

## SUPPLEMENTARY TABLES

**Supplementary table 1.** Patient socio-demographic and clinical characteristics at baseline in the subpopulations treated with medium-to-high fentanyl doses ( $\geq 200$   $\mu\text{g}$ ) for BTcP.

Characteristic	Fentanyl 200 $\mu\text{g}$ (n = 8) <sup>a</sup>	Fentanyl 267 $\mu\text{g}$ (n = 9) <sup>b</sup>	Fentanyl 400 $\mu\text{g}$ (n = 14) <sup>c</sup>	Fentanyl 533 $\mu\text{g}$ (n = 1) <sup>d</sup>
<b>Age, mean (SD)</b>	64.2 (17.1)	74.5 (12.8)	58.9 (14.3)	62.1
<b>Age classification, n (%)</b>				
<60 years	3 (37.5)	2 (22.2)	6 (42.9)	0
60-80 years	4 (50.0)	4 (44.4)	7 (50.0)	1 (100.0)
>80 years	1 (12.5)	3 (33.3)	1 (7.1)	0
<b>Men, n (%)</b>	3 (37.5)	5 (55.6)	9 (64.3)	1 (100.0)
<b>Type of patient, n (%)</b>				
Outpatient	8 (100.0)	6 (66.7)	13 (92.9)	1 (100.0)
Hospitalized	0	3 (33.3)	1 (7.1)	0
<b>Clinical data, n (%)</b>				
Cachexia	4 (50.0)	0 (0)	5 (35.7)	1 (100.0)
Xerostomia	6 (75.0)	3 (33.3)	8 (57.1)	1 (100.0)
Addictive behaviour	0	0	1 (7.1)	0
<b>Comorbidities<sup>e</sup>, n (%)</b>				
COPD	0	1 (11.1)	0	0
Diabetes mellitus	3 (37.5)	3 (33.3)	4 (28.6)	1 (100.0)
Chronic heart failure	2 (25.0)	3 (33.3)	2 (14.3)	0
Chronic liver disease	2 (25.0)	0	3 (21.4)	1 (100.0)
Other chronic conditions	7 (87.5)	4 (44.4)	5 (35.7)	1 (100.0)
<b>Charlson Index, mean (SD)</b>	8.6 (1.8)	6.4 (2.6)	6.9 (2.6)	10
<b>Tumour type<sup>e</sup>, n (%)</b>				
Pancreatic	0	0	2 (14.3)	0
Lung	1 (12.5)	0	1 (7.1)	1 (100.0)
Breast	2 (25.0)	1 (11.1)	1 (7.1)	0
Gastric	1 (12.5)	2 (22.2)	3 (21.4)	0
Prostatic	0	0	3 (21.4)	0
Others	4 (50.0)	6 (66.7)	4 (28.6)	0
<b>Stage, n (%)</b>				
III	0	3 (33.3)	0	0
IV	8 (100.0)	6 (66.7)	14 (100.0)	1 (100.0)
<b>ECOG-PS, n (%)</b>				
0	0	1 (11.1)	0	0
1	3 (37.5)	5 (55.5)	4 (28.6)	0
2	4 (50.0)	2 (22.2)	8 (57.1)	1 (100.0)
3	1 (12.5)	1 (11.1)	2 (14.3)	0
<b>Site of metastasis<sup>e</sup>, n (%)</b>				
Lung	3 (37.5)	3 (33.3)	3 (21.4)	1 (100.0)
Liver	3 (37.5)	2 (22.2)	4 (28.6)	1 (100.0)
Bone	3 (37.5)	2 (22.2)	9 (64.3)	1 (100.0)
Lymphatic nodes	4 (50.0)	3 (33.3)	2 (14.3)	1 (100.0)
Others	4 (50.0)	0	3 (21.4)	1 (100.0)
<b>Cognitive status, n (%)</b>				
No cognitive impairment	8 (100.0)	9 (100.0)	14 (100.0)	1 (100.0)
Mild cognitive impairment (Pfeiffer test $\leq 4$ )	0	0	0	0
<b>Falls over the previous month, mean (SD)</b>	0	0.2 (0.7)	0	0

<sup>a</sup>Patients who received  $\geq 1$  dose of 200  $\mu\text{g}$  transmucosal fentanyl during the study period. <sup>b</sup>Patients who received  $\geq 1$  dose of 267  $\mu\text{g}$  transmucosal fentanyl during the study period. <sup>c</sup>Patients who received  $\geq 1$  dose of 400  $\mu\text{g}$  transmucosal fentanyl during the study period. <sup>d</sup>Patients who received  $\geq 1$  dose of 533  $\mu\text{g}$

transmucosal fentanyl during the study period. <sup>e</sup>Only the most frequent tumour types and sites of metastasis are shown. Patients may present more than one site of metastasis.

BTcP, breakthrough cancer pain; COPD, chronic obstructive pulmonary disease; ECOG-PS, Eastern Cooperative Oncology Group Performance Status.

**Supplementary table 2.** Clinical features of background pain and BTcP at baseline in the subpopulations treated with medium-to-high fentanyl doses ( $\geq 200$   $\mu\text{g}$ ) for BTcP.

	Fentanyl 200 $\mu\text{g}$ (n = 8) <sup>a</sup>	Fentanyl 267 $\mu\text{g}$ (n = 9) <sup>b</sup>	Fentanyl 400 $\mu\text{g}$ (n = 14) <sup>c</sup>	Fentanyl 533 $\mu\text{g}$ (n = 1) <sup>d</sup>
<b>Background pain</b>				
<b>Treatment, n (%)</b>				
Transdermal fentanyl	6 (75.0)	4 (44.4)	8 (57.1)	1 (100.0)
Morphine	0	1 (11.1)	2 (14.3)	0
Oxycodone/naloxone	0	2 (22.2)	2 (14.3)	0
Oxycodone	1 (12.5)	2 (22.2)	2 (14.3)	0
<b>Characteristics, mean (SD)</b>				
VAS	4.9 (1.9)	5.1 (1.7)	4.1 (2.0)	7
<b>Breakthrough cancer pain (BTcP)</b>				
<b>Type, n (%)</b>				
Mixed	4 (50.0)	4 (44.4)	9 (64.3)	0
Neuropathic	0	0	0	0
Visceral nociceptive	2 (25.0)	2 (22.2)	2 (14.3)	0
Somatic nociceptive	2 (25.0)	3 (33.3)	3 (21.4)	1 (100.0)
<b>Triggering factor, n (%)</b>				
Spontaneous or idiopathic	4 (50.0)	4 (44.4)	7 (50.0)	1 (100.0)
Incident	4 (50.0)	5 (55.6)	7 (50.0)	0
Volitional	2 (25.0)	0	3 (21.4)	0
Non volitional	1 (12.5)	2 (22.2)	1 (7.1)	0
Procedural	1 (12.5)	3 (33.3)	3 (21.4)	0
<b>Location<sup>e</sup>, n (%)</b>				
Abdominal	2 (25.0)	3 (33.3)	6 (42.9)	0
Thoracic	2 (25.0)	1 (11.1)	2 (14.3)	1 (100.0)
Lumbar	0	2 (22.2)	2 (14.3)	0
Upper / lower limbs	0	0	1 (7.1)	0
Neck	0	1 (11.1)	0	0
Dorsal	0	2 (22.2)	3 (21.4)	0
Others	4 (50.0)	3 (33.3)	3 (21.4)	0
<b>Characteristics, mean (SD)</b>				
VAS	8.0 (1.4)	8.1 (0.9)	8.2 (1.3)	8
No. episodes in the last 24h	4.5 (1.9)	2.8 (1.3)	3.3 (1.9)	5
Duration of BTcP episodes (min)	18.5 (11.6)	25.6 (15.3)	20.4 (12.0)	10
<b>Pharmacological treatment at enrolment, n (%)</b>				
Fentanyl	7 (87.5)	9 (100.0)	14 (100.0)	1 (100.0)
Morphine	7 (87.5)	9 (100.0)	14 (100.0)	1 (100.0)
	0	0 (0.0)	0 (0.0)	0
<b>Adjuvant non-drug treatment, n (%)</b>				
	1 (12.5)	0	3 (21.4)	0
<b>Adjuvant analgesia<sup>e</sup>, n (%)</b>				
Corticoids	1 (12.5)	5 (55.6)	9 (64.3)	0
Anticonvulsants	1 (12.5)	3 (33.3)	6 (42.9)	0
Antidepressants	2 (25.0)	1 (11.1)	3 (21.4)	0
Benzodiazepines	2 (25.0)	3 (33.3)	2 (14.3)	1 (100.0)
Others	0	1 (11.1)	1 (7.1)	0

<sup>a</sup>Patients who received  $\geq 1$  dose of 200  $\mu\text{g}$  transmucosal fentanyl during the study period. <sup>b</sup>Patients who received  $\geq 1$  dose of 267  $\mu\text{g}$  transmucosal fentanyl during the study period. <sup>c</sup>Patients who received  $\geq 1$  dose of 400  $\mu\text{g}$  transmucosal fentanyl during the study period. <sup>d</sup>Patients who received  $\geq 1$  dose of 533  $\mu\text{g}$  transmucosal fentanyl during the study period. <sup>e</sup>Only the most frequent locations of pain and adjuvant analgesia are shown. Patients may have received more than one adjuvant drug.

BTcP, breakthrough cancer pain; VAS, visual analogue scale.

**Supplementary table 3.** Evolution of background pain and BTcP over the study period in the subpopulations treated with medium-to-high fentanyl doses ( $\geq 200$   $\mu\text{g}$ ) for BTcP.

	V0	V8	V15	V28	V90
<b>Patients, n</b>					
Fentanyl 200 $\mu\text{g}^a$	8	8	8	8	7
Fentanyl 267 $\mu\text{g}^b$	9	9	9	9	8
Fentanyl 400 $\mu\text{g}^c$	14	14	14	13	13
Fentanyl 533 $\mu\text{g}^d$	1	1	1	1	1
<b>Background pain</b>					
<b>VAS<sup>e</sup>, mean (SD)</b>					
Fentanyl 200 $\mu\text{g}^a$	4.9 (1.9)	4.0 (2.3)	3.3 (1.8)	3.4 (2.1)	2.4 (1.4)
Fentanyl 267 $\mu\text{g}^b$	5.1 (1.7)	3.9 (2.5)	1.9 (0.8)	1.3 (0.9)	1.4 (0.7)
Fentanyl 400 $\mu\text{g}^c$	4.1 (2.0)	3.4 (2.4)	3.1 (1.7)	3.0 (1.6)	2.4 (0.9)
Fentanyl 533 $\mu\text{g}^d$	7	5	3	5	4
<b>Changes in therapy, n (%)</b>					
Fentanyl 200 $\mu\text{g}^a$	-	5 (62.5)	3 (37.5)	4 (50.0)	3 (37.5)
Fentanyl 267 $\mu\text{g}^b$	-	5 (55.6)	2 (22.2)	0 (0.0)	0 (0.0)
Fentanyl 400 $\mu\text{g}^c$	-	7 (50.0)	7 (50.0)	5 (35.7)	1 (7.1)
Fentanyl 533 $\mu\text{g}^d$	-	1 (100.0)	0 (0.0)	1 (100.0)	0 (0.0)
<b>Breakthrough cancer pain</b>					
<b>VAS<sup>e</sup>, mean (SD)</b>					
Fentanyl 200 $\mu\text{g}^a$	8.0 (1.4)	6.4 (3.0)	5.8 (2.8)	5.3 (2.2)	4.9 (2.7)
Fentanyl 267 $\mu\text{g}^b$	8.1 (0.9)	6.4 (1.2)	4.7 (1.1)	4.2 (1.2)	3.8 (0.7)
Fentanyl 400 $\mu\text{g}^c$	8.2 (1.3)	6.9 (1.5)	6.1 (1.7)	5.6 (1.9)	5.0 (1.6)
Fentanyl 533 $\mu\text{g}^d$	8	8	6	5	5
<b>No. episodes in the last 24h, mean (SD)</b>					
Fentanyl 200 $\mu\text{g}^a$	4.5 (1.9)	2.8 (2.1)	3.0 (2.0)	2.0 (1.2)	1.9 (1.9)
Fentanyl 267 $\mu\text{g}^b$	2.8 (1.3)	2.8 (0.4)	1.8 (0.8)	1.1 (0.9)	1.2 (1.0)
Fentanyl 400 $\mu\text{g}^c$	3.3 (1.9)	2.8 (1.4)	3.0 (1.3)	2.5 (1.1)	1.9 (1.0)
Fentanyl 533 $\mu\text{g}^d$	5	5	4	3	3
<b>Duration of BTcP episodes (min), mean (SD)</b>					
Fentanyl 200 $\mu\text{g}^a$	-	21.9 (18.7)	35.6 (39.0)	23.8 (9.9)	21.4 (14.1)
Fentanyl 267 $\mu\text{g}^b$	-	23.9 (12.2)	18.9 (8.2)	15.0 (6.1)	18.4 (9.2)
Fentanyl 400 $\mu\text{g}^c$	-	15.3 (8.4)	16.5 (11.1)	18.6 (12.4)	13.8 (11.2)
Fentanyl 533 $\mu\text{g}^d$	-	20	20	35	35
<b>Time to pain relief (min), mean (SD)</b>					
Fentanyl 200 $\mu\text{g}^a$	-	10.0 (5.3)	8.5 (4.7)	11.5 (3.5)	10.0 (5.8)
Fentanyl 267 $\mu\text{g}^b$	-	12.8 (3.6)	8.7 (3.2)	7.8 (2.6)	8.3 (3.8)
Fentanyl 400 $\mu\text{g}^c$	-	7.9 (4.8)	9.9 (7.1)	9.8 (5.6)	9.2 (6.2)
Fentanyl 533 $\mu\text{g}^d$	-	15	10	15	15
<b>Changes in therapy, n (%)</b>					
Fentanyl 200 $\mu\text{g}^a$	-	5 (62.5)	3 (37.5)	1 (12.5)	2 (25.0)
Fentanyl 267 $\mu\text{g}^b$	-	5 (55.6)	6 (66.7)	1 (11.1)	0 (0.0)
Fentanyl 400 $\mu\text{g}^c$	-	6 (42.9)	4 (28.6)	4 (28.6)	2 (15.4)
Fentanyl 533 $\mu\text{g}^d$	-	1 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)

Data collected on baseline visit (V0) and subsequent visits on day 8 (V8), 15 (V15), 28 (V28) and 90 (V90) are shown. <sup>a</sup>Patients who received  $\geq 1$  dose of 200  $\mu\text{g}$  transmucosal fentanyl during the study period.

<sup>b</sup>Patients who received  $\geq 1$  dose of 267  $\mu\text{g}$  transmucosal fentanyl during the study period. <sup>c</sup>Patients who received  $\geq 1$  dose of 400  $\mu\text{g}$  transmucosal fentanyl during the study period. <sup>d</sup>Patients who received  $\geq 1$  dose of 533  $\mu\text{g}$  transmucosal fentanyl during the study period. <sup>e</sup>Fentanyl 200  $\mu\text{g}$  subgroup: statistically significant differences were observed between baseline and subsequent visits for both background pain and BTcP, except for background pain V0 vs. V8 ( $p = 0.244$ ) and V0 vs. V28 ( $p = 0.072$ ). Fentanyl 267  $\mu\text{g}$  subgroup: statistically significant differences were observed between baseline and subsequent visits for both background pain and BTcP, except for V0 vs. V8 for background pain ( $p = 0.216$ ).  $P$  value was  $<0.001$  in all comparisons for BTcP excepting V0 vs. V8 ( $p = 0.008$ ). Fentanyl 400  $\mu\text{g}$  subgroup:

statistically significant differences were observed between V0 vs. V15 and V0 vs. V90 for background pain, and in all comparisons for BTcP.

BTcP, breakthrough cancer pain; VAS, visual analogue scale.

**Supplementary table 4.** Quality of life outcomes according to the EORTC QLQ-C30 in the subpopulations treated with medium-to-high fentanyl doses ( $\geq 200$   $\mu\text{g}$ ) for BTcP.

	Fentanyl 200 $\mu\text{g}$ (n = 8) <sup>a</sup>			Fentanyl 267 $\mu\text{g}$ (n = 9) <sup>b</sup>			Fentanyl 400 $\mu\text{g}$ (n = 14) <sup>c</sup>			Fentanyl 533 $\mu\text{g}$ (n = 1) <sup>d</sup>	
Scale, mean (SD)	V0 (n = 8)	V28 (n = 8)	p value	V0 (n = 9)	V28 (n = 9)	p value	V0 (n = 14)	V28 (n = 13)	p value	V0 (n = 1)	V28 (n = 1)
<b>Global health status</b>	37.5 (18.9)	43.8 (25.5)	0.445	38.9 (26.4)	61.1 (24.79)	0.106	33.3 (18.2)	48.1 (21.6)	0.027	25.0	16.7
<b>Functional scales</b>											
Physical	64.2 (33.6)	58.3 (18.1)	0.541	63.0 (25.0)	63.0 (29.1)	>0.999	70.5 (22.6)	58.5 (24.4)	0.180	13.3	40.0
Role	33.3 (34.5)	43.8 (30.8)	0.384	38.9 (26.4)	42.6 (22.2)	0.622	34.5 (20.1)	47.4 (27.9)	0.075	0.0	33.3
Emotional	42.7 (32.3)	54.2 (29.2)	0.333	50.9 (29.0)	70.4 (19.6)	0.006	33.3 (27.5)	47.4 (25.1)	0.031	50.0	41.0
Cognitive	54.2 (26.4)	64.6 (24.3)	0.278	61.6 (26.4)	77.8 (23.6)	0.017	59.5 (16.9)	65.4 (24.0)	0.190	66.7	50.0
Social	29.2 (26.4)	52.1 (16.5)	0.022	51.9 (22.7)	55.6 (36.3)	0.782	39.3 (25.0)	48.7 (25.0)	0.201	16.7	33.3
<b>Symptom scales</b>											
Fatigue	68.1 (24.1)	55.6 (22.2)	0.168	48.1 (26.6)	48.1 (18.4)	>0.999	61.1 (21.7)	49.6 (20.1)	0.041	88.9	66.7
Pain	79.2 (19.4)	47.9 (20.8)	0.003	68.5 (25.6)	37.0 (7.3)	0.002	71.4 (29.5)	57.7 (25.1)	0.057	83.3	66.7
Nausea and vomiting	25.0 (26.7)	16.7 (29.5)	0.445	3.7 (7.3)	1.9 (5.6)	0.594	9.5 (14.2)	2.6 (6.3)	0.137	16.7	16.7
Dyspnea	12.5 (17.3)	12.5 (17.3)	>0.999	7.4 (14.7)	7.4 (14.7)	>0.999	19.0 (21.5)	7.7 (14.6)	0.054	33.3	33.3
Insomnia	45.8 (39.6)	25.0 (23.6)	0.012	40.7 (40.1)	11.1 (16.7)	0.035	59.5 (32.5)	25.6 (24.2)	0.001	33.3	33.3
Appetite loss	45.8 (35.4)	33.3 (30.9)	0.320	40.7 (27.8)	14.8 (17.6)	0.008	40.5 (14.2)	25.6 (20.0)	0.053	33.3	33.3
Constipation	16.7 (25.2)	37.5 (27.8)	0.068	22.2 (16.7)	22.2 (16.7)	-	47.6 (31.3)	46.2 (21.7)	0.436	33.3	33.3
Diarrhea	0	4.2 (11.8)	0.316	0	0	-	0	2.6 (9.2)	0.337	0.0	0.0
Financial difficulties	45.8 (39.6)	41.7 (34.5)	0.757	29.6 (26.1)	37.0 (30.9)	0.512	45.2 (24.8)	35.9 (31.8)	0.175	66.7	33.3

<sup>a</sup>Patients who received  $\geq 1$  dose of 200  $\mu\text{g}$  transmucosal fentanyl during the study period. <sup>b</sup>Patients who received  $\geq 1$  dose of 267  $\mu\text{g}$  transmucosal fentanyl during the study period. <sup>c</sup>Patients who received  $\geq 1$  dose of 400  $\mu\text{g}$  transmucosal fentanyl during the study period. <sup>d</sup>Patients who received  $\geq 1$  dose of 533  $\mu\text{g}$  transmucosal fentanyl during the study period.

BTcP, breakthrough cancer pain; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items; V0, baseline visit; V28, visit on day 28.

**Supplementary table 5.** Global impression of improvement according to patient's (PGI-I) and physician's (CGI-I) perspective in the subpopulations treated with medium-to-high fentanyl doses ( $\geq 200$   $\mu\text{g}$ ) for BTcP.

N, %	Fentanyl 200 $\mu\text{g}$ (n = 8) <sup>a</sup>	Fentanyl 267 $\mu\text{g}$ (n = 9) <sup>b</sup>	Fentanyl 400 $\mu\text{g}$ (n = 13) <sup>c</sup>	Fentanyl 533 $\mu\text{g}$ (n = 1) <sup>d</sup>
<b>Patient</b>				
Very much better	0	2 (22.2)	0	0
Much better	2 (25.0)	3 (33.3)	5 (38.5)	0
A little better	4 (50.0)	2 (22.2)	4 (30.8)	0
No change	0	0	0	0
A little worse	0	1 (11.1)	0	0
Much worse	2 (25.0)	1 (11.1)	4 (30.8)	1 (100.0)
Very much worse	0	0	0	0
<b>Physician</b>				
Very much better	0	5 (55.6)	3 (23.1)	0
Much better	5 (62.5)	2 (22.2)	4 (30.8)	0
A little better	1 (12.5)	0	1 (7.7)	0
No change	2 (25.0)	2 (22.2)	4 (30.8)	1 (100.0)
A little worse	0	0	1 (7.7)	0
Much worse	0	0	0	0
Very much worse	0	0	0	0

<sup>a</sup>Patients who received  $\geq 1$  dose of 200  $\mu\text{g}$  transmucosal fentanyl during the study period. <sup>b</sup>Patients who received  $\geq 1$  dose of 267  $\mu\text{g}$  transmucosal fentanyl during the study period. <sup>c</sup>Patients who received  $\geq 1$  dose of 400  $\mu\text{g}$  transmucosal fentanyl during the study period. <sup>d</sup>Patients who received  $\geq 1$  dose of 533  $\mu\text{g}$  transmucosal fentanyl during the study period.

BTcP, breakthrough cancer pain.