NEKTAR®

NKTR-181

Oral Human Abuse Potential Study Topline Results

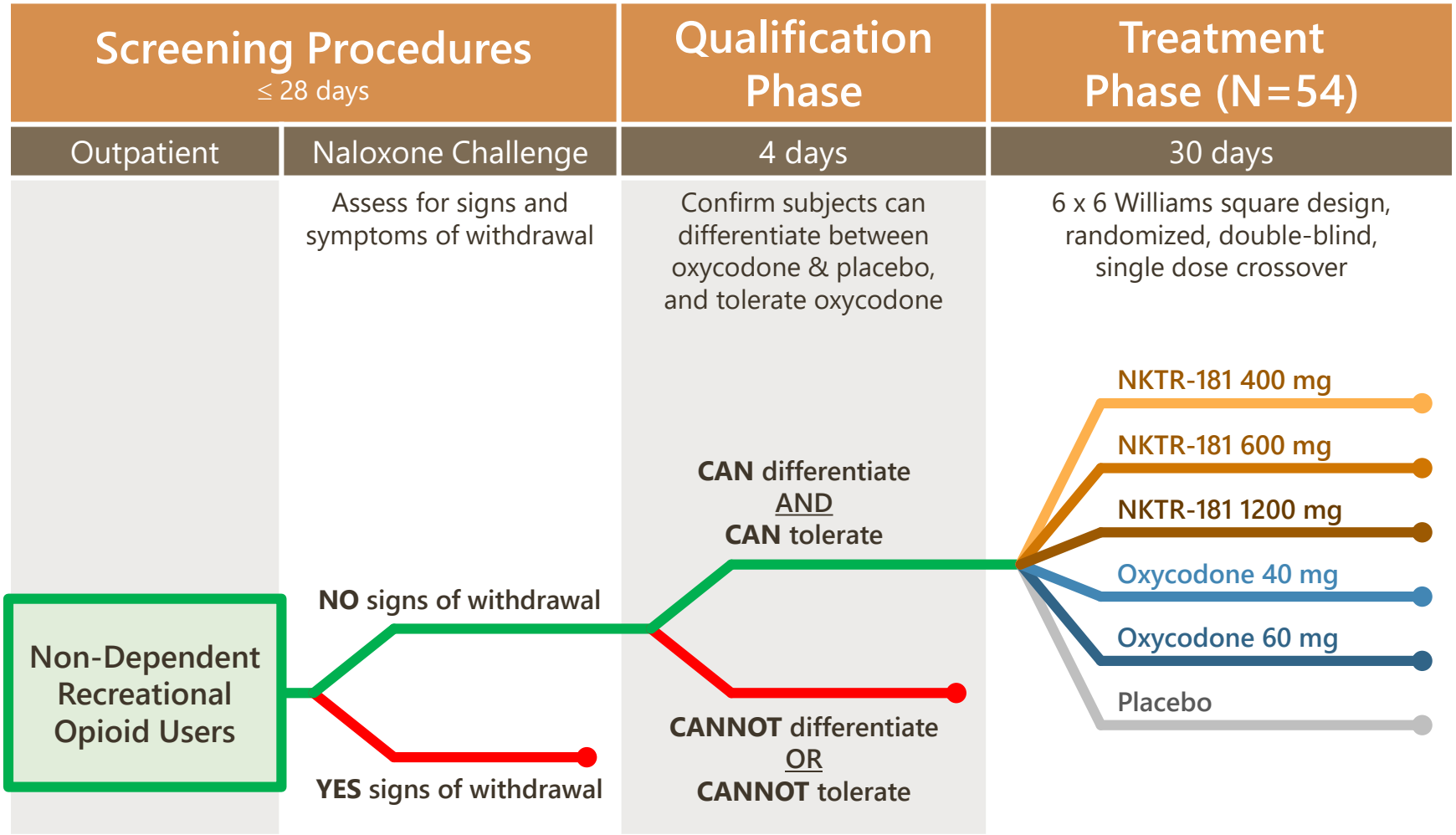
Investor Call

July 18, 2017

Goals of Oral Human Abuse Potential (HAP) Study

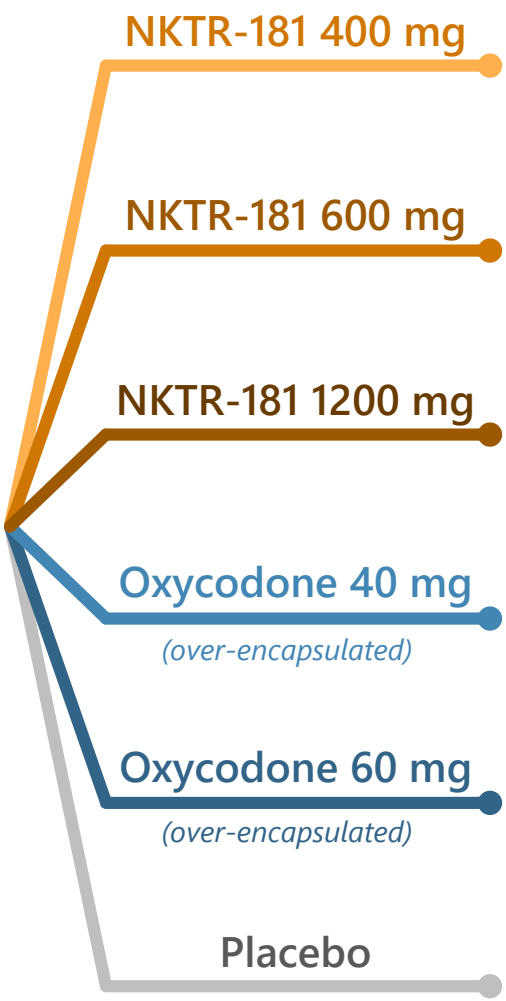
- Confirm that NKTR-181 has significantly less abuse potential than a Schedule II opioid
- Confirm that the likeability for NKTR-181 during the critical early time period after dosing is dramatically lower than a Schedule II opioid
- Confirm that the likeability time profile for NKTR-181 is consistent with slow brain-entry kinetics
- Demonstrate that a supratherapeutic dose of NKTR-181 (1200 mg) differentiates from a therapeutic dose of oxycodone (60 mg)
- Study contributes to data package for assessment of abuse potential and satisfies FDA guidelines for NDA submissions of CNS active new molecular entities (NMEs)
  - Supports rationale for less restrictive scheduling (CIII or CIV)

Design of Human Abuse Potential (HAP) Study



Study powered to detect a relative peak (Emax) Drug Liking score difference between oxycodone 60 mg and NKTR-181 1200 mg

Oral Tablet Dosages Evaluated in Human Abuse Potential (HAP) Study



- Top therapeutic dose from SUMMIT-07 Efficacy Study, which successfully demonstrated efficacy in a dose range of 100 – 400 mg
- Evaluated in first HAP study (May 2013), included to re-confirm results

- Top dose from SUMMIT-08 Long-Term Safety Study
- 1.5- to 6-times greater than the efficacious dose range established in the SUMMIT-07 Efficacy Study

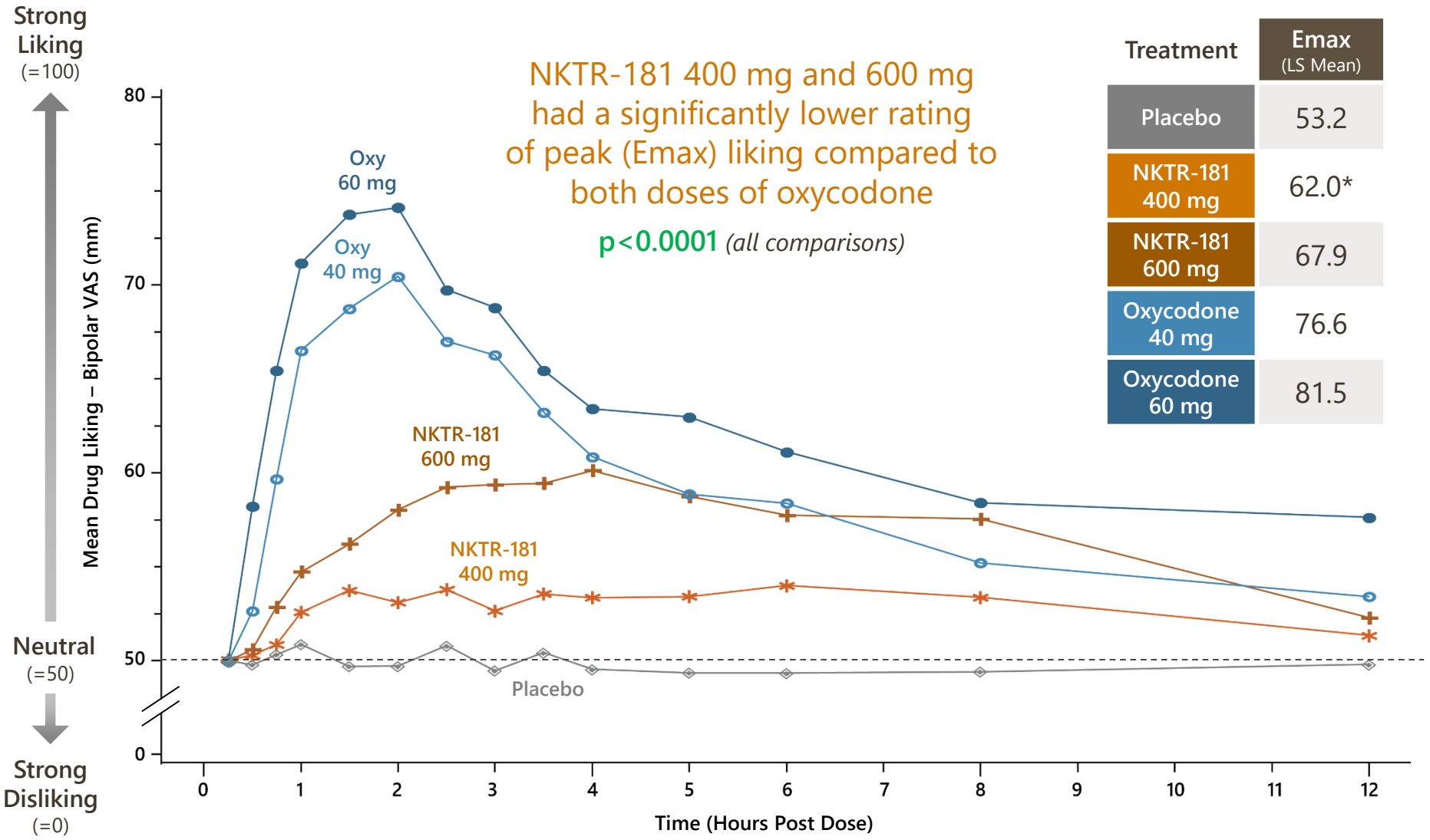
- "Supratherapeutic Dose" of NKTR-181
- 3- to 12-times greater than the efficacious dose range established in the SUMMIT-07 Efficacy Study

- Evaluated in first HAP study (May 2013)
- Moderate therapeutic dose of oxycodone

- High dose comparator to NKTR-181 supratherapeutic dose
- High therapeutic dose of oxycodone

Primary Endpoint – Drug Liking

NKTR-181 400 mg & 600 mg Dose Comparison to Oxycodone



NKTR-181 400 mg and 600 mg had a significantly lower rating of peak (Emax) liking compared to both doses of oxycodone

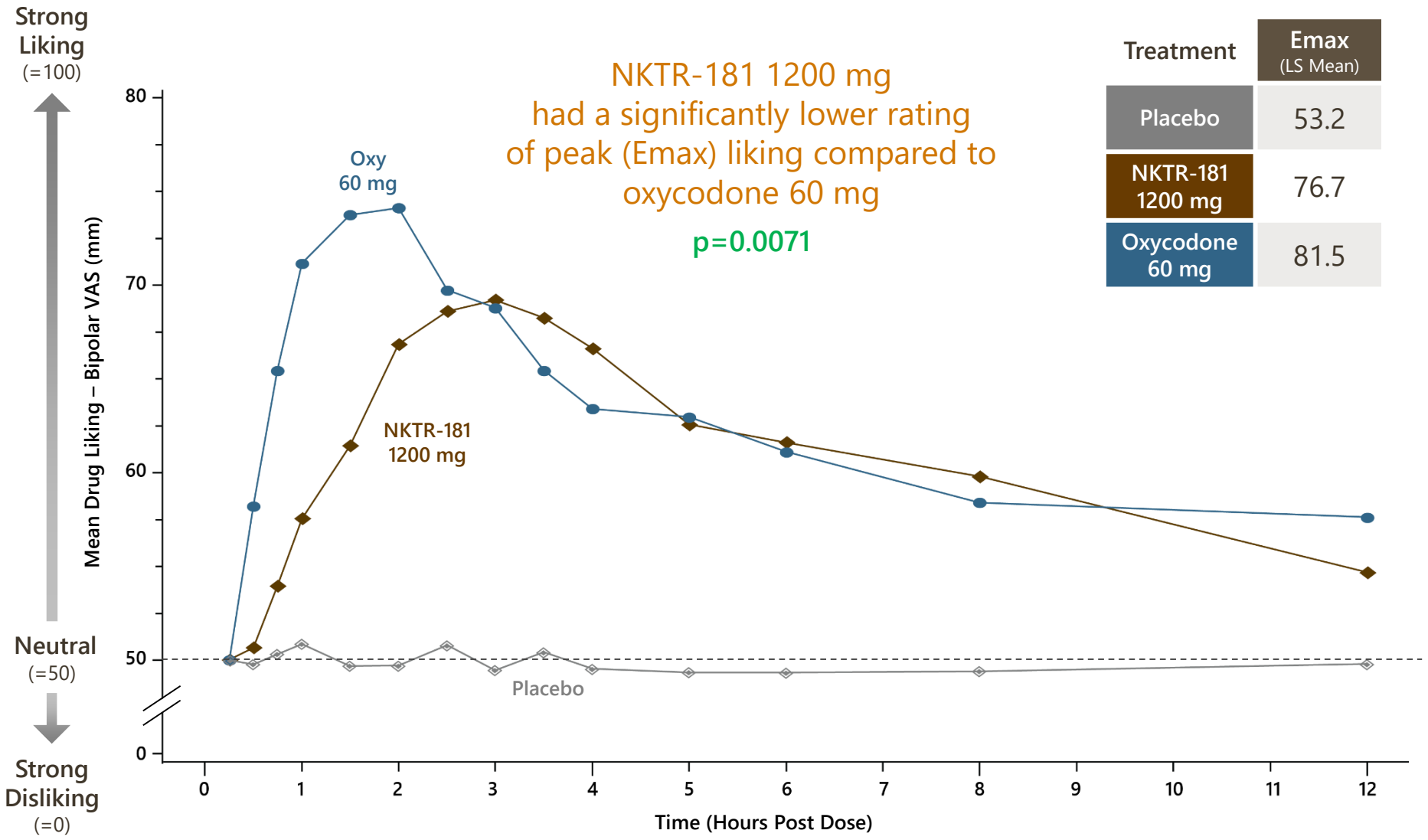
$p<0.0001$ *(all comparisons)*

Treatment	Emax (LS Mean)
Placebo	53.2
NKTR-181 400 mg	62.0*
NKTR-181 600 mg	67.9
Oxycodone 40 mg	76.6
Oxycodone 60 mg	81.5

*The peak liking score for NKTR-181 400 mg oral tablet confirmed the same peak liking score for NKTR-181 400 mg oral solution evaluated in the company's prior HAP study (62.0 vs 62.3**).
** Webster et al.; Human Abuse Potential of the New Opioid Analgesic Molecule NKTR-181 Compared with Oxycodone. Pain Med 2017 pnw344. doi: 10.1093/pm/pnw344

Primary Endpoint – Drug Liking

NKTR-181 Supratherapeutic Dose (3-12x the Efficacious Dose Range in SUMMIT-07) Comparison to Oxycodone 60 mg



NKTR-181 1200 mg had a significantly lower rating of peak (Emax) liking compared to oxycodone 60 mg

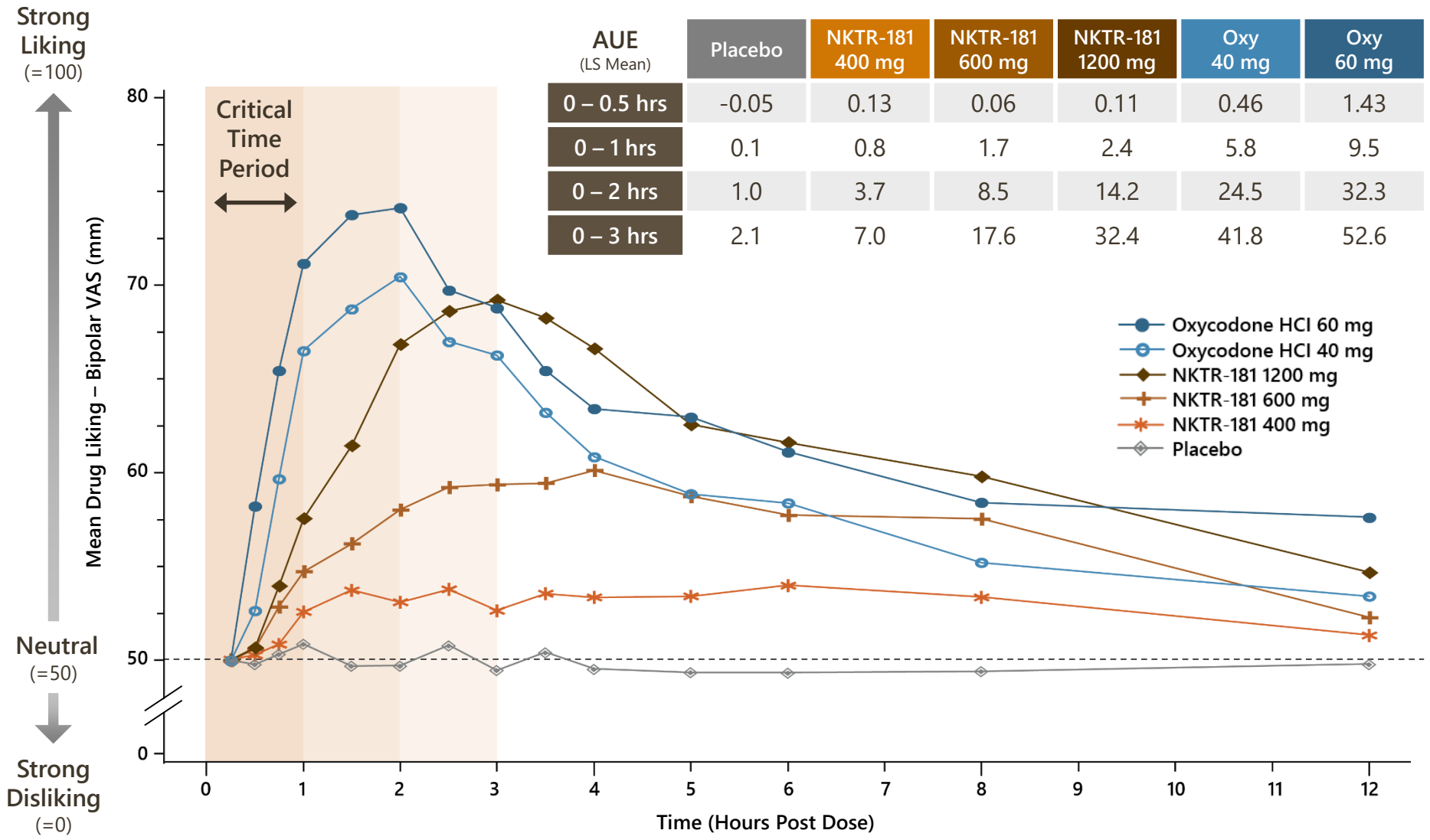
p=0.0071

Treatment	Emax (LS Mean)
Placebo	53.2
NKTR-181 1200 mg	76.7
Oxycodone 60 mg	81.5

Key Secondary Endpoint:

Area Under Effect (AUE) for Mean Drug Liking at 0.5, 1, 2, & 3 Hours Post-Dose

AUE (LS Mean)	Placebo	NKTR-181 400 mg	NKTR-181 600 mg	NKTR-181 1200 mg	Oxy 40 mg	Oxy 60 mg
0 – 0.5 hrs	-0.05	0.13	0.06	0.11	0.46	1.43
0 – 1 hrs	0.1	0.8	1.7	2.4	5.8	9.5
0 – 2 hrs	1.0	3.7	8.5	14.2	24.5	32.3
0 – 3 hrs	2.1	7.0	17.6	32.4	41.8	52.6



N=54

Key Secondary Endpoint:
Area Under Effect (AUE) for Mean Drug Liking at 0.5, 1, 2, & 3 Hours Post-Dose

- All doses of NKTR-181 tested are significantly less likeable than oxycodone in first 3 hours post-dose

"Supratherapeutic" Dose:
3-12x Greater than Efficacious Doses in SUMMIT-07

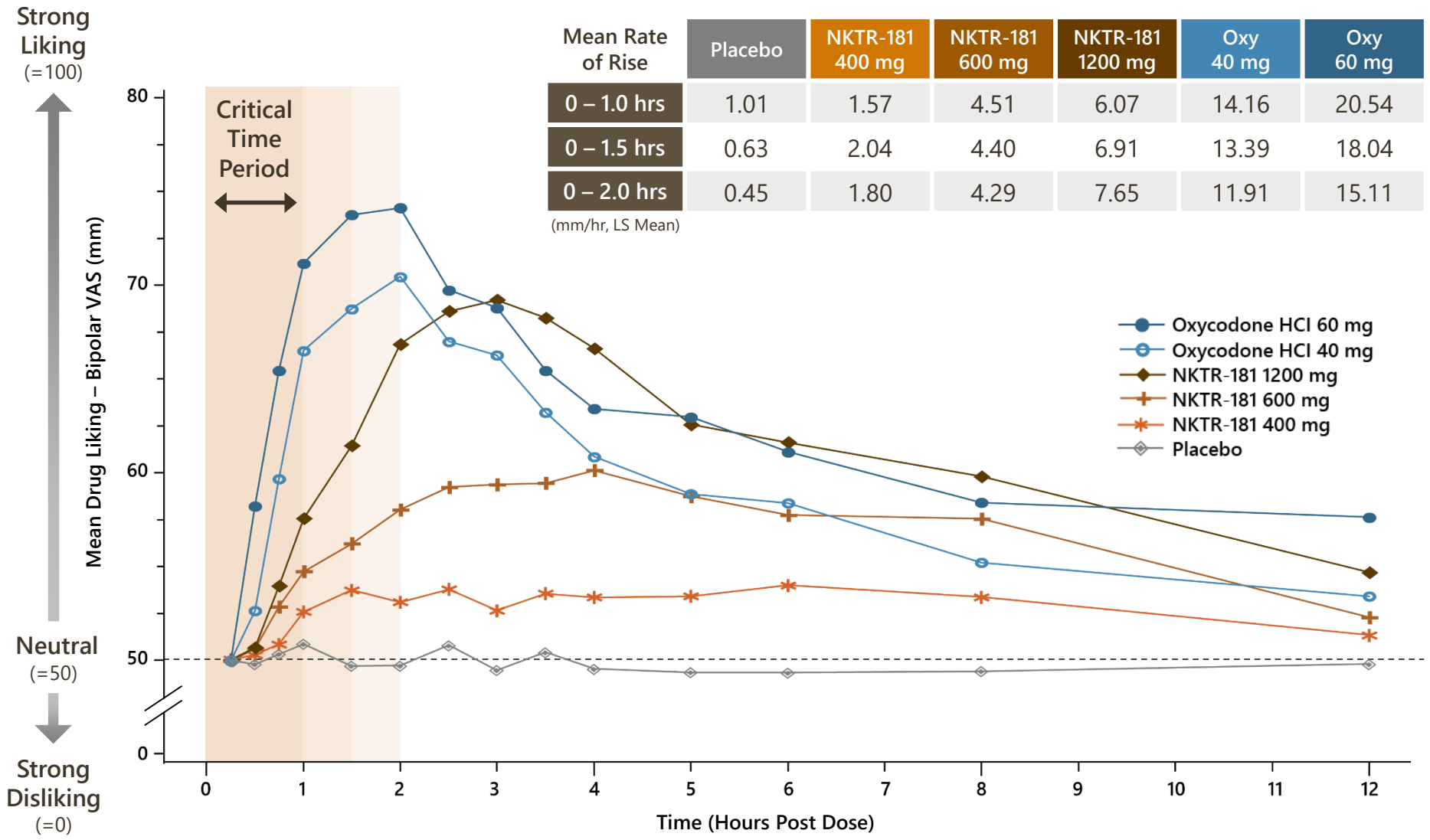
Area Under Effect (AUE) (LS Mean)	Placebo (N=54)	NKTR-181 400 mg (N=54)	NKTR-181 600 mg (N=54)	NKTR-181 1200 mg (N=54)	Oxycodone 40 mg (N=54)	Oxycodone 60 mg (N=54)
0 – 0.5 hrs	-0.05	0.13	0.06	0.11	0.46	1.43
vs. Oxy 40		p=0.0035	p=0.0100	p=0.0074		
vs. Oxy 60		p<0.0001	p<0.0001	p<0.0001		
0 – 1.0 hrs	0.1	0.8	1.7	2.4	5.8	9.5
vs. Oxy 40		p<0.0001	p<0.0001	p=0.0002		
vs. Oxy 60		p<0.0001	p<0.0001	p<0.0001		
0 – 2.0 hrs	1.0	3.7	8.5	14.2	24.5	32.3
vs. Oxy 40		p<0.0001	p<0.0001	p=0.0010		
vs. Oxy 60		p<0.0001	p<0.0001	p<0.0001		
0 – 3.0 hrs	2.1	7.0	17.6	32.4	41.8	52.6
vs. Oxy 40		p<0.0001	p<0.0001	p=0.0396		
vs. Oxy 60		p<0.0001	p<0.0001	p=0.0003		

Mean Rate of Rise:

Steepness of Drug Liking Response of Oxycodone Compared to NKTR-181

Mean Rate of Rise	Placebo	NKTR-181 400 mg	NKTR-181 600 mg	NKTR-181 1200 mg	Oxy 40 mg	Oxy 60 mg
0 – 1.0 hrs	1.01	1.57	4.51	6.07	14.16	20.54
0 – 1.5 hrs	0.63	2.04	4.40	6.91	13.39	18.04
0 – 2.0 hrs	0.45	1.80	4.29	7.65	11.91	15.11

(mm/hr, LS Mean)



Post-hoc Analysis. N=54.

Mean Rate of Rise:
Steepness of Drug Liking Response of Oxycodone Compared to NKTR-181

- Onset of drug liking is significantly steeper with oxycodone as compared to all doses of NKTR-181 in the first 2 hours

"Supratherapeutic" Dose:
3-12x Greater than Efficacious Doses in SUMMIT-07

Mean Rate of Rise (mm/hr, LS Mean)	Placebo (N=54)	NKTR-181 400 mg (N=54)	NKTR-181 600 mg (N=54)	NKTR-181 1200 mg (N=54)	Oxycodone 40 mg (N=54)	Oxycodone 60 mg (N=54)
0 – 1.0 hrs	1.01	1.57	4.51	6.07	14.16	20.54
vs. Oxy 40		p<0.0001	p<0.0001	p<0.0001		
vs. Oxy 60		p<0.0001	p<0.0001	p<0.0001		
0 – 1.5 hrs	0.63	2.04	4.40	6.91	13.39	18.04
vs. Oxy 40		p<0.0001	p<0.0001	p<0.0001		
vs. Oxy 60		p<0.0001	p<0.0001	p<0.0001		
0 – 2.0 hrs	0.45	1.80	4.29	7.65	11.91	15.11
vs. Oxy 40		p<0.0001	p<0.0001	p=0.0032		
vs. Oxy 60		p<0.0001	p<0.0001	p<0.0001		

Post-hoc Analysis

Key Secondary Endpoints:
Drug High and Take Drug Again

Drug High:

- NKTR-181 400 mg had significantly lower ratings of peak (Emax) Drug High compared to both oxycodone 40 mg and 60 mg ($p<0.0001$).
- NKTR-181 600 mg had significantly lower ratings of peak (Emax) Drug High compared to both oxycodone 40 mg and 60 mg ($p<0.0001$).
- NKTR-181 1200 mg had a significantly lower rating of peak (Emax) Drug High compared to 60 mg oxycodone ($p=0.0071$).

The peak Drug High score for NKTR-181 400 mg oral tablet confirmed the peak Drug High score in the first HAP trial, which evaluated 400 mg NKTR-181 as an oral solution (21.3 vs 22.59*).

Take Drug Again:

- NKTR-181 400 mg had significantly lower ratings of peak (Emax) Take Drug Again compared to the 40 mg and 60 mg oxycodone ($p<0.0001$).
- NKTR-181 600 mg had significantly lower ratings of peak (Emax) Take Drug Again compared to the 40 mg and 60 mg oxycodone ($p=0.0004$ and $p<0.0001$, respectively).
- NKTR-181 1200 mg had a significantly lower rating of peak Take Drug Again compared to 60 mg oxycodone ($p=0.011$).

* Webster et al.; Human Abuse Potential of the New Opioid Analgesic Molecule NKTR-181 Compared with Oxycodone. Pain Med 2017 pnw344. doi: 10.1093/pm/pnw344

Scheduling Placement Based on Analysis of 8 Factors

1. Actual or relative potential for abuse
2. Scientific evidence of its pharmacological effect, if known
3. The state of current scientific knowledge regarding the drug or other substance
4. History and current pattern of abuse
5. Scope, duration and significance of abuse
6. Risk, if any, to the public health
7. Dependence potential
8. Whether the substance is an immediate precursor of a substance already controlled

NKTR-181 is a new molecular entity (NME) that has never before been scheduled.

It is therefore a candidate for differentiated scheduling from other opioids.

Physicochemical Properties of NKTR-181:
Laboratory Manipulation and Extraction Studies (Category 1 *In Vitro* Data)

CHEMICAL HYDROLYSIS

NEGATIVE ✓

22 chemicals and 39 conditions tested. No morphinan derivatives generated, decomposition of API (NKTR-181) occurs.

ENZYMATIC HYDROLYSIS

NEGATIVE ✓

NKTR-181 unchanged by enzyme library.

VAPORIZATION

NEGATIVE ✓

Decomposition of API (NKTR-181) occurs.

- NKTR-181 *is not* an immediate precursor to a rapid-acting Schedule II opioid.
- No chemical or physical tampering method has yet been identified that can alter the NKTR-181 molecule to an active form that has a higher rate of entry into the CNS.
- Comprehensive battery of in vitro studies show no formation of morphinan derivatives from NKTR-181.
- These properties are inherent to the molecular structure itself, and *are not* a result of any formulation.

Conclusions from Human Abuse Potential (HAP) Study

- NKTR-181 is a new molecular entity (NME) that has significantly less abuse potential than a conventional Schedule II opioid (oxycodone IR at therapeutic doses)
- Likeability for all doses of NKTR-181 during the critical early time period after dosing is dramatically lower than oxycodone
- Likeability time profile for all doses of NKTR-181 is consistent with slow brain-entry kinetics
- A supratherapeutic dose of NKTR-181 (1200 mg) differentiates on key endpoints of Drug Liking, Drug High, and Take Drug Again as compared to a therapeutic dose of oxycodone (60 mg)
- Supports rationale for less restrictive scheduling (CIII or CIV)

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