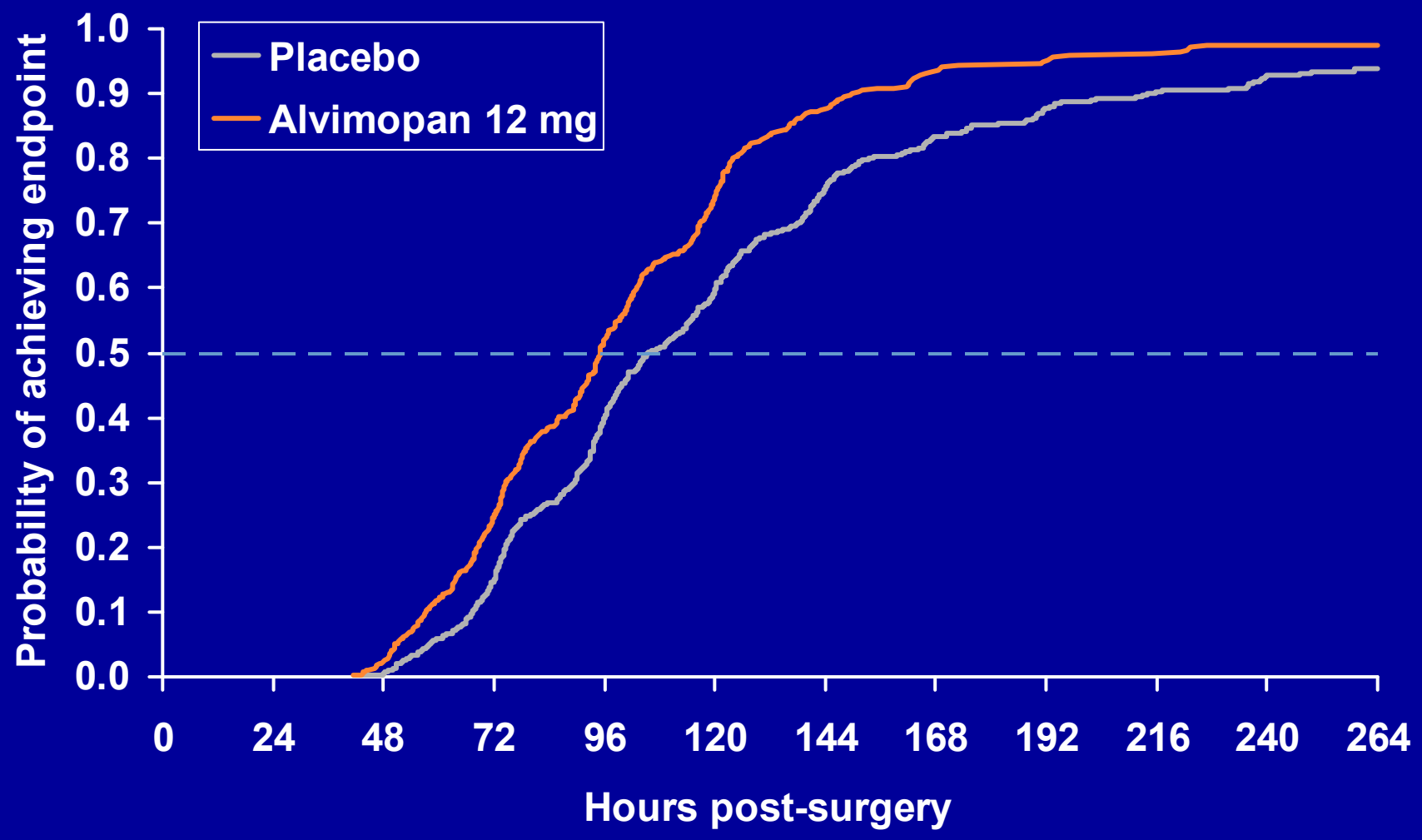
GI-2 KM Estimates
IV Morphine After Surgery
Pooled Studies 314, 313, 308, 302—BR Only



Postoperative Complications of Interest

Pooled Studies 314, 313, 308, 302—BR Only

	Patients, %			
		Alvimopan		
Complication	Placebo n = 720	6 mg n = 397	12 mg n = 734	Total n = 1131
DVT-PE	1.0	1.3	1.0	1.1
Mean age (SD), 65.3 (11.7) n = 19				
Postoperative infection	13.2	8.3	9.5	9.1
Mean age (SD), 62.6 (14.2) n = 198				
Postoperative wound infection	7.8	4.8	5.7	5.4
Respiratory infections	1.5	1.5	1.1	1.2
Sepsis	0.7	0.5	0.4	0.4
Urinary tract infections	3.8	2.3	2.5	2.4

Most Common Reasons for Hospital Readmission Within 10 Days of Discharge

Pooled Studies 314, 313, 308, 302—BR Only

		Patients, n (%)	
	Reason for readmission	Placebo n = 695	Alvimopan 12 mg n = 714
GI TEAEs	Constipation	2 (0.3)	2 (0.3)
	Diarrhea	2 (0.3)	0
	Postoperative ileus	6 (0.9)	2 (0.3)
	Small intestinal obstruction	8 (1.2)	7 (1.0)
	Vomiting	3 (0.4)	0
Surgical complications	Anastomotic leak	5 (0.7)	1 (0.1)
	Post procedural hemorrhage	0	2 (0.3)
	Postoperative abscess	4 (0.6)	2 (0.3)
	Postoperative infection	4 (0.6)	6 (0.8)
	Wound dehiscence	1 (0.1)	2 (0.3)
Other	Cardiac failure congestive	2 (0.3)	0
	Clostridium colitis	0	3 (0.4)
	Dehydration	2 (0.3)	1 (0.1)
	Pancreatitis	2 (0.3)	0
	Urinary tract infection	2 (0.3)	0

QC (1544) Source: ise2 T 12.1

Cardiovascular Safety Baseline Risk Factors

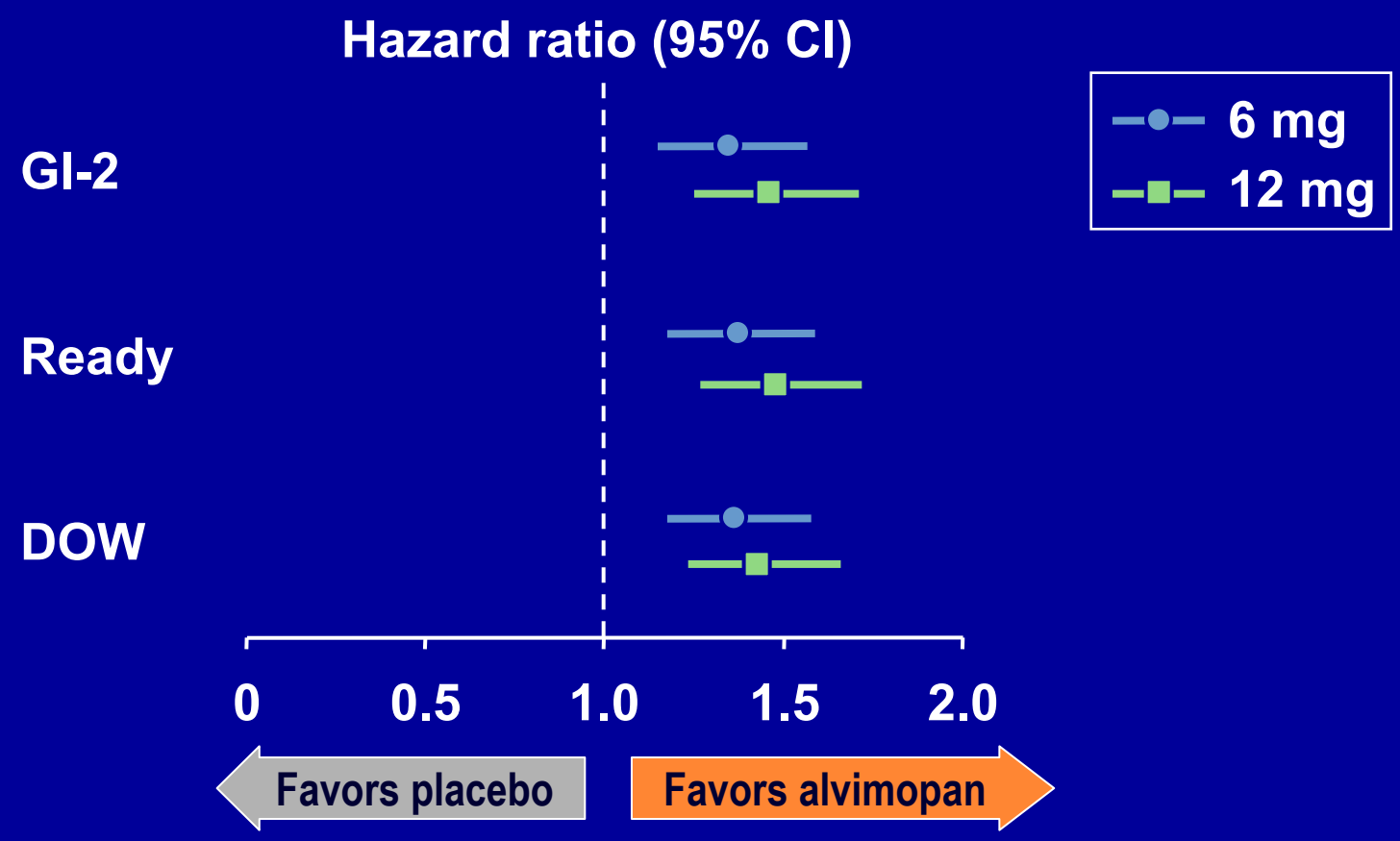
	Worldwide POI population with CV event		BR POI population with CV event	
	Placebo n = 44	Alvimopan[a] n = 56	Placebo n = 39	Alvimopan[a] n = 45
Established CV disease	9 (20.5)	20 (35.7)	9 (23.1)	17 (37.8)
CV risk factors				
Any	36 (81.8)	46 (82.1)	33 (84.6)	37 (82.2)
Smoking	10 (22.7)	13 (23.2)	9 (23.1)	9 (20.0)
Hypertension	29 (65.9)	34 (60.7)	27 (69.2)	28 (62.2)
Hyperlipidemia	17 (38.6)	23 (41.1)	16 (41.0)	17 (37.8)
Obesity	6 (13.6)	9 (16.1)	6 (15.4)	8 (17.8)

[a] Alvimopan 6 and 12 mg.

DV (1672) Table 2 (12-17-07) PDF; Complete Response T 1.1.5, 1.1.6

Hazard Ratios for GI-2, Ready, and DOW

Pooled Studies 313, 308, 302—BR Only



Baseline CV Risk Factors

Worldwide POI Safety Population and BR Only

CV risk factor	Worldwide		BR only	
	Placebo n = 1365	Alvimopan n = 2610	Placebo n = 986	Alvimopan n = 1681
Mean age (SD)	58 (14)	57 (15)	62 (14)	62 (14)
BMI ≥ 30, %	32	29	29	25
Diabetes, %	10	12	12	14
Hypertension, %	43	39	46	45
Smoking, %	10	8	11	9

(15170) WW data: IR September 21, 2006; BR data:___

Ischemic CV Events by Study IDMC Adjudicated

GSK Study	Patients, n/N (%)			Relative risk (95% CI)
	Placebo	Alvimopan	Total	
011	1/129 (0.8)	3/393 (0.8)	4/522 (0.8)	0.98 (0.10, 9.38)
012	2/172 (1.2)	1/346 (0.3)	3/518 (0.6)	0.25 (0.02, 2.72)
013	1/164 (0.6)	0/321	1/485 (0.2)	0.17 (0.01, 4.17)
014	0/267	9/538 (1.7)	9/805 (1.1)	9.45 (0.55, 161.70)
008	1/70 (1.4)	0/160	1/230 (0.4)	0.15 (0.01, 3.56)
ABD101684	1/15 (6.7)	0/50	1/65 (1.5)	0.10 (0.01, 2.44)
Total	6/817 (0.7)	13/1808 (0.7)	19/2625 (0.7)	0.98 (0.37, 2.57)

(1918) Source:

Ischemic CV Events IDMC Adjudicated

	Placebo n = 817		Alvimopan n = 1808	
	Events, n	Patients, n (%)	Events, n	Patients, n (%)
Any ischemic CV event	8	6 (0.73)	14	13 (0.72)
Acute MI	2	2 (0.24)	8	8 (0.44)
New onset/unstable angina	1	1 (0.12)	4	4 (0.22)
Congestive cardiac failure	2	2 (0.24)	1	1 (0.06)
Cerebrovascular accident/TIA	1	1 (0.12)	0	0
Cardiac arrest	1	1 (0.12)	1	1 (0.06)
Sudden death	1	1 (0.12)	0	0

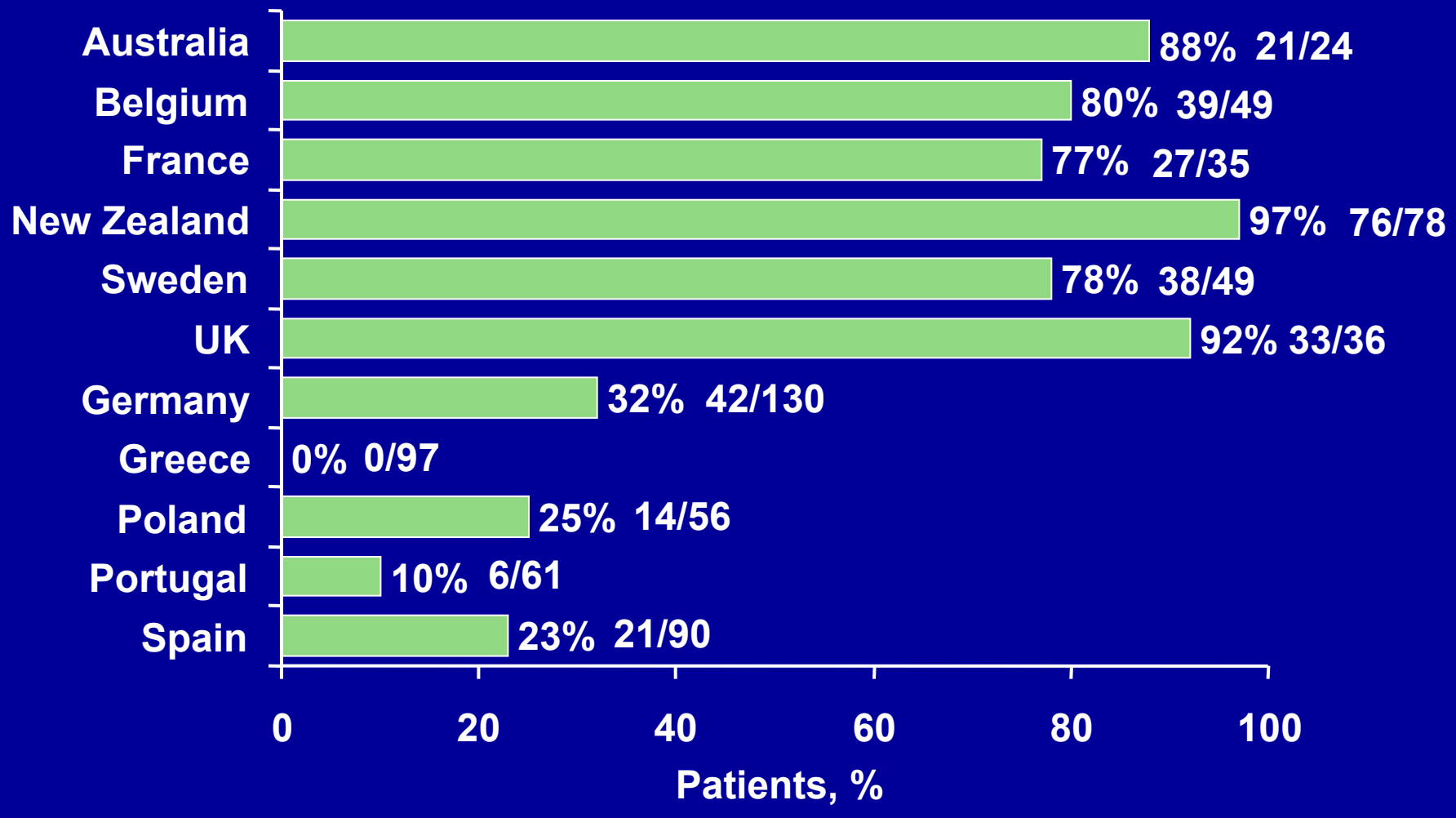
Concomitant Medications of Interest
Pooled Studies 314, 313, 308, 302—BR Only

Medication	Patients, %	
	Placebo n = 695	Alvimopan 12 mg n = 714
5-HT3[a]	67.6	66.4
Metoclopramide	29.4	26.5
Erythromycin	9.4	12.0
Laxatives	11.2	10.6
Cathartics	5.0	5.7
5-HT4[b]	0.1	0.1
Other anti-emetics[c]	12.7	10.4

[a] 5-HT3 medications include dolasetron, granisetron, ondasetron
[b] 5-HT4 medications include tegaserod
[c] Other anti-emetics include dronabinol, droperidol, hyoscine, prochlorperazine, trimethobenzamide; in addition, one subject took an "unknown" anti-emetic.

(1560) Source: AC Table 7.6

PCA Opioids in First 48 Hours by Country
Study 001



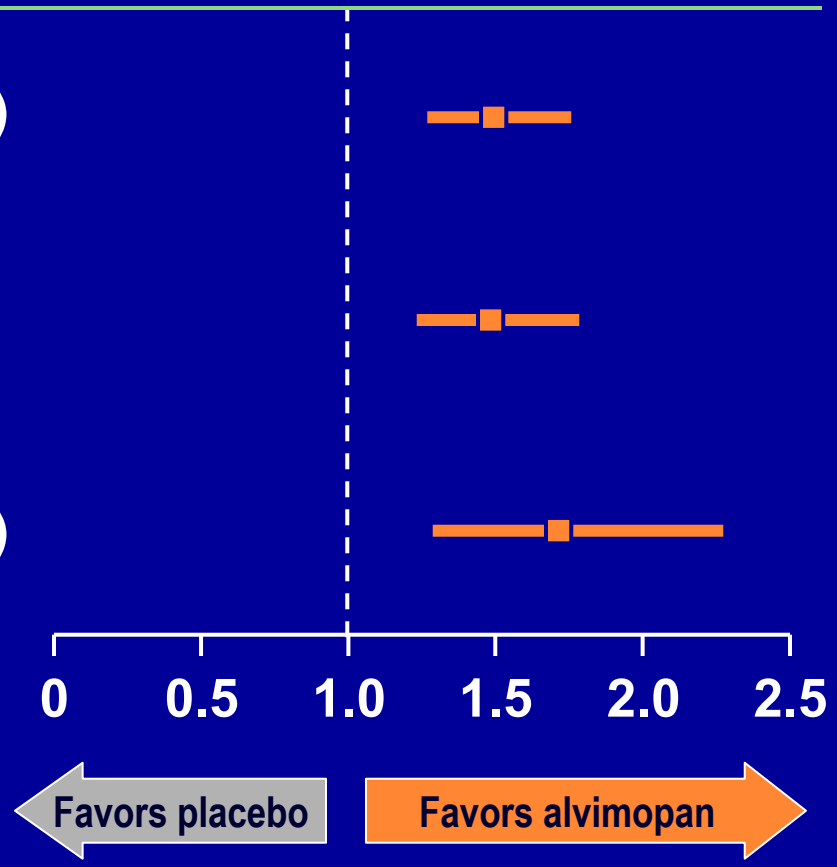
(1567) Source: 001-01-csr-body-supplement.pdf T 1

GI-2 by Age

Pooled Studies 314, 313, 308, 302—BR Only[a]

Age	Difference (hr) from placebo in KM means (95% CI)
< 65 years (n = 810)	19.8 (12.3, 27.2)
≥ 65 years (n = 599)	17.9 (9.4, 26.3)
≥ 75 years (n = 239)	25.3 (11.4, 39.1)

Hazard ratio (95% CI)

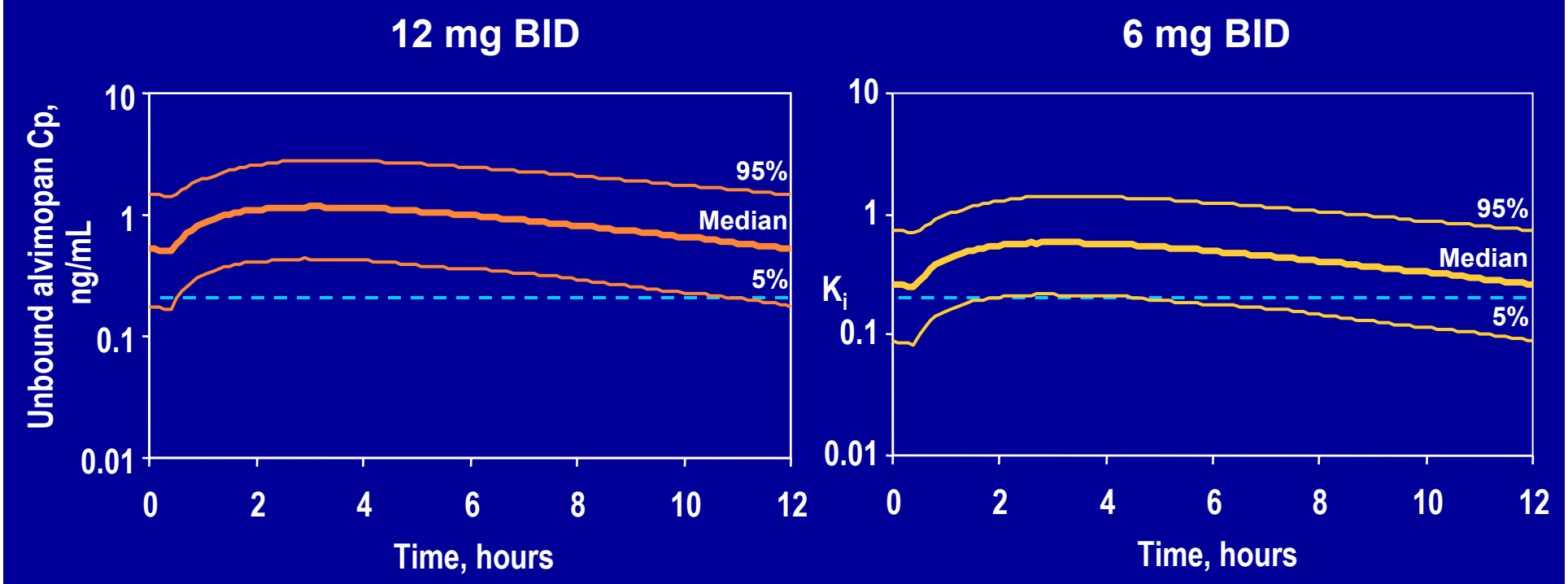


[a] Alvimopan 12 mg.

Hazard Ratio Summary for Risk of Death
OBD GSK Studies 008 and ABD101684

Variable	HR (CI)
Univariate model	
Alvimopan (unadjusted)	2.1 (0.62, 7.10)
Multivariate model	
Non-small cell lung cancer	2.8 (1.16, 6.78)
Per 10-point lower Karnofsky	1.5 (1.13, 2.04)
Per additional metastatic site	1.9 (1.26, 2.80)
Alvimopan (adjusted)	1.4 (0.40, 5.04)

Dose Selection
Time Above K_i for μ-Opioid Receptors
Alvimopan 6 mg or 12 mg BID



Concentrations are above K_i for μ-opioid receptors for ~ 12 hr in 95% of patients receiving 12 mg BID in POI patients