2018 CPDD Meeting
Wednesday, June 13
1:30 pm-1:45 pm (Pain Session)

Assessment of Drug Abuse-Related Events with MADDERS in SUMMIT-07: A Phase-3 Study of NKTR-181 in Patients With Moderate to Severe Chronic Low-Back Pain

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Presenter Disclosure Information

Dr. Ryan Lanier, Analgesic Solutions

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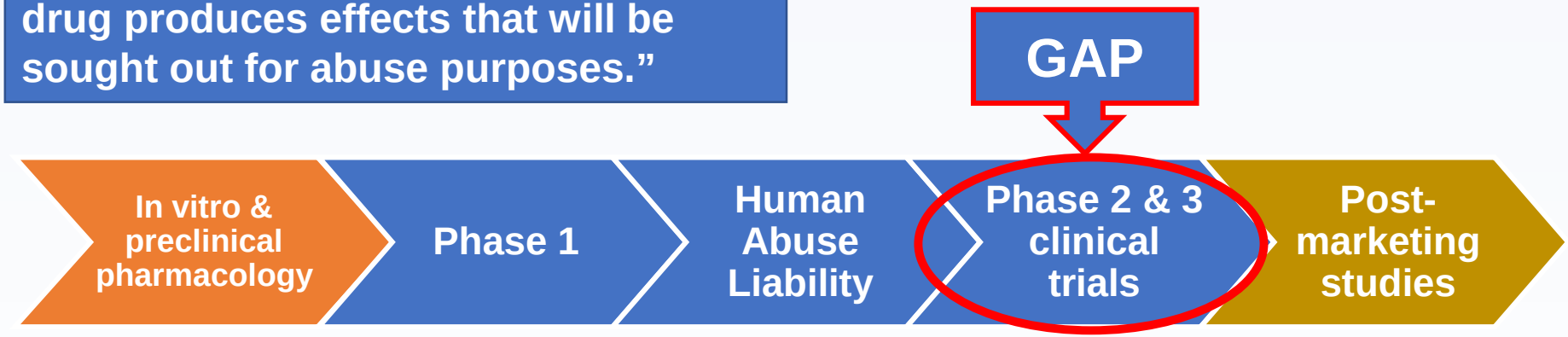
Assessment of Abuse Potential in Clinical Trials

FDA Guidance 2017:
"All clinical safety and efficacy studies should be evaluated for CNS-related AEs that may suggest the test drug produces effects that will be sought out for abuse purposes."

- **Traditional methods of assessing abuse potential in clinical trials are inadequate and can cause misclassification of events**



- **These trials most closely approximate the use of study drug post-approval and can provide valuable information in target patient populations**
- **Identifying abuse potential requires a prospective and systematic approach that captures sufficient data to distinguish signals of abuse potential from other plausible explanations**

Misuse, Abuse and Diversion Drug Event Reporting System (MADDERS®)

- **MADDERS was developed to fill the gap based on recommendations made by ACTTION, a public-private partnership with FDA[1-3]**
- **It is a system to standardize:**
  - **Identification of *potentially abuse-related* events**
  - **Collection of relevant information in "real time"**
  - **Formal classification of events based on consensus terminology**
  - **Tabulating and reporting events**
- **MADDERS also probes for events at study end not triggered during the study**
- **Used in 15 clinical trials to date; opioids and cannabinioids, adult and pediatric populations, pain and non-pain indications**
- **This is the first time MADDERS data have been presented from a study investigating an opioid**

1. Smith SN et al. *Pain.* 2013; 2. Smith SN et al. *J Pain.* 2017; 3. Treister R et al. *Am J Addict.* 2016.

The MADDERS System

1

Identify Triggering Event

Trained staff identifies a triggering event, either an Adverse Event (AE) or Drug Accountability Discrepancy Event (DADE).

2

Interview Subject

Supplemental AE or DADE Form is completed by staff through a guided interview with the subject. Event Narrative is written.
PI classifies event.

3

Medication Use Survey

<u>All</u> subjects complete the Medication Use Survey upon completion of the study to ensure all events are captured.

4

Adjudication & Classification

Adjudicators review subject & event-related information to come to a consensus classification, captured in a Final Classification Form.

5

Statistical Analysis & Reporting

Data are analyzed to produce TLFs, and a Final MADDERS Study Report is written for the Sponsor to include in CSR.

Triggeri

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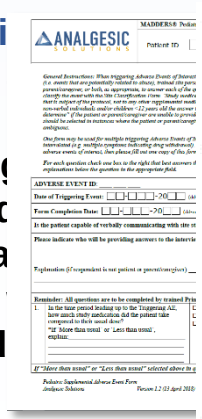
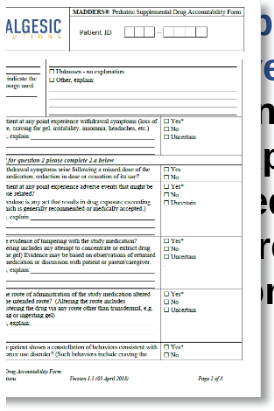
- **Thoug suicid**
- **Thera**
- **Drug withd**



Event Category:
*Select **ONE** event category that best describes the event.*

Supplemental Designations: *Place an 'x' in the box(es) that apply. You may select more than 1 if it applies. Those boxes that are grey cannot be selected for that category.*

EVENT CATEGORIES	Tampering	Withdrawal	Addiction-related Indicator	Diversion	Overdose
☐ Misuse-event Indicator	☐	☐		☐	☐
☐ Abuse-event Indicator	☐	☐	☐	☐	☐
☐ Suicide-related Event	☐	☐	☐	☐	☐
☐ Therapeutic Error	☐	☐			☐
☐ None of the Above	☐	☐	☐	☐	☐
☐ Unknown	☐	☐	☐	☐	☐



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MADDERS: Adjudication and Classification of Events

- **Panel of 2-4 adjudicators reviews case documentation and classifies events according to consensus terminology (as published in Smith et al, *Pain*, 2013)**
- **Events are classified into 1 of 6 primary Event Categories, and any Supplemental Designations that apply**
  - **Could be none, or ≥1 Supplemental Designation applied to each event**

Event Category: *Select **ONE** event category that best describes the event.*			***Supplemental Designations:*** *Place an 'x' in the box(es) that apply. You may select more than 1 if it applies. Those boxes that are grey cannot be selected for that category.*				
			Tampering	Withdrawal	Addiction-related Indicator	Diversion	Overdose
EVENT CATEGORIES	☐	**Misuse-event Indicator**	☐	☐		☐	☐
	☐	**Abuse-event Indicator**	☐	☐	☐	☐	☐
	☐	**Suicide-related Event**	☐	☐	☐	☐	☐
	☐	**Therapeutic Error**	☐	☐			☐
	☐	**None of the Above**	☐	☐	☐	☐	☐
	☐	**Unknown**	☐	☐	☐	☐	☐

ACTTION Consensus Terminology and Definitions

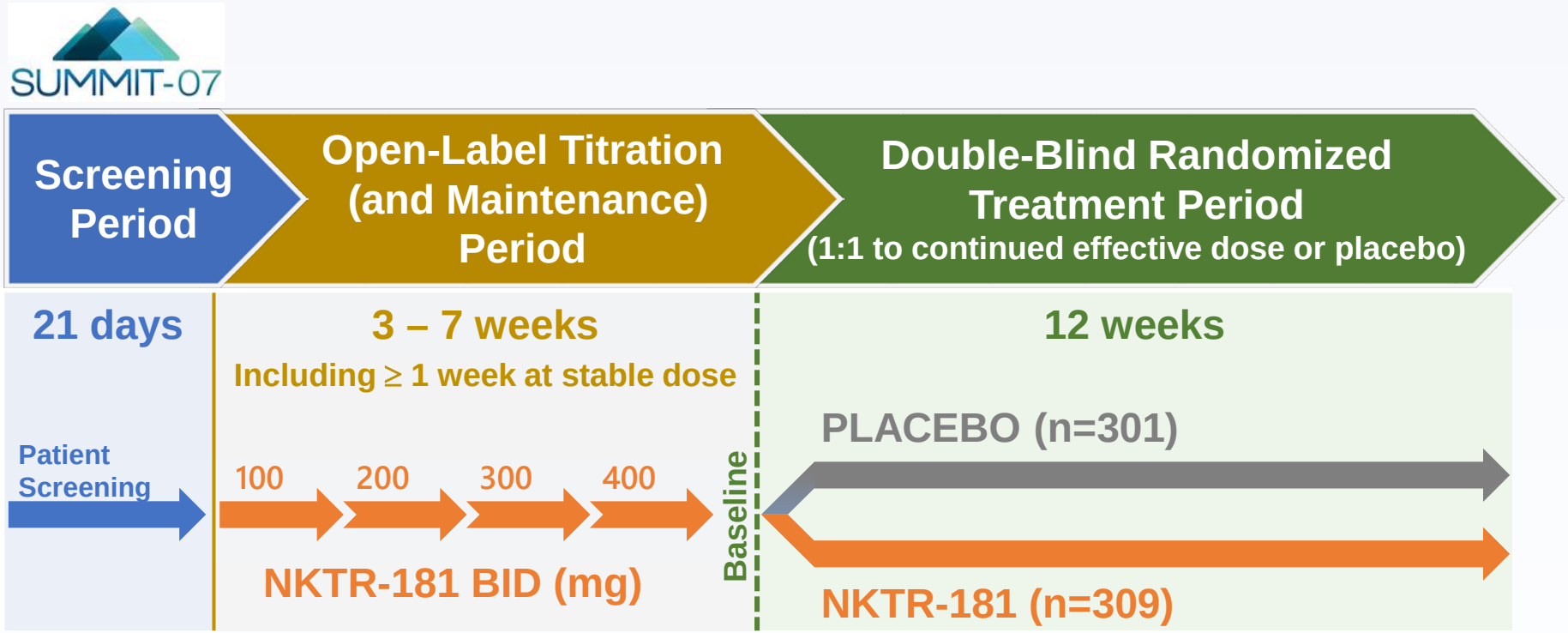
Primary Classifications		Supplemental Designations	
Misuse	Intentional therapeutic use of drug in an inappropriate way	Tampering	Inappropriate manipulation of drug
Abuse	Intentional nontherapeutic use of drug, even once, for psychotropic effect	Withdrawal	Syndrome due to decline in blood concentration of drug or administration of antagonist
Suicide	Self-injurious behavior associated with intent to die	Addiction	Constellation of behaviors including craving, difficulties controlling drug use, use despite harm
Therapeutic error	Unintentional mistake in a therapeutic regimen	Diversion	Transferring drug to unlawful possession
None of the above	Sufficient information to determine none of the previous categories apply	Overdose	Act resulting in excessive exposure
Unknown	Insufficient information exists to determine which category applies		

Smith SM et al. *Pain*. 2013;154(11):2287-9.

NKTR-181

- **NKTR-181 is a new molecular entity, full mu-opioid receptor agonist in clinical development for the treatment of chronic low back pain in adult patients new to opioid therapy**
- **Its unique physicochemical properties result in a relatively slow rate of entry into the central nervous system (CNS) relative to conventional opioids, and there is no known chemical or physical method to alter NKTR-181 to increase its CNS entry speed**
- **Because rapid entry into the CNS is an important factor that makes an opioid attractive for abuse, NKTR-181 may have less potential for abuse, without sacrificing clinically meaningful analgesia, relative to conventional opioids**
- **In SUMMIT-07, a Phase 3 RCT, NKTR-181 administered at 100 mg to 400 mg twice daily for 12 weeks produced clinically meaningful, highly statistically significant analgesia in patients with moderate-to-severe chronic low-back pain**
- **MADDERS was used to prospectively evaluate *potentially abuse-related events* in SUMMIT-07**

Phase 3 SUMMIT-07 Design: Enriched Enrollment Randomized Withdrawal (EERW) Study



- **Patient population: moderate-to-severe chronic low back pain (opioid naïve: ≤ 10mg MSE in 14 days prior to signing consent)**

Demographics and Baseline Characteristics

Characteristic		Titration Period	Randomization Period	
		Total (N = 1189)	NKTR-181 (N = 309)	Placebo (N = 301)
Age (years)	Mean (SD)	51.0 (12.61)	52.0 (12.67)	50.7 (12.49)
	(Min, Max)	(19, 75)	(20, 74)	(20, 75)
Sex, n (%)	Male	495 (41.6)	122 (39.5)	131 (43.5)
	Female	694 (58.4)	187 (60.5)	170 (56.5)
Race, n (%)	Black or African American	357 (30.0)	95 (30.7)	93 (30.9)
	White	792 (66.6)	205 (66.3)	196 (65.1)
	Others	40 (3.4)	9 (2.9)	12 (4.0)
BMI (kg/m^2)	Mean (SD)	30.4 (5.2)	30.5 (5.4)	30.5 (5.1)
Time from LBP Onset (years)	Mean (SD)	13.1 (10.1)	13.3 (10.0)	13.0 (9.8)

BMI = Body Mass Index
LBP = Low Back Pain

MADDERS Results: Primary Classification of Events

	Titration Period	Randomization Period	
	Total (N = 1189)	NKTR-181 (N=309)	Placebo (N =301)
All subjects with adjudicated events, n (%)	48 (4.0)	17 (5.5)	14 (4.7)
Abuse, n (%)	3 (0.3)	0	2 (0.7)
Misuse, n (%)	9 (0.8)	3 (1.0)	3 (1.0)
Suicide-related, n (%)	0	0	0
Therapeutic error, n (%)	6 (0.5)	3 (1.0)	0
None of the above, n (%)	28 (2.4)	9 (2.9)	9 (3.0)
Unknown, n (%)	3 (0.3)	3 (1.0)	1 (0.3)

- **All 5 events adjudicated as possible *Abuse* were from triggering drug accountability discrepancy events involving missing pills (none from AEs)**

MADDERS Results: Supplemental Designations

	Titration Period	Randomization Period	
	Total (N = 1189)	NKTR-181 (N = 309)	Placebo (N = 301)
All subjects with adjudicated events, n (%)	48 (4.0)	17 (5.5)	14 (4.7)
Subjects with an event that received a supplemental designation, n (%)	27 (2.3)	10 (3.2)	11 (3.6)
Addiction-related Behavior, n (%)	0	0	0
Diversion, n (%)	2 (0.2)	1 (0.3)	0
Overdose, n (%)	1 (0.1)	0	0
Tampering, n (%)	1 (0.1)	0	0
Withdrawal, n (%)	23 (1.9)	9 (2.9)	11 (3.6)

- Note: Adjudicators were not required to select a Supplemental Designation for each event, but could choose ≥ 1 per event if applicable

MADDERS Medication Use Survey Results

- **No discernible difference was detected in responses between NKTR-181 and placebo treated groups**
- **Very few (~ 5% per group) subjects reported taking more medication than instructed either unintentionally (Therapeutic Error) or intentionally (Misuse) for a therapeutic purpose**
- **Withdrawal symptoms were reported by 7 (2.9%) and 5 (2.1%) subjects in the NKTR-181 and placebo groups, respectively**
- **No subjects acknowledged abusing the drug, being addicted to it, changing the route of administration or using it to attempt suicide**
  - **This is common for self-reported survey instruments**
  - **The main role of this survey is to complement the primary event-driven approach of MADDERS**
  - **Values are based on subjects completing Medication Use Survey (N = 243 for NKTR-181 and N = 236 for placebo)**

MADDERS Results Summary

- **Only 5 of the 1189 (0.4%) subjects had an event classified by the adjudication committee as possible *Abuse***
  - **The 2 suspected cases of *Abuse* during Randomization occurred in placebo-treated subjects (i.e., "background noise")**
- **43 of the 1189 (2.9%) subjects had an event classified as *Withdrawal***
- **No events were classified as *Suicide-related* or *Addiction-related Behavior***
  - **Very few events of possible *Diversion*, *Overdose*, or *Tampering***
- **The incidence of events was low overall, and similar between the NKTR-181 and placebo treated groups during Randomization**
- **These results are consistent with other measures in SUMMIT-07 and studies suggesting low abuse potential of NKTR-181**

SUMMIT-07 MADDERS Conclusions

- **MADDERS was successfully implemented to evaluate potentially abuse-related events in this Phase 3 clinical trial to evaluate the efficacy, safety, and tolerability of NKTR-181 in opioid-naïve subjects with chronic low back pain**
  - **MADDERS revealed no discernible evidence of an abuse potential signal or risk of diversion or addiction with the use of NKTR-181**
- **A certain level of "background noise" in identifying abuse-related signals in clinical trials is expected, as shown by 2 adjudicated events of Abuse in placebo-treated subjects**
  - **MADDERS may reduce that level through systematic collection of subject and event-related data and independent review by adjudicators**
- **MADDERS is the only system currently available for prospectively and systematically classifying and quantifying potentially abuse-related events in clinical trials**

Thank you!

Thanks to my co-authors, all those who helped with this study and presentation, and the audience.

Any questions?

ANALGESIC SOLUTIONS