, New York, New York, USA; **Acknowledgements:** This work was funded by the Hospital for Special Surgery Department of Anesthesiology, Critical Care & Pain Management Mission Fund and the C.V. Starr Foundation. This work was also supported by grant number UL1 TR 002384 from the National Center for Advancing Translational Sciences (NCATS) of the National Institutes of Health (NIH).



**Weill Cornell
Medicine**



INTRODUCTION

- ❖ Cannabidiol (CBD) is a non-intoxicating phytocannabinoid with a complex pharmacological profile, distinct from delta-9-tetrahydrocannabinol (THC). [1-2] In studies using animal models of acute and chronic pain, CBD relieves hyperalgesia and edema associated with inflammation, and reduces allodynia and anxiety associated with nerve injury. [2]
- ❖ Epidiolex® is the only CBD formulation approved by the Food and Drug Administration (FDA) and is indicated for the treatment of seizures associated with Lennox-Gastaut Syndrome, Dravet Syndrome, and tuberous sclerosis complex.
- ❖ Given the promising animal literature on CBD's effects on pain behaviors and inflammation, and the increasing use of CBD in patients presenting for orthopedic surgery, we conducted a pilot study of off-label Epidiolex® versus placebo in bilateral total knee arthroplasty patients to assess opioid requirements, pain levels, inflammatory markers, tolerability, effect on sleep and mood, and pharmacokinetics.

METHODS

- ❖ After IRB approval for this randomized, triple-blinded, placebo-controlled pilot study evaluating off-label use of FDA-approved CBD oral solution (Epidiolex®) in adult patients undergoing bilateral total knee arthroplasty, the study was registered on clinicaltrials.gov (NCT04749628); 36 patients were enrolled and randomized to placebo (Ora-Sweet SF) (n=12), 400mg (n=12) or 800mg (n=12) CBD between October 28th, 2022 and September 30th, 2024 (Figure 1).
- ❖ The Consolidated Standards of Reporting Trials (CONSORT) guidelines were followed throughout the study.
- ❖ All patients received a standard anesthesia and analgesia regimen which included neuraxial anesthesia, and adductor canal block, infiltration between the popliteal artery and capsule of the knee block, acetaminophen, and non-steroidal anti-inflammatory drugs for postoperative pain control.
- ❖ The primary outcome was cumulative 72-hour opioid consumption, calculated from procedure end, in morphine milligram equivalents (MMEs).
- ❖ Secondary outcomes included cumulative 72-hour non-opioid analgesic consumption.
- ❖ Descriptive statistics were used to summarize patient and case characteristics and preliminary findings on pain medication use; t-tests were used to compare MMEs in the intervention groups to placebo.

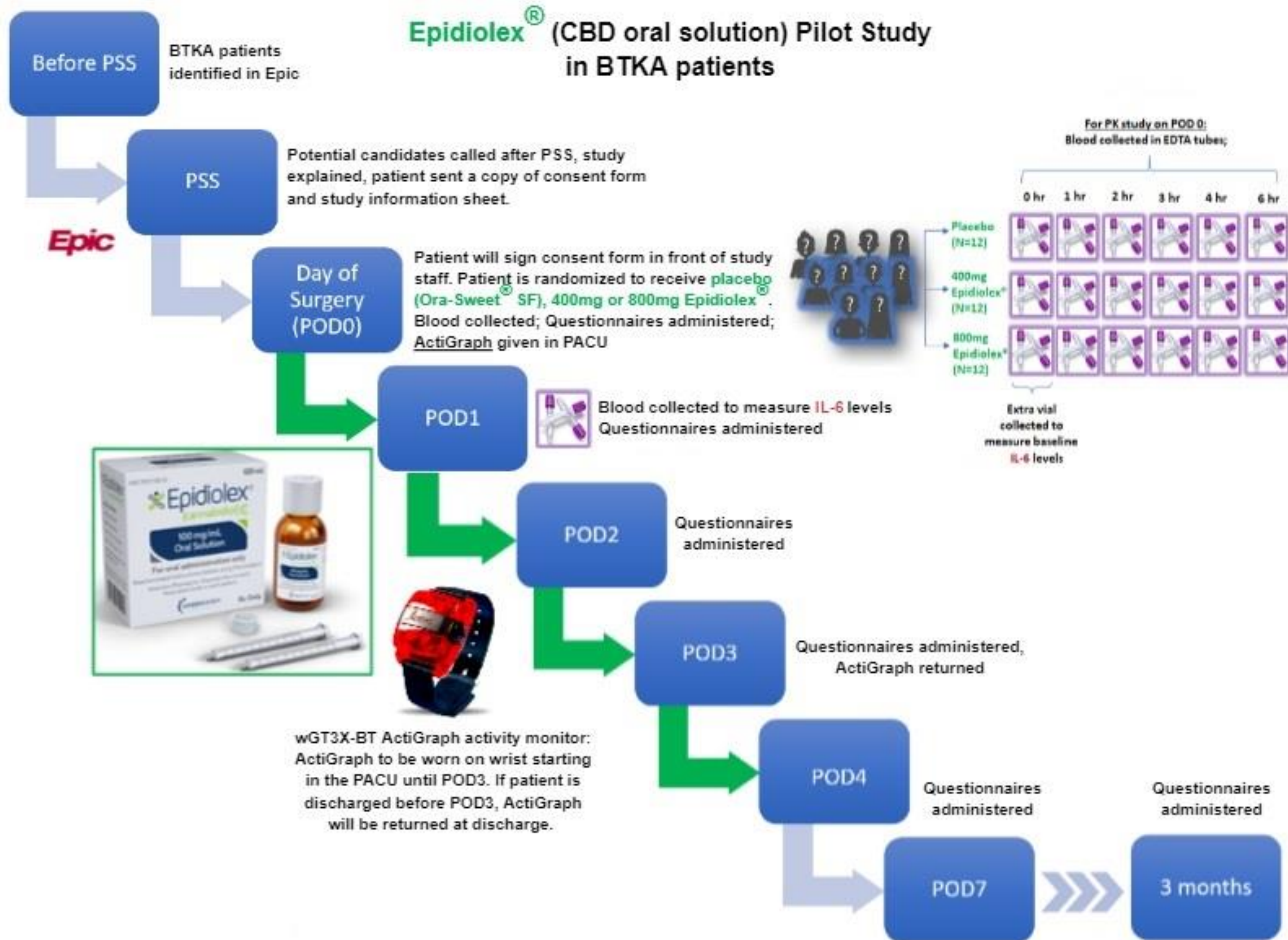


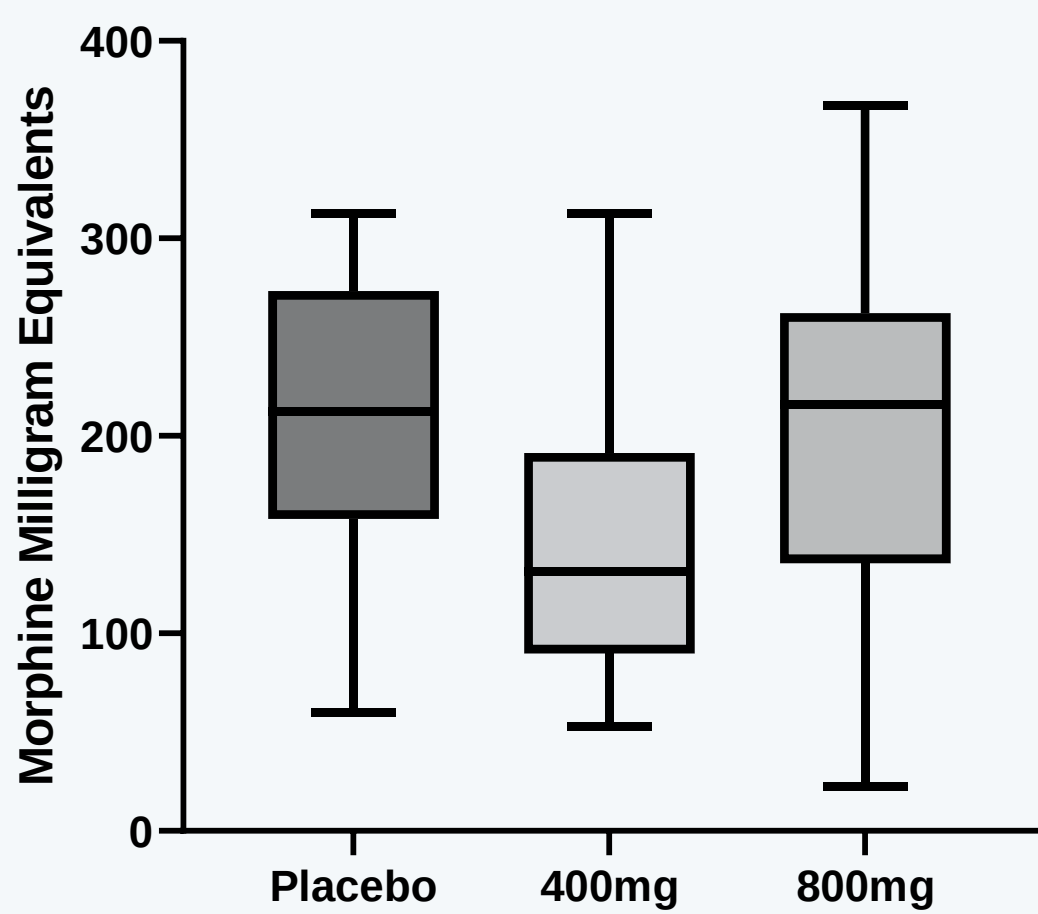
Figure 1:

Compared to placebo, patients who received 400mg CBD had lower cumulative 72-hour opioid requirements, with no difference between placebo and 800mg CBD or between 400mg and 800mg CBD.

Table 3: 72-hr non-opioid analgesic consumption (in mg)

	group	Mean	Std Dev	Minimum	Maximum
ACETAMINOPHEN	placebo	7612.5	1951.24	3600	10300
	400 mg	7695.83	1214.77	5550	10100
	800 mg	8145.83	1626.41	6200	12000
ASPIRIN	placebo	1123.83	891.382	0	2275
	400 mg	270.5	398.4304	0	1300
	800 mg	365	387.895	0	1137
KETOROLAC	placebo	50	21.53222	0	90
	400 mg	47.5	5.838742	45	60
	800 mg	51.25	18.60169	30	90
MELOXICAM	placebo	13.125	5.653338	0	22.5
	400 mg	17.5	3.692745	15	22.5
	800 mg	21.875	8.127185	15	37.5

Figure 2: Cumulative 72-hr opioid consumption



RESULTS

- ❖ Study patients were mostly white, Non-Hispanic or Latino, ASA 2, with a preponderance of male patients in the placebo group (Table 1 & Table 2).
- ❖ All randomized patients received the first (preoperative) and second (evening of postoperative day 1) dose of their allocated intervention, but one patient missed their third dose.
- ❖ Compared to placebo, patients who received 400mg CBD had lower cumulative 72-hour opioid requirements (mean (SD): 209 mg versus 144 mg; p = 0.04), with no difference between placebo and 800mg CBD (p=0.9) or between 400mg and 800mg CBD (p=0.09) (Figure 2).
- ❖ Non-opioid analgesic use is summarized in Table 3.

Table 1: Demographics

	Control (n=12)	400mg (n=12)	800mg (n=12)
Age, mean (SD)	60.7 (7.9)	60.0 (7.5)	61.0 (5.1)
BMI, mean (SD)	30.4 (3.0)	30.9 (4.9)	29.5 (4.4)
Males, n (%)	11 (91.7)	4 (33.3)	5 (41.7)
Race, n (%)			
Asian	0 (0.0)	1 (8.3)	1 (8.3)
Black or African American	2 (16.7)	3 (25.0)	0 (0.0)
Other/Declined to Answer	4 (33.3)	0 (0.0)	1 (8.3)
White	6 (50.0)	8 (66.7)	10 (83.3)
Not Hispanic or Latino, n (%)	10 (83.3)	9 (75.0)	10 (83.3)

Table 2: Case characteristics

	Control (n=12)	400mg (n=12)	800mg (n=12)
ASA status (I/II), n	1/11	1/11	1/11
Procedure duration in minutes, mean (SD)	191.6 (20.1)	153.3 (50.8)	128.8 (37.7)
PACU LOS in hours, mean (SD)	9.4 (2.6)	11.8 (3.1)	12.4 (6.0)
Hospital LOS in days, mean (SD)	3.3 (1.0)	3.9 (1.8)	3.9 (1.1)

LOS = length of stay

DISCUSSION

- ❖ In our pilot study, most patients received the first three doses; the one patient who missed the third dose was randomized to the 800 mg CBD arm, potentially impacting the primary outcome.
- ❖ Though not powered to detect statistical significance, the approximate 30% lower opioid requirements in patients who received 400mg oral cannabidiol solution suggests promising efficacy of this dose, but inconclusive results for 800 mg.
- ❖ Additional analyses of our pilot data will help elucidate tolerability of CBD and reasons for an apparent lack of dose response, including potential biphasic effects of CBD at higher doses.

References →

