Naloxegol

an investigational drug for the treatment of Opioid-Induced Constipation

October 2012

AstraZeneca

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In order, among other things, to utilise the 'safe harbour' provisions of the US Private Securities Litigation Reform Act 1995, we are providing the following cautionary statement: This presentation contains certain forward-looking statements with respect to the operations, performance and financial condition of the Group. Although we believe our expectations are based on reasonable assumptions, any forward-looking statements, by their very nature, involve risks and uncertainties and may be influenced by factors that could cause actual outcomes and results to be materially different from those predicted. The forward-looking statements reflect knowledge and information available at the date of preparation of this presentation and AstraZeneca undertakes no obligation to update these forward-looking statements. We identify the forward-looking statements by using the words 'anticipates', 'believes', 'expects', 'intends' and similar expressions in such statements. Important factors that could cause actual results to differ materially from those contained in forward-looking statements, certain of which are beyond our control, include, among other things: the loss or expiration of patents, marketing exclusivity or trade marks, or the risk of failure to obtain patent protection; the risk of substantial adverse litigation/government investigation claims and insufficient insurance coverage; exchange rate fluctuations; the risk that R&D will not yield new products that achieve commercial success; the risk that strategic alliances and acquisitions will be unsuccessful; the impact of competition, price controls and price reductions; taxation risks; the risk of substantial product liability claims; the impact of any failure by third parties to supply materials or services; the risk of failure to manage a crisis; the risk of delay to new product launches; the difficulties of obtaining and maintaining regulatory approvals for products; the risk of failure to observe ongoing regulatory oversight; the risk that new products do not perform as we expect; the risk of environmental liabilities; the risks associated with conducting business in emerging markets; the risk of reputational damage; the risk of product counterfeiting; the risk of failure to successfully implement planned cost reduction measures through productivity initiatives and restructuring programmes; the risk that regulatory approval processes for biosimilars could have an adverse effect on future commercial prospects; and the impact of increasing implementation and enforcement of more stringent anti-bribery and anti-corruption legislation. Nothing in this presentation should be construed as a profit forecast.

Introduction and Overview

Section	Speaker
Introduction	Kathy Cantagallo naloxegol VP, Development
Overview of the Opioid Market	Mike Gibbs VP Brand Marketing
Naloxegol: Overview of the molecule and its development	Mark Sostek, M.D. Executive Director, Development
Overview and Summary	Kathy Cantagallo naloxegol VP, Development
Q&A	

Introduction

Key Facts

1 AstraZeneca and Nektar Therapeutics entered into an exclusive worldwide license agreement for naloxegol on 21 September 2009. AstraZeneca has development and commercialization rights for naloxegol (previously NKTR-118). Nektar received an upfront payment of $125m.

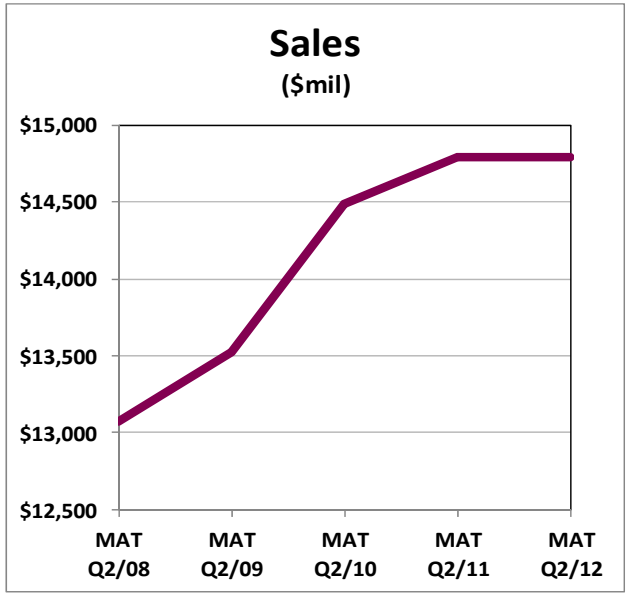
2 Naloxegol is a once a day oral, peripherally acting, μ-opioid receptor antagonist under investigation for the treatment of constipation as a side effect of prescription opioid pain medicines ("opioid-induced constipation" or OIC).

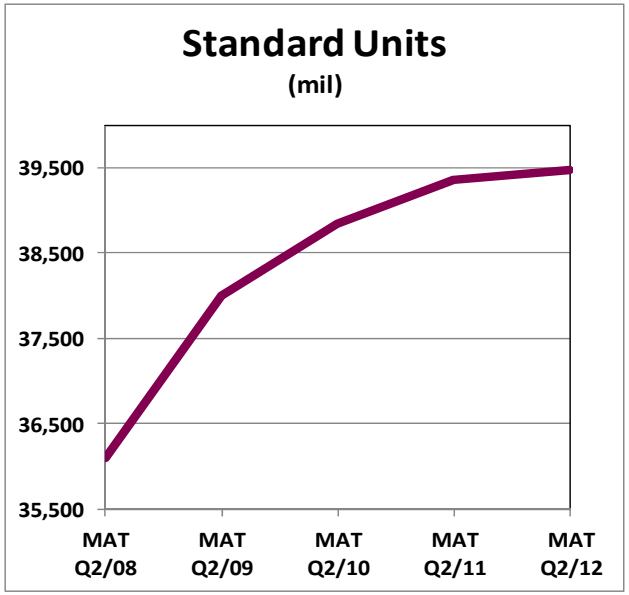
3 The core Phase III KODIAC program for naloxegol comprises four clinical studies which are designed to investigate the safety and efficacy of naloxegol for the chronic treatment of OIC in patients with non-cancer related pain:

- We anticipate having high level results for the Phase III program in Q4 2012.

Opioid Market Overview

Worldwide total opioid sales and volume*



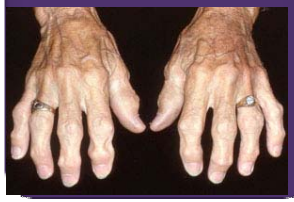


Approximately 85% of opioid volume is long-term use (>30days)**

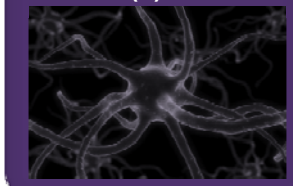
Leading diagnoses for opioid use***

Chronic Back Pain (24)%

Osteoarthritis (15)%



Neuropathic Pain (4)%



Cancer Pain (4)%

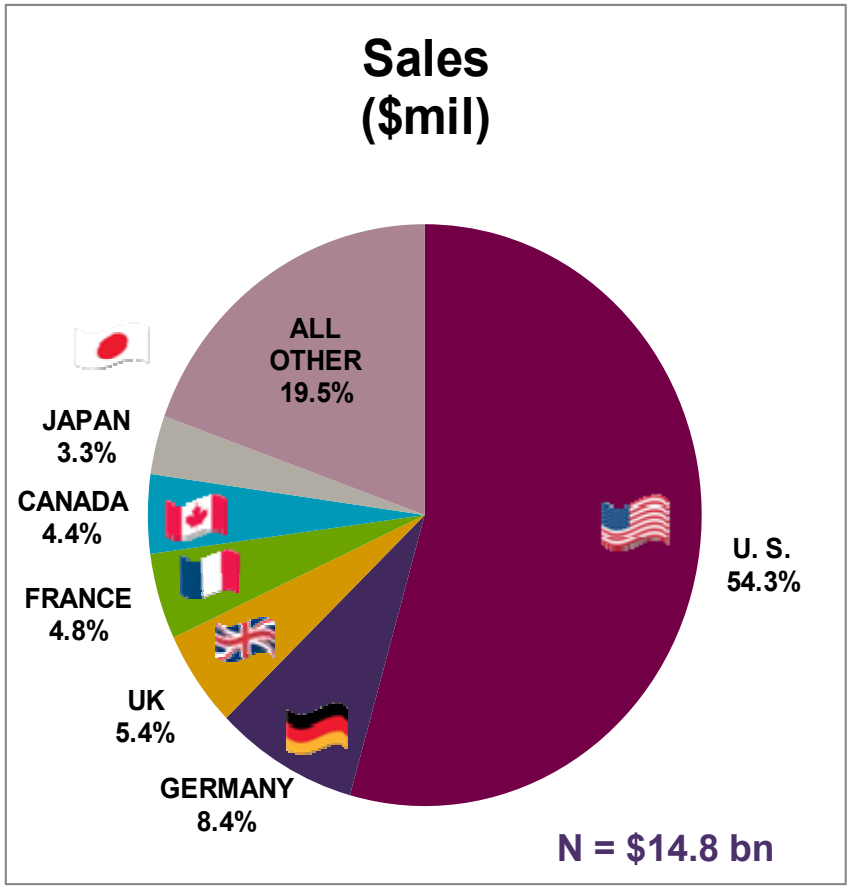
Fibromyalgia (1)%

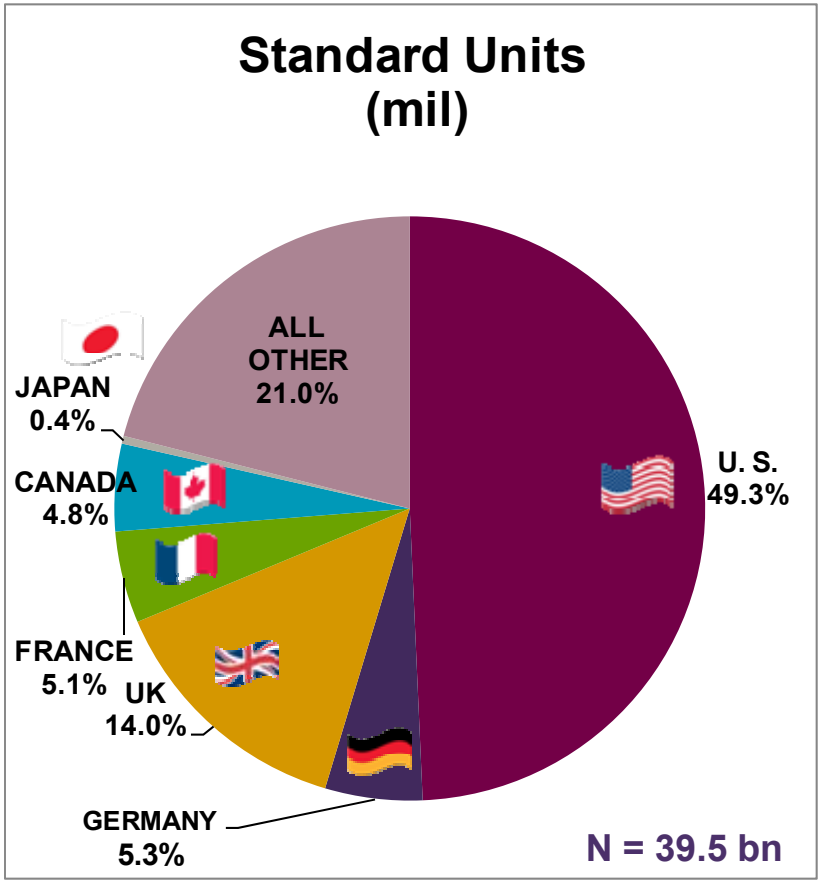
*Source: IMS MDART MAT-2Q12

**Source: NKTR-118 OIC Patient Quantitative Study, Mar-2010 US, UK, Ger, Fra, Can

***Source: IMS Medical Database, MAT @Q2012; based on Rxs by diag; other diags account for less than 1% each but add up to the other 50%; US, UK, Ger, Fra, Can

The opioid market is dominated by US, Canada, France, Germany and UK*





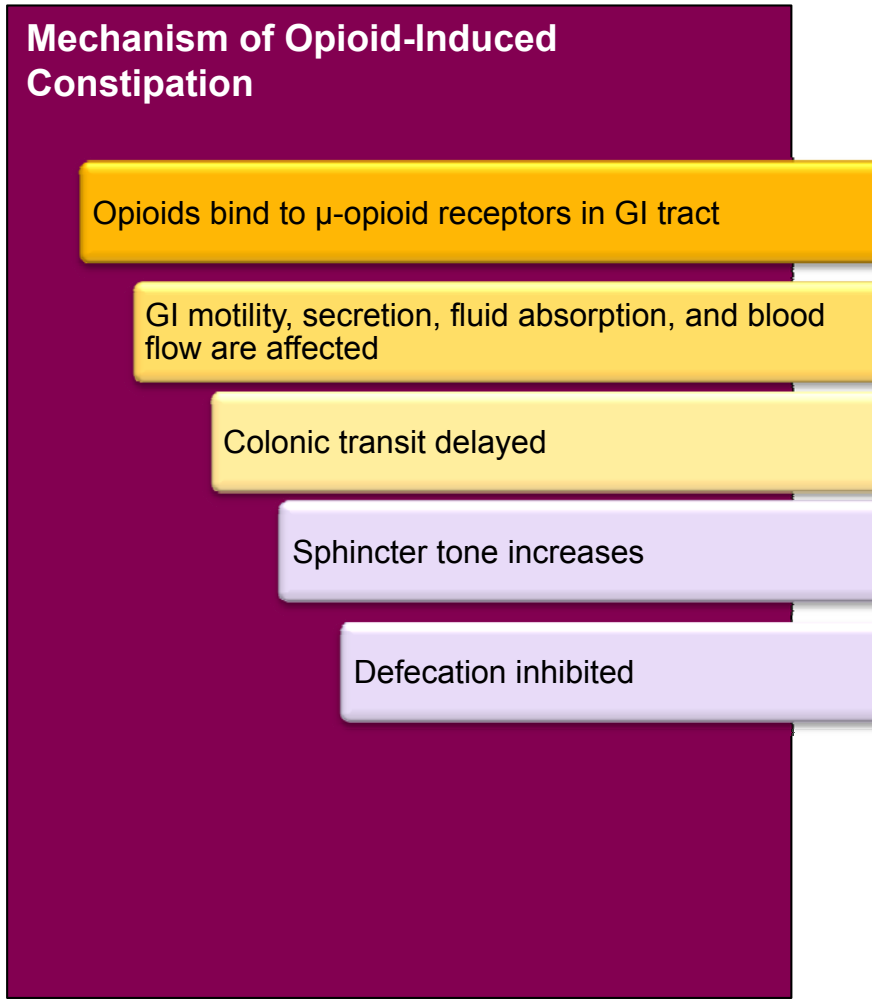
*IMS MDART MAT-2Q12.

Opioid Induced Constipation

Although highly effective in the control of pain, the use of opioids is associated with a key side effect - **constipation**[1] – affecting 40-50% of patients.[2]

Constipation can negatively impact patient quality of life[3] and may result in patients avoiding or discontinuing pain therapy with strong opioids, compromising effective analgesia.[1,3,4]

OIC is often overlooked and inadequately managed.[5,6,7] Whilst conventional laxatives can be used in conjunction with opioids to alleviate OIC symptoms, they do not treat the cause of the problem[3] and often do not achieve the desired treatment outcome. [1,8]



[1]Bell TJ *et al*. *Pain Medicine*. 2008
[2]Yuan CS *et al*. 2005 *Handbook of Opioid Bowel Syndrome*
[3] Panchal SJ *et al. Int J Clin Pract*. 2007
[4] Thorpe DM. *Curr Pain Headache Rep*. 2001
[5] McMillan *et al*. *Cancer Nurs*. 2000
[6] Tittle Met al. Am J Crit Care. 1994
[7] Pappagallo M. Am J Surg. 2001
[8] Holzer Regulatory Peptides 155 (2009) 11-17.

The Opioid Induced Constipation (OIC) opportunity

$14.8 Billion

Of the $14.8 billion global opioid market, five markets account for ~80% of total unit volume: US (49%), UK (14%), Germany (5%), Canada (5), France (5%).[1] PCPs and Pain Management Specialists comprise the majority of prescribers in these markets.[2]

69 Million

In these five markets, there are 69 million patients taking opioids for chronic pain (>30 days treatment).[3] For these chronic pain opioid users, opioid induced constipation (OIC) is the most common side effect. [4, 5]

28-35 Million*

Approximately 40–50% (28-35 million) patients taking opioids for long-term pain develop constipation.[1, 2, 3]

11-18 Million*

About 40–50% (11-18 million) of those OIC sufferers achieve the desired treatment outcomes with current options that include OTC and Rx laxatives.[6, 7]

[1] *IMS Health MIDAS MAT-2Q12*
[2] *IMS Health NPA MAT-2Q12, Cegedim MAT-2Q11)*
[3] *IMS patient level data MAT-2Q09IMS patient level data MAT-2Q09*
[4] *Panchal, S et al. Opioid-Induced Bowel Dysfunction: Prevalence, Pathophysiology and Burden. Int J Clin Pract. 2007;61(7):1181-1187.*
[5] *Reimer, K et al. Meeting the Challenges of Opioid-Induced Constipation in Chronic Pain Management – A Novel Approach. Pharmacology. 2009;83:10–17.*
[6] *Pappagallo, M. (2001). Incidence, prevalence, and management of opioid bowel.*
dysfunction. Am J Surg 182(5A Suppl), 11S−18S.
[7] *Holzer Regulatory Peptides 155 (2009) 11-17.*

**Number of patients in major opioid markets*

Competitive landscape for OIC

<u>Peripherally Acting mu-Opioid Receptor Antagonists</u>:

RELISTOR (methylnaltrexone bromide) SQ - Salix/Progenics

- Indicated for OIC in patients with advanced medical illness who are receiving palliative care, when response to laxative therapy has not been sufficient
- Introduced in 2008

RELISTOR (methlynaltrexone bromide) SQ - Salix/Progenics

- Investigated for use in non-chronic non-cancer pain patients with OIC
- CRL July 2012

RELISTOR (methlynaltrexone bromide) Oral - Salix/Progenics

- Pre-registration

Bevenopran (formerly CB-5945) – Cubist

- Phase 2 complete, Phase 3 anticipated EOY 2012

TD-1211 – Theravance

- Phase 2 recruitment completed; seeking partner to commence Phase 3

Naldemedine (formerly S297995) – Shionogi

- Phase 2b recruitment delays; Phase 3 start anticipated 2013

Amitiza (lubiprostone) Oral – Sucampo [chloride channel activator]

- Approved for Chronic Constipation
- sNDA for Opioid Bowel Disease (OBD) filed July 2012, granted fast track review for potential launch Q2 2013

OIC from a Customer Perspective:

Patients, Physicians, Payers

People with OIC are being treated with a host of drugs, but largely ineffectively.
-- US MCO payer

"I would love to go out on dates and get out more often – I'm not over the hill yet! I can't do that with where I am right now. How are you going to explain something like this to someone who doesn't know?" –US Female, OIC patient, 60

"My OIC symptoms have really created distance and animosity in my personal relationships. It's messing up timelines, social plans and other things that (my friends and family) want to do with their lives."
– US Female patient, 26

"It's [OIC treatments] a big hassle. They don't always work; they're unpredictable, and when they do work, the patient finds them unpleasant… diarrhea, urgency, cramping…"
– US Gastroenterologist

"OIC is a huge problem. If you're using opioids, you're going to have problems, and you have to be on top of this." – US Physiatrist

"The treatments are not all that adequate. They don't always restore patients to their normal level."
– US Physiatrist

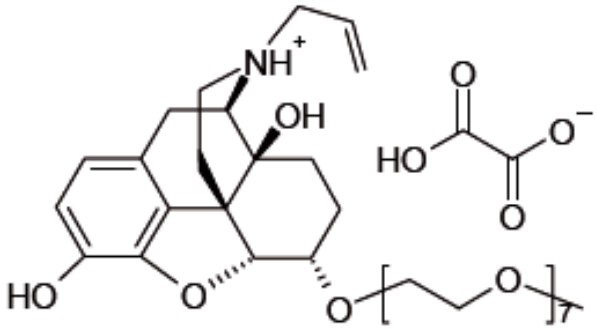
Source: Patient quotes are from qualitative interviews with US OIC patients, August 2012.
HCP quotes are from qualitative interviews with US HCPs, October 2009.; Payor quote from qualitative interviews with US payors, January 2012.

Naloxegol

An overview of the molecule and development

Naloxegol
Mechanism of Action

- Opioids bind to mu-opioid receptors located throughout the body (including brain and gut)[1]
- When opioids bind to mu-opioid receptors in the brain the outcome is pain relief[1]
- When opioids bind to mu-opioid receptors in the GI tract/gut the outcome is decreased GI motility which may lead to constipation[1, 2, 3, 4]
- Naloxegol is a PEGylated mu-opioid antagonist that blocks the opioid at the receptor site in the gut.[5]
- Due to PEGylation, uptake of naloxegol across the Blood-Brain Barrier is limited[6]



Naloxegol-chemical structure

[1] Gutstein HB et al *Goodman & Gilman's; The Pharmacological Basis of Therapeutics*, 10th ed. New York, McGraw-Hill 2001; 569-620

[2]Holzer P. Opioid receptors in the gastrointestinal tract. Regul Pept. 155(1-3); 2009; 11-17

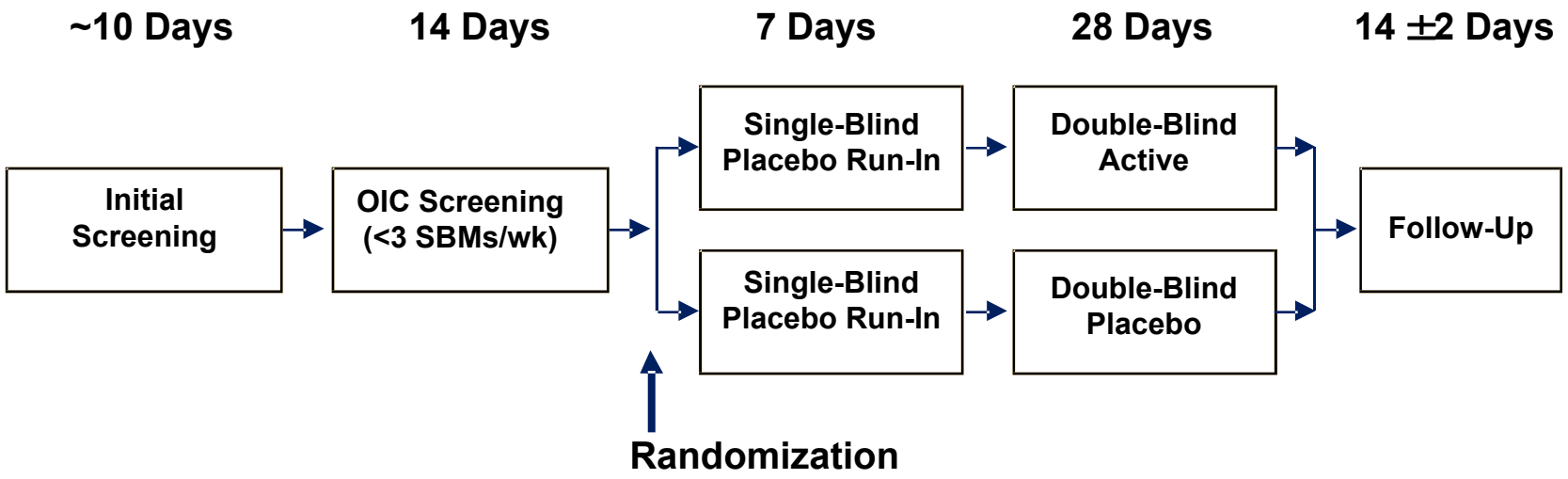
[3]Kurz A and Sessler DI. Opioid-induced bowel dysfunction: pathophysiology and potential new therapies. Drugs 63(7); 2003; 649-671

[4]DeHaven-Hudkins DL et al. The involvement of the u-opioid receptor in gastrointestinal pathophysiology: Therapeutic opportunities for antagonism at this receptor. Pharmacology & Therapeutics 117; 2008; 162-187

[5]Neumann et al. poster 27 presented at 18th Annual Clinical Meeting of the American Academy of Pain Management; September 27-30, 2007; Las Vegas, NV

[6]Eldon et al. poster 28 presented at 18th Annual Clinical Meeting of the American Academy of Pain Management; September 27-30, 2007; Las Vegas, NV

NKTR-118: Phase II Study 07-IN-NX003 Design



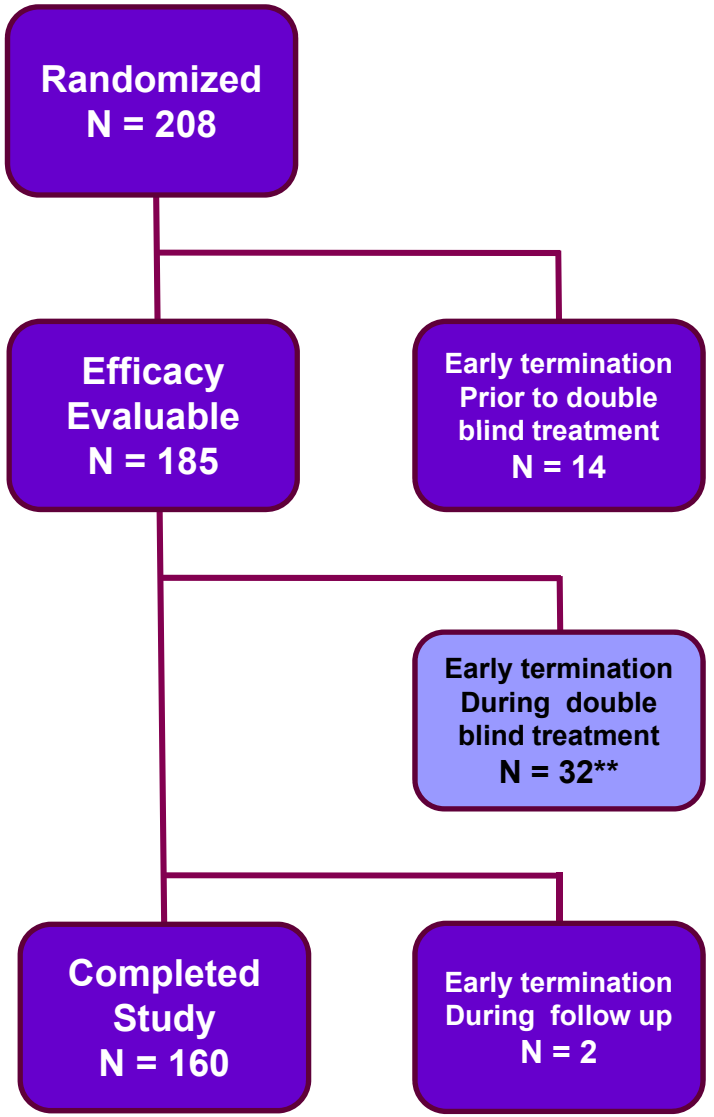
Daily oral dosing for 28 days

5, 25, and 50 mg QD cohorts (n=28 placebo and n=28 active patients planned per cohort) in sequence with an independent Dose Escalation Safety Committee review prior to dose escalation

Webster et al. Am J Gastroenterol 2009; 104 (Suppl 3) : S 466

Summary of Patient Demographics and Disposition (Phase II Study)

	5 mg QD		25 mg QD		50 mg QD		Total
	Pbo (N=36)	NKTR-118 (N=35)	Pbo (N=29)	NKTR-118 (N=31)	Pbo (N=39)	NKTR-118 (N=37)	N=207
Age (years)							
Mean (SD)	48.0 (12.2)	50.5 (12.7)	51.2 (12.8)	51.8 (11.1)	48.7 (10.2)	51.4 (11.4)	50.2 (11.7)
Sex							
Female	23 (63.9%)	22 (62.9%)	19 (65.5%)	16 (51.6%)	24 (61.5%)	25 (67.6%)	129 (62.3%)
Opioid Stratum							
>100 MEU*	23 (63.9%)	21 (60%)	14 (48.3%)	18 (58.1%)	19 (48.7%)	21 (56.8%)	116 (56%)

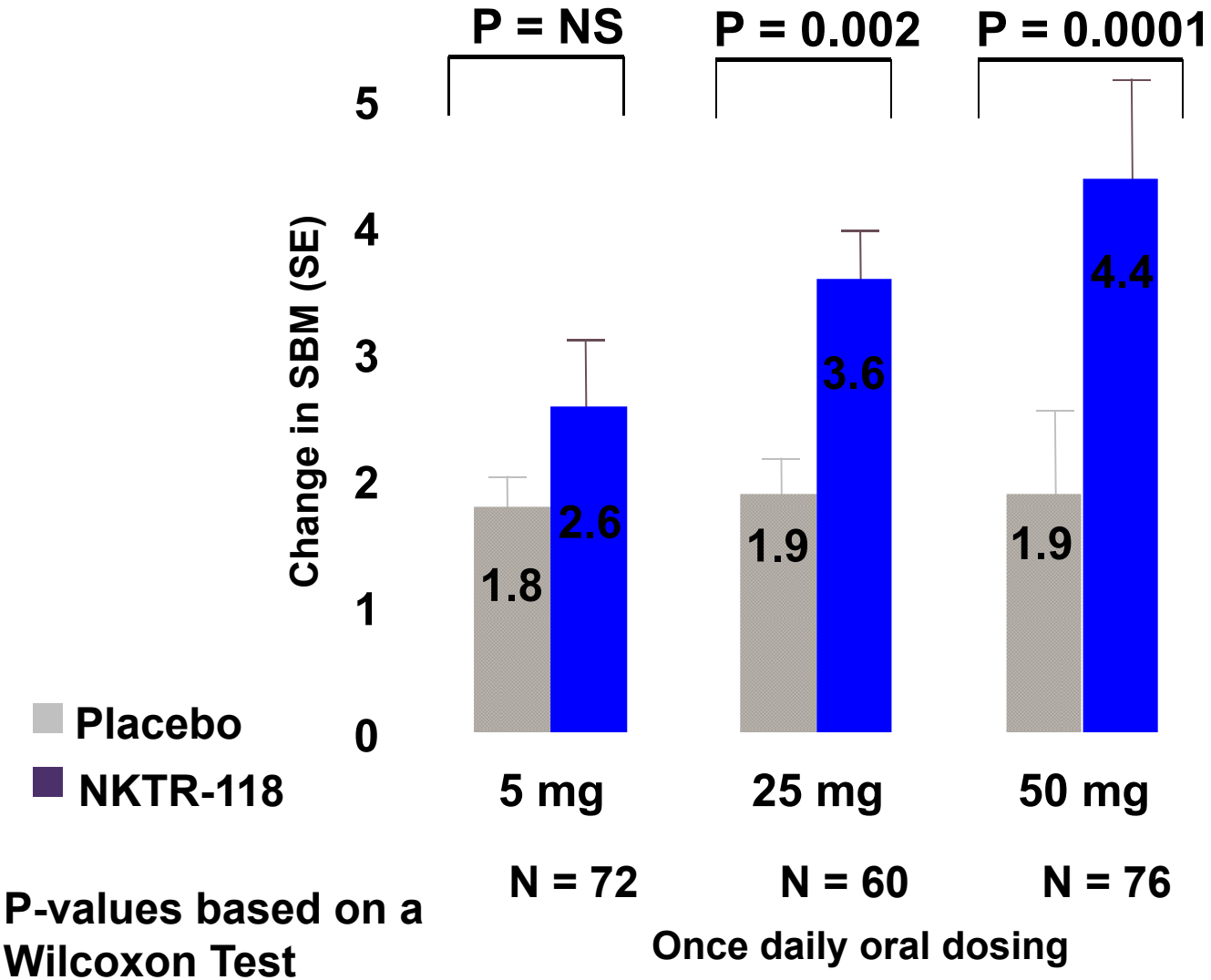


**Drop-outs During Double Blind Treatment			
	5 mg	25 mg	50 mg
PBO	5	0	6
NKTR-118	5	2	14

Webster et al. Am J Gastroenterol 2009; 104 (Suppl 3) : S 466

Phase II Study
Primary Efficacy Endpoint: Change from Baseline in Spontaneous Bowel Movements (SBMs/week)

Week 1 of Double Blind Treatment



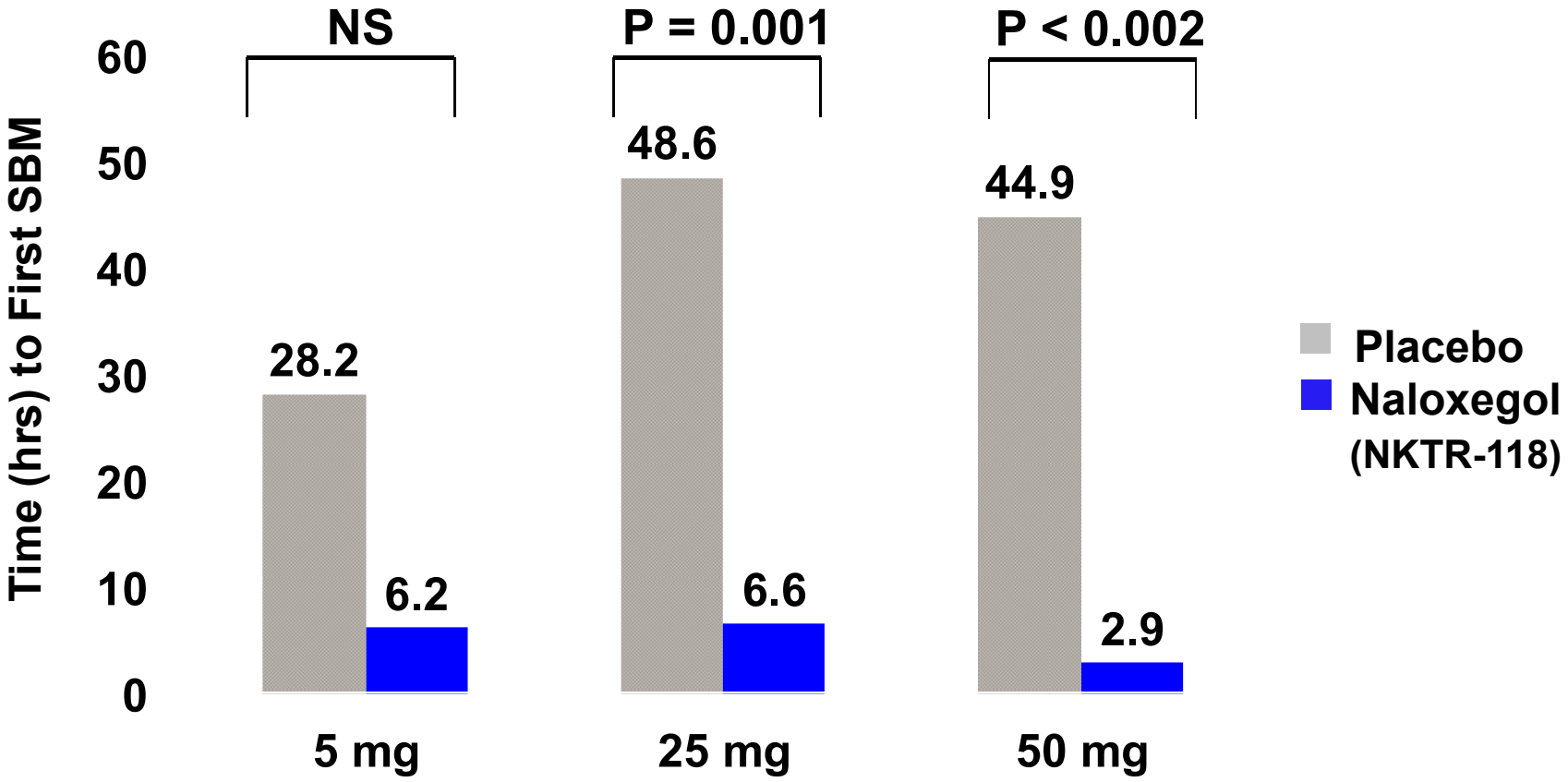
5 mg: 4.4 SBM/week
25 mg: 5.0 SBM/week
50 mg: 6.0 SBM/week

Significant over 4-wk treatment period for 25 mg (P=0.002) and 50 mg (P< 0.0001)

P-values based on a Wilcoxon Test

Webster et al. Am J Gastroenterol 2009; 104 (Suppl 3) : S 466

Phase II Study
Median Time (hrs) to First Spontaneous Bowel Movements



Webster et al. Am J Gastroenterol 2009; 104 (Suppl 3) : S 466

P-values based on a log rank test

Safety: Most Common Adverse Events (Phase II)

(>10%, any grade)

	5 mg QD		*25 mg QD*		*50 mg QD*	
% of Patients Reporting at Least 1 Adverse Event	Placebo (N=32)	NKTR-118 (N=33)	Placebo (N=27)	NKTR-118 (N=30)	Placebo (N=37)	NKTR-118 (N=35)
Abdominal Pain	3	3	7	30	0	17
Nausea	3	15	19	13	8	20
Diarrhea	16	15	4	13	5	31
Vomiting	6	0	4	13	5	11
Upper Abdominal Pain	0	18	4	10	5	29

- No treatment related SAEs at 5 or 25 mg/day, as assessed by investigator
- Total 3 SAEs NGL and 2 for placebo
- One patient hospitalized overnight for abdominal cramping at 50 mg/day (SAE)

Webster et al. Am J Gastroenterol 2009; 104 (Suppl 3) : S 466; adapted

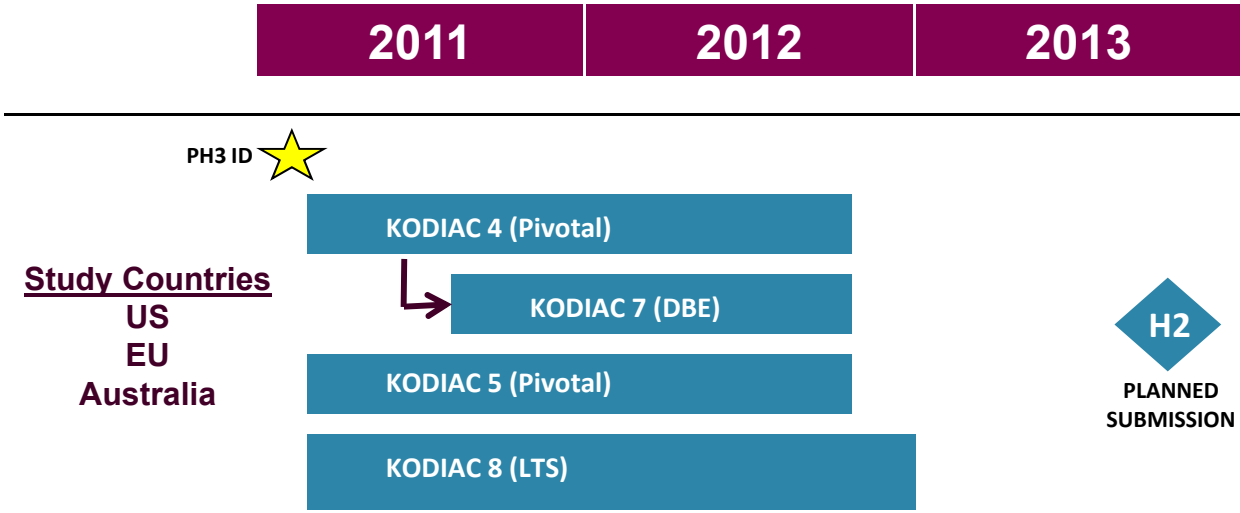
Summary of Key Outcomes in Phase II study

- Primary Endpoint
  - Statistically Significant difference versus placebo for 25 and 50 mg doses in change from Baseline in Spontaneous Bowel Movements (SBM) at week 1

- Secondary Safety Endpoints
  - Patient Pain Assesment
    - No statistically significant difference compared with placebo for any dose, as measure by daily NRS pain scores
  - Opioid Dosing Requirement
    - No statistically significant increase in mean daily opioid dose for 25 and 50 mg doses compared with placebo
  - Adjudicated Opioid withdrawal events (MSOWS)
    - None for any NGL dose

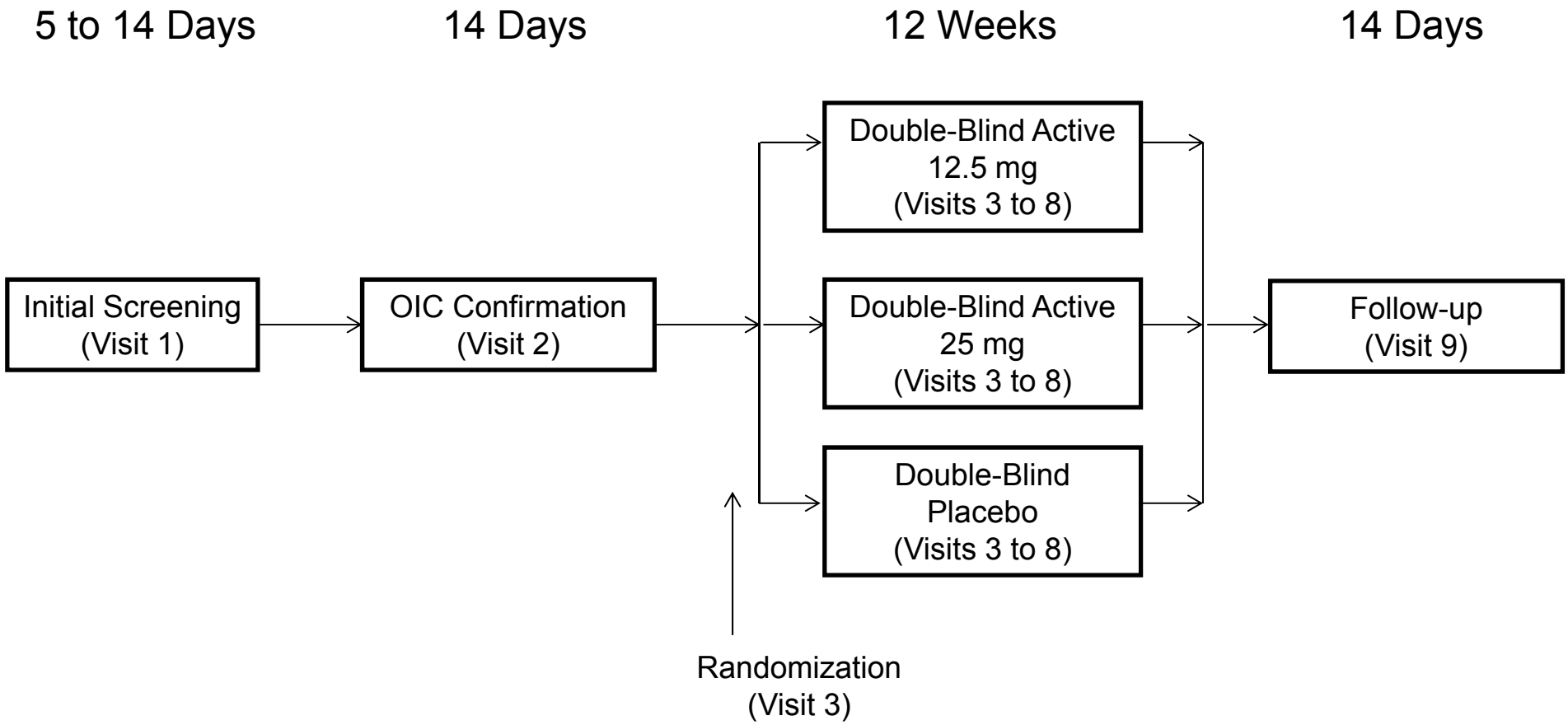
- Safety Findings
  - Most common side effects GI in nature

Naloxegol core KODIAC Phase III Clinical Program



Primary Endpoint -	**Percentage of responders over 12 weeks** **(Responder: ≥3 SBMs/week with improvement of ≥ 1 over baseline for 9 out of 12 weeks and 3 out of the last 4 weeks)**
Key Secondary Endpoints -	**1) Laxative Inadequate Responders (LIR) subgroup % responders over 12 weeks** **2) Median time (hours) to first post dose laxation** **3) Mean number of days/week with SBM**

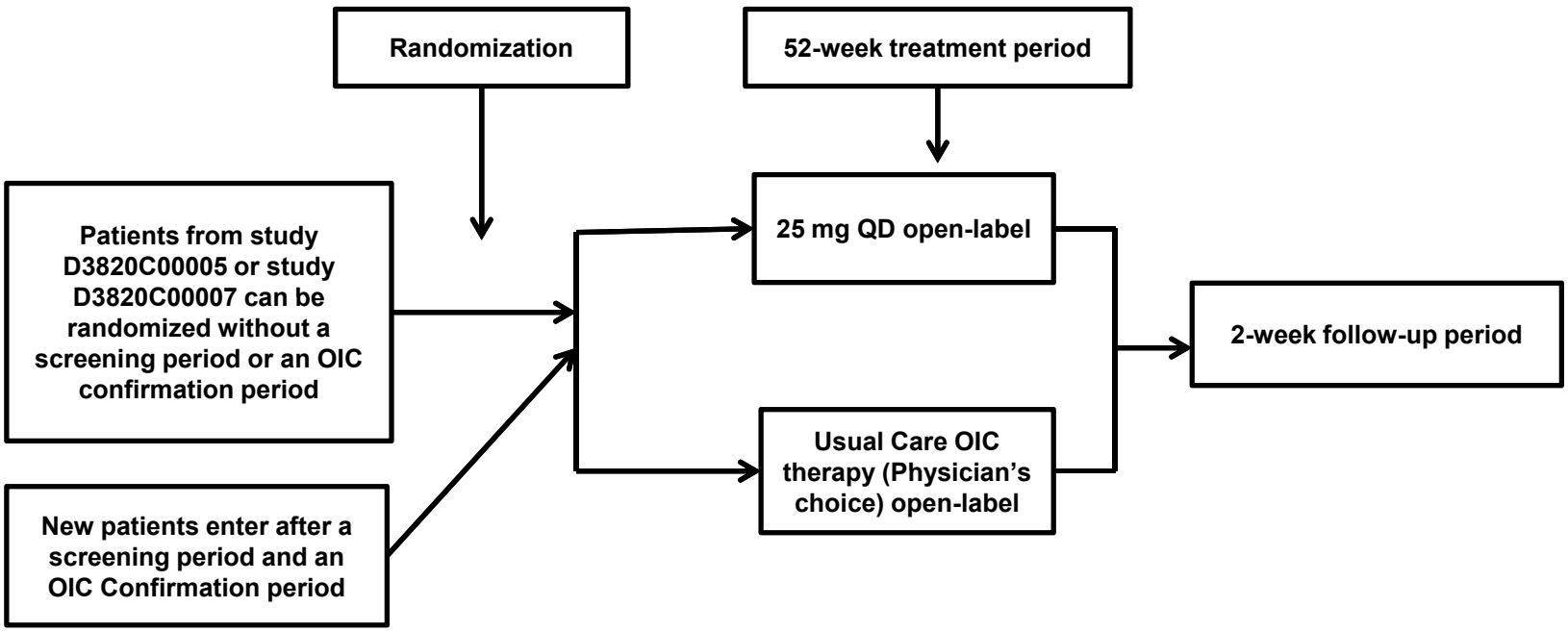
Phase III (Study 4 and 5) Design



N= 210/arm

Adapted from Clinical trial.gov

Phase III Long Term Safety Study (8) Design



2:1 randomization; NGL 560 patients, Usual Care 280 patients (approximate)

Adapted from Clinical trial.gov

Naloxegol
Key Facts

Summary Key Facts

- Naloxegol is a once a day oral, peripherally acting, μ-opioid receptor antagonist under investigation for the treatment of Opioid-Induced Constipation (OIC).

- OIC may occur when opioids bind to opioid receptors in gastrointestinal tract causing decreased GI motility.

- Phase II results indicate naloxegol at doses of 25 and 50 mg/day:
  - met the primary efficacy endpoint
  - was not associated with changes in opioid-mediated analgesia compared with placebo, while
  - most common side effects were GI related.

- Phase III clinical development for naloxegol started in March 2011. We anticipate having high level efficacy results in 4Q 2012.

Summary Key Facts

- Global opioid market:
  - Of the $14.8 billion global opioid market, five markets account for ~80% of total unit volume: US (49%), UK (14%), Germany (5%), Canada (5), France (5%).
  - In these five markets there are 69 million patients taking opioids for chronic pain (>30 days treatment). For these chronic pain opioid users, OIC is the most common side effect.
  - Approximately 40–50% (28-35 million) patients taking opioids for long-term pain develop constipation.
  - About 40–50% (11-18 million) of those OIC sufferers achieve the desired treatment outcomes with current options that include OTC and Rx laxatives.

Naloxegol

Q&A