Entereg® (alvimopan)
OBD Study GSK014 Safety Findings

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OBD Indication and Patient Population

- Opioid-induced bowel dysfunction (OBD) is a chronic condition characterized by severe constipation and associated symptoms
- Different population
  - Chronic pain treated with opioids for months, years
- Proposed dose regimen is 0.5 mg BID given continuously while receiving opioids

Clinical History of Pain and Opioid Use

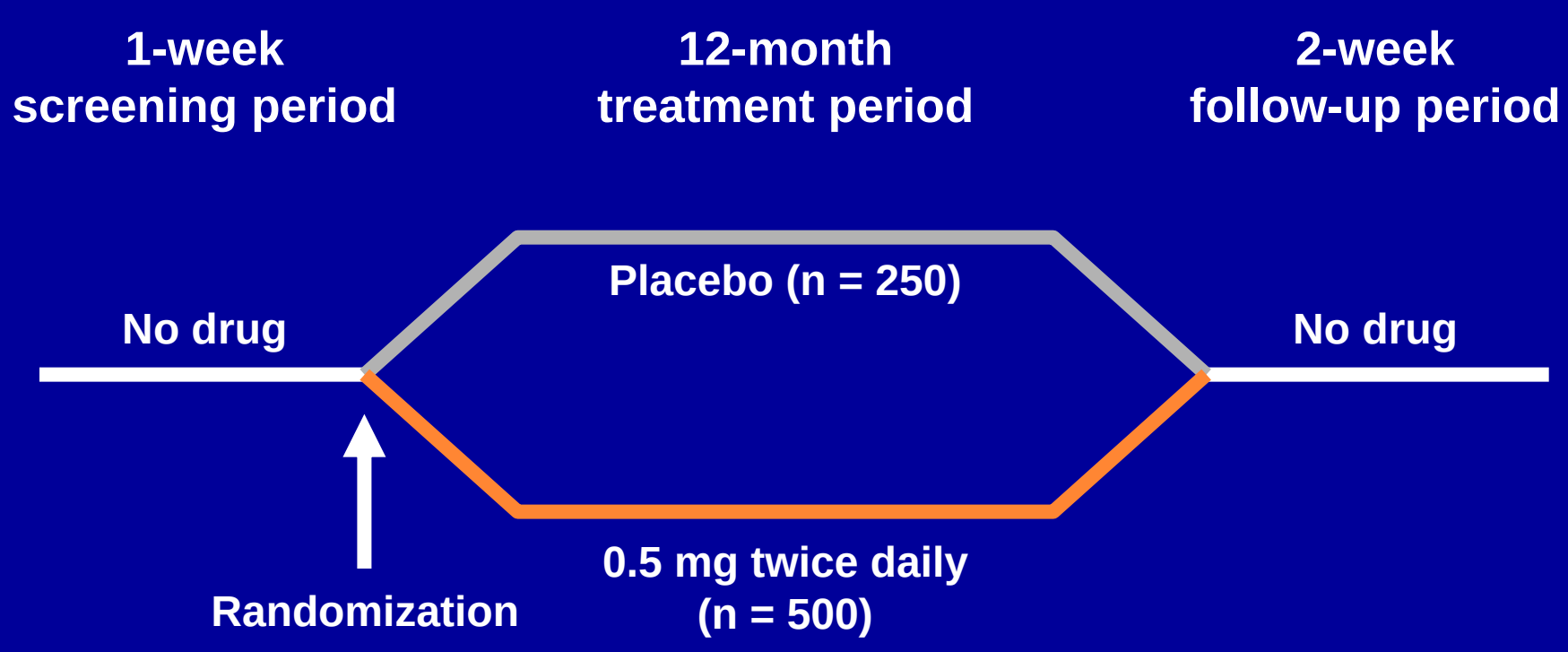
OBD Study GSK014 vs POI Studies

	OBD	POI
Duration of current pain condition	10.6 yr (0.2 - 55.0)	NA
Duration of opioid use	7.6 yr (0.1 - 39.0)	≤ 10 days
Morphine equivalents mean total daily dose	232 mg (0.0 - 2345.6)	28 mg

OBD Study GSK014—Design

12-Month Safety Study—Chronic Noncancer Pain

Double-blind, placebo-controlled trial, 2:1 randomization



Safety Findings
OBD Study GSK014

- Imbalance in incidence of MI, neoplasia (benign + malignant), and bone fracture for alvimopan-treated patients vs placebo
- Evaluation of safety findings
  - Examination of index cases
  - Review of literature and preclinical data
  - Assessment of exposure-response relationship
  - Epidemiologic investigation
  - External review

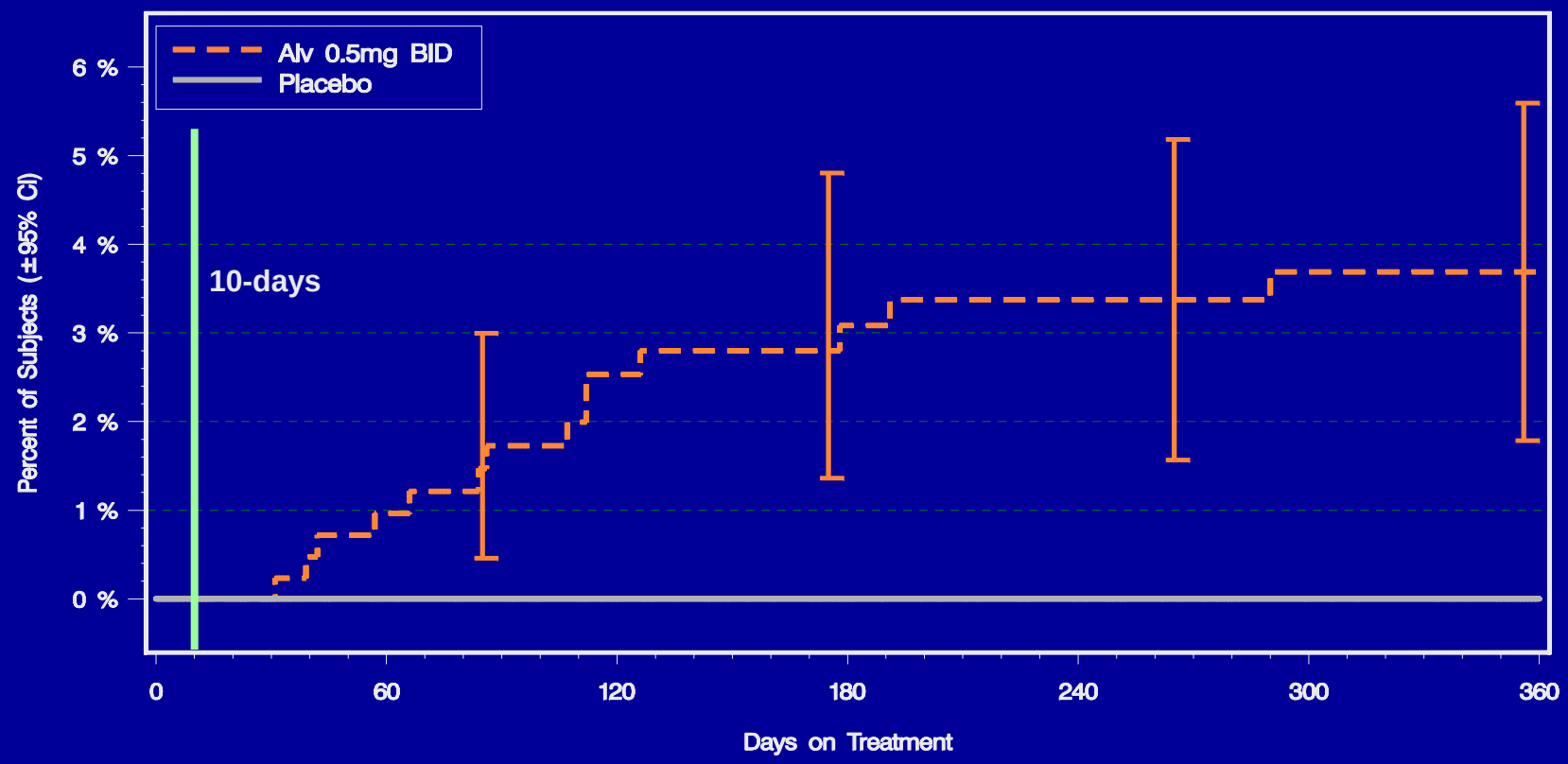
Cardiovascular Events

OBD Study GSK014

CV event category	Patients, n (%) Placebo n = 267	Alvimopan 0.5 mg BID n = 538	Relative risk alvimopan/ placebo
MI	0	7 (1.30)	7.46 (0.43, 130.1)
Unstable angina	0	3 (0.56)	3.48 (0.18, 67.1)
Non-fatal CVA	0	1 (0.19)	1.49 (0.06, 36.5)
CHF	0	1 (0.19)	1.49 (0.06, 36.5)
Serious arrhythmia	0	2 (0.37)	2.49 (0.12, 51.6)
Death from CV events	0	1 (0.19)	1.49 (0.06, 36.5)
All-cause death	2 (0.75)	2 (0.37)	0.50 (0.07, 3.50)

(0532) Source: Table X.X.X. from GSK

Time to Cardiovascular[a] Events
OBD Study GSK014



Subjects At Risk

Placebo	267	195	175	160	150	138	74
Alv 0.5mg BID	538	398	363	339	322	305	173

[a] CV events include cardiovascular death, nonfatal MI, CHF, stroke, unstable angina, serious arrhythmia.

Cardiovascular Events

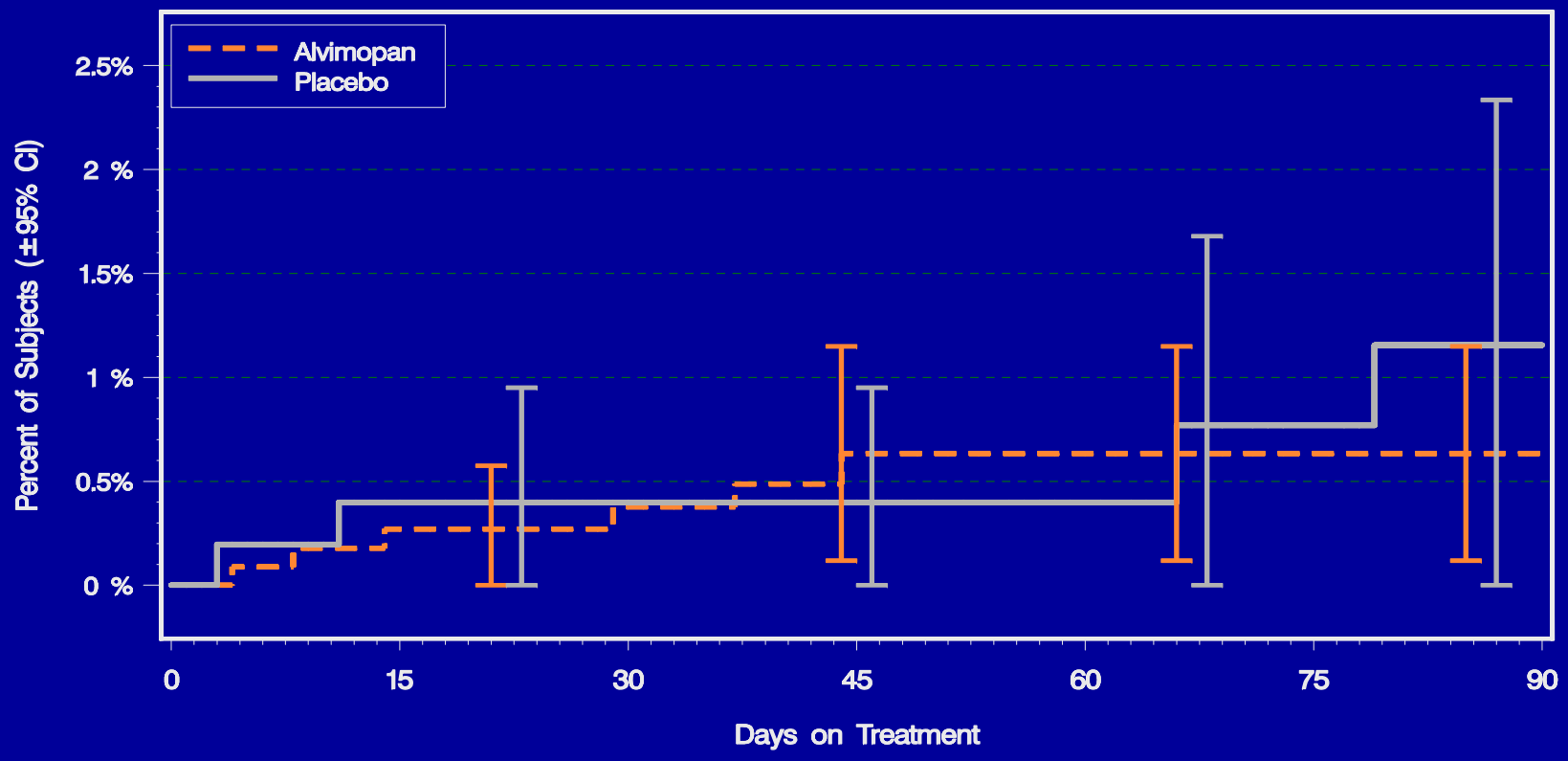
OBD Noncancer Pain Population Excluding GSK014[a]

CV event category	Patients, n (%) Placebo n = 523	Alvimopan All Doses n = 1190	Relative risk alvimopan/ placebo
MI	2 (0.38)	1 (0.08)	0.22 (0.02, 2.42)
Unstable angina	0	1 (0.08)	1.32 (0.05, 32.3)
Non-fatal CVA	1 (0.19)	1 (0.08)	0.44 (0.03, 7.01)
CHF	2 (0.38)	1 (0.08)	0.22 (0.02, 2.42)
Serious arrhythmia	0	3 (0.25)	3.08 (0.16, 59.5)
Death from CV events	0	1 (0.08)	1.32 (0.05, 32.3)
All-cause death	0	2 (0.17)	2.20 (0.11, 45.7)

[a] Studies 011, 012, 013, 217, and 304.

Time to Cardiovascular[a] Events

Noncancer OBD Studies Excluding GSK014[b]



Subjects At Risk

Placebo	523	483	402	293	272	260	25
Alvimopan	1190	1079	922	611	547	525	64

[a] CV events include cardiovascular death, nonfatal MI, CHF, stroke, unstable angina, serious arrhythmia.
[b] Kaplan-Meier estimates from studies 217, 304, 011, 012, and 013.

Cardiovascular Events
All Noncancer OBD Population

CV event category	Patients, n (%) Placebo n = 790	Alvimopan all doses n = 1728	Relative risk alvimopan/ placebo
MI	2 (0.25)	8(0.46)	1.83 (0.39, 8.59)
Unstable angina	0	4 (0.23)	4.12 (0.22, 76.4)
Non-fatal CVA	1 (0.13)	2 (0.12)	0.91 (0.08, 10.1)
CHF	2 (0.25)	2 (0.12)	0.46 (0.06, 3.24)
Serious arrhythmia	0	5 (0.29)	5.03 (0.28, 90.9)
Death from CV events	0	2 (0.12)	2.29 (0.11, 47.6)
All-cause death	2 (0.25)	4 (0.23)	0.91 (0.17, 4.98)

[a] Studies 011, 012, 013, 014, 217, and 304.

Cardiovascular Events
IDMC Adjudicated—OBD Population

	Placebo n = 817	Alvimopan n = 1807	Relative risk (95% CI) Alv/Pla
Adjudicated cases, n	21	63	—
All CV events, n (%)	9 (1.1)	26 (1.4)	1.30 (0.61, 2.77)
Ischemic CV events, n (%)	6 (0.7)	13 (0.7)	0.98 (0.37, 2.57)
Other non-ischemic CV events, n (%)	3 (0.4)	14 (0.8)	2.11 (0.61, 7.32)

IDMC OBD Study Conclusions

- Risk of ischemic heart disease largely discharged
- Incidence of other (non-ischemic) CV events with alvimopan vs placebo not statistically significant
- Further OBD studies should confirm conclusions
  - Evaluation of CV risk, enhanced monitoring for CV events, and IDMC oversight should continue

Neoplasm Event Summary
OBD Studies—All Neoplasms

	Patients, n/N (%)		Relative risk
	Placebo	Alvimopan	Alv/Pla (95% CI)
GSK014 (initial finding)	2/267 (0.7)	15/538 (2.8)	3.7 (0.86, 16.16)
GSK014 (including post-study case)	3/267 (1.1)	15/538 (2.8)	2.5 (0.72, 8.50)
Noncancer studies[a]	4[b]/732 (0.5)	23[b]/1598 (1.4)	2.6 (0.91, 7.59)

[a] Studies 011, 012, 013, and 014, includes post-study cases.
[b] Includes one observation reported subsequent to study completion.

Neoplasm Event Summary

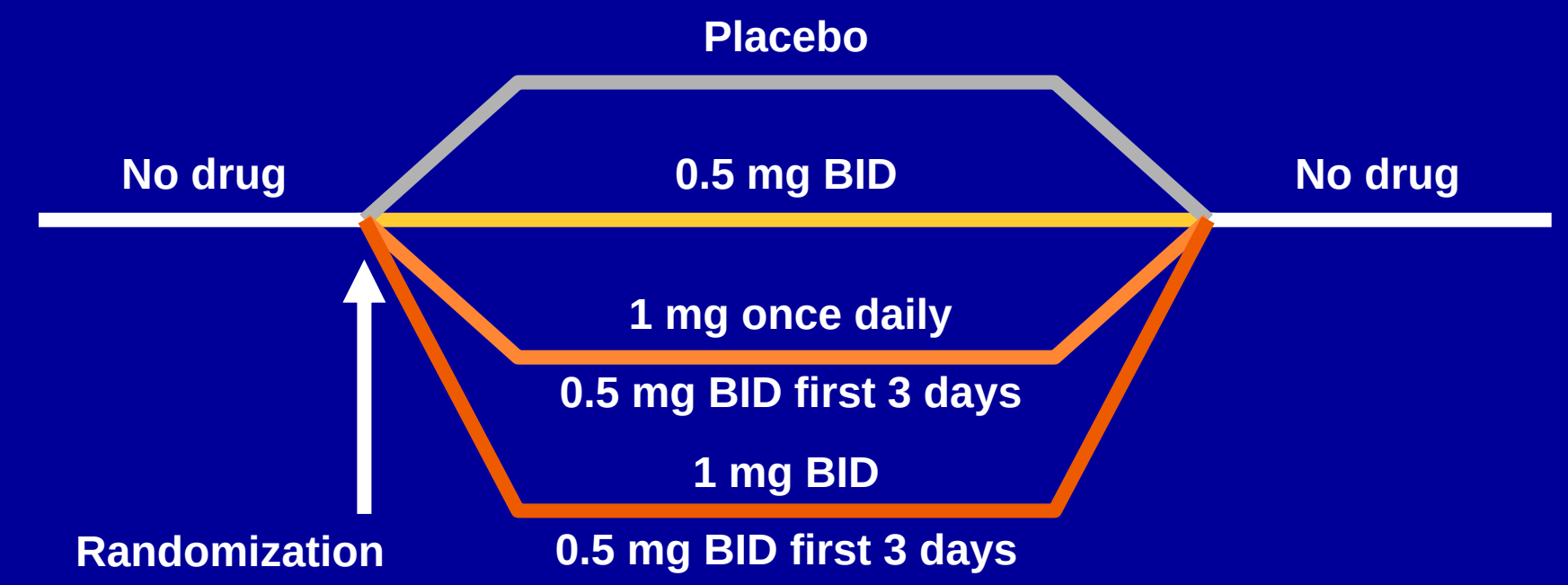
Malignant Neoplasms in OBD Studies

	Patients, n/N (%)		Relative risk
	Placebo	Alvimopan	Alv/Pla (95% CI)
GSK014 (initial finding)	1/267 (0.4)	5/538 (0.9)	2.3 (0.27, 20.04)
GSK014 (including post-study case)	2[b]/267 (0.7)	5/538 (0.9)	1.2 (0.24, 6.35)
Noncancer studies[a]	3[b]/732 (0.4)	10[b]/1598 (0.6)	1.5 (0.42, 5.53)

[a] Studies 011, 012, 013, and 014.
[b] Includes one observation reported subsequent to study completion.

OBD in Patients with Cancer Pain

GSK Studies 008 and ABD101684—Design



Patients completing GSK008 permitted access on continuing blinded therapy in extension study (ABD101684)

Neoplasia Events Summary
OBD GSK Studies 008 and ABD101684

- Imbalance in deaths noted—
  20/160 (12.5%) alvimopan vs 3/70 (4%) placebo;
  HR (CI) Alv/Pla 2.1 (0.62, 7.10)
  - Studies not designed to ensure balance of prognostic factors for disease progression
- Marked imbalance in exposure between groups
  - Alvimopan (32.4) vs placebo (6.7) patient-years
- Alvimopan patients in extension study had more advanced disease than placebo patients
  - Lower Karnofsky scores, more sites of metastasis
  - Multivariate modeling suggests alvimopan is not a significant predictor for risk of death

Fracture Event Summary
OBD Studies

	Patients, n/N (%)		Relative risk (Alv/Pla)
	Placebo	Alvimopan	
GSK014	3/267 (1.1)	20/538 (3.7)	3.31 (0.99, 11.04)
Noncancer studies[a]	9/732 (1.23)	24/1598 (1.5)	1.22 (0.57, 2.61)
Cancer studies	1/70 (1.4)	1/160 (0.6)	0.44 (0.03, 6.90)

[a] Studies 011, 012, 013, and 014.

Summary of OBD Clinical Data

- High-risk population
  - Overweight, tobacco users, hypertension
- Low frequency of events results in wide CIs
  - Difficult to interpret relative risk in the presence of such small numbers of events
  - Observations principally confined to GSK014

Preclinical Evaluations of Alvimopan

- CV
  - Negative hERG study with alvimopan and metabolite[a]
  - Negative dog Purkinje fiber study with alvimopan and metabolite[b]
  - No CV or QT effects in safety pharmacology studies in dogs following IV dosing of alvimopan[c]
- Neoplasia
  - Negative clastogenicity and mutagenicity studies with alvimopan and metabolite
  - Negative carcinogenicity in 2 species
    - 2-year rat study
    - 2-year mouse study

[a] Study 14TX021; [b] Study 14PH017; [c] Studies 012121-1 and 14PH018.

Clinical Studies and Literature Review

- Negative QT studies
  - No effect on QT interval in a “Thorough QT Study” in humans (6 mg and 24 mg BID for 7 days)
- No exposure response relationship observed for patients with CV events, neoplasia or fractures
- Literature review
  - Overall, animal and human data do not suggest a clear pattern of either beneficial or deleterious effects on CV function, neoplasia, or fractures associated with long-term treatment with the opioid agonists or antagonists

OBD Safety Summary

- Findings principally isolated to 1 study in the OBD population—GSK014
- Timeframe of events in GSK014 did not overlap the proposed indication for POI
- IDMC concluded—treatment risk of ischemic heart disease in OBD studies largely discharged
- GSK proposes additional study to confirm safety in the OBD population

- These findings not observed in the POI population