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Do Pre-Marketing Studies Anticipate Post-Market Consequences? A Case Study of Reformulated Oxycontin

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Disclosure

- DL Global Partners Inc. provides advice to pharmaceutical and device companies and contract research organizations that provide services to these companies on the development of psychoactive drugs. This includes advising them on assessment of abuse liability and abuse deterrence.
- DL Global has provided independent consultant services to Purdue Pharma. Compensation for these services was not contingent in any way on any regulatory decisions or product success
- DL Global is not receiving compensation or reimbursement for participation in this meeting from any source

Background on Reformulated Extended Release Oxycodone ("OxyContin")

OxyContin was reformulated with physicochemical properties to make it more difficult to manipulate for the purposes of abuse and misuse

- More difficult to crush
- Retains extended-release characteristics even if crushed/ground
- Forms a gel if dissolved in liquid

Manufacturer shipments of the original formulation of OxyContin ceased on Aug 5, 2010 and on Aug 9, 2010 shipments for reformulated OxyContin started.

Overall Strategy to Characterize Degree of Abuse Deterrence

Pre-Marketing

A	*In Vitro* Tamper Testing Studies	▪ Evaluate the physical and chemical properties of the reformulation
B	Pharmacokinetic Testing	▪ Determine the bioavailability and pharmacokinetic profile of tablets administered intact and manipulated (orally and intranasally)
C	Abuse Potential Studies	▪ Examine various subjective measures related to liking and abuse of the reformulation

Post-Marketing

D	Epidemiology Studies	▪ Assess real-world impact using post-marketing outcome data

Summary of Results from *In Vitro* Testing*

Reformulated OxyContin tablets:

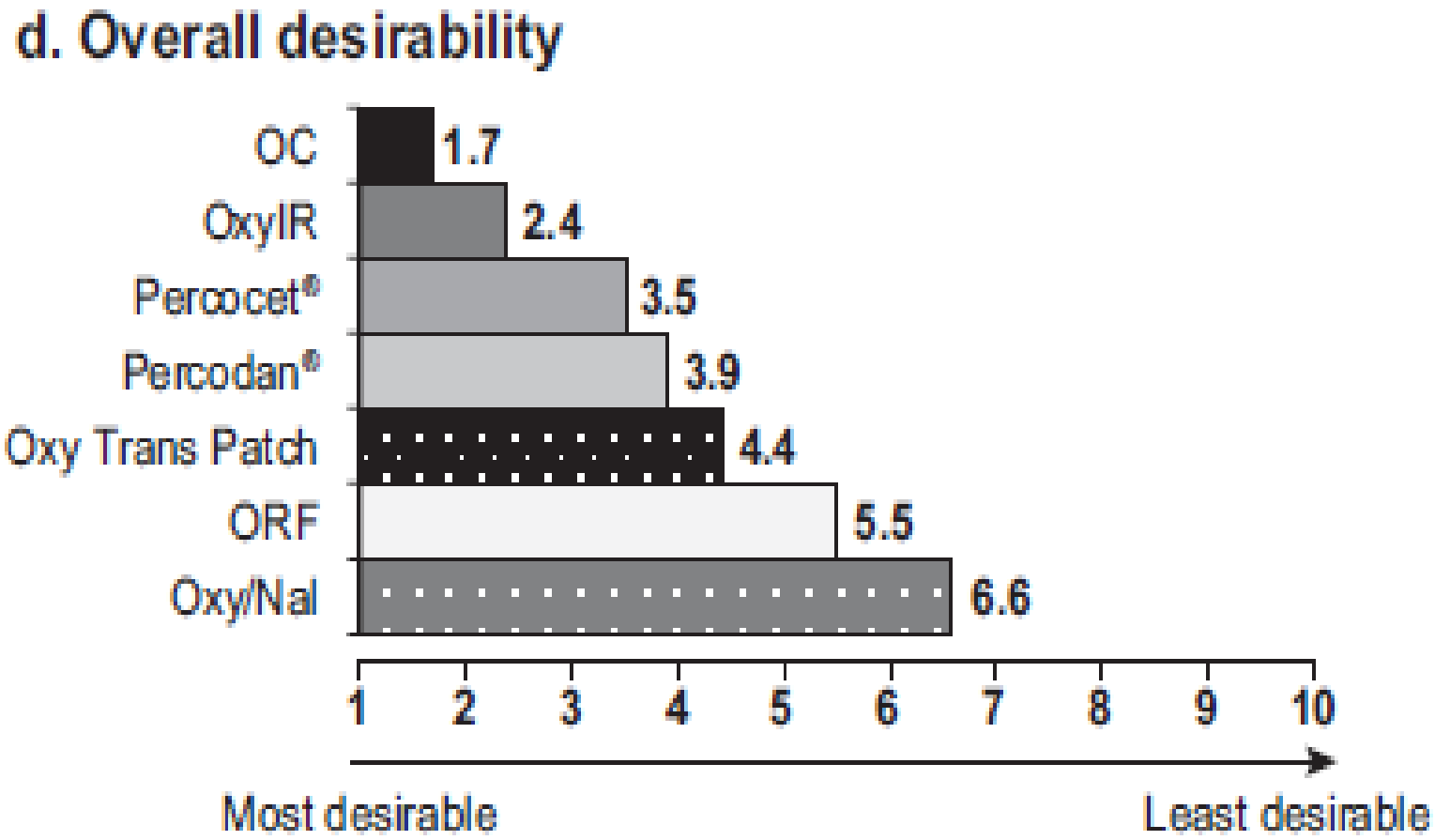
- Hard and difficult to crush
- Reformulated oxycodone HCl release lower than original OxyContin tablets in a range of solvents, even when reduced to particles
- Did not “dose dump” oxycodone HCl in alcohol, even when reduced to particles
- Difficult to prepare for snorting or injection (via an insulin syringe) than original OxyContin
- Difficult to vaporize for abuse via smoking

*Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee (ALSDAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM) on Reformulated OxyContin (September 24, 2009)

In Vivo Pharmacokinetic and Pharmacodynamic Studies

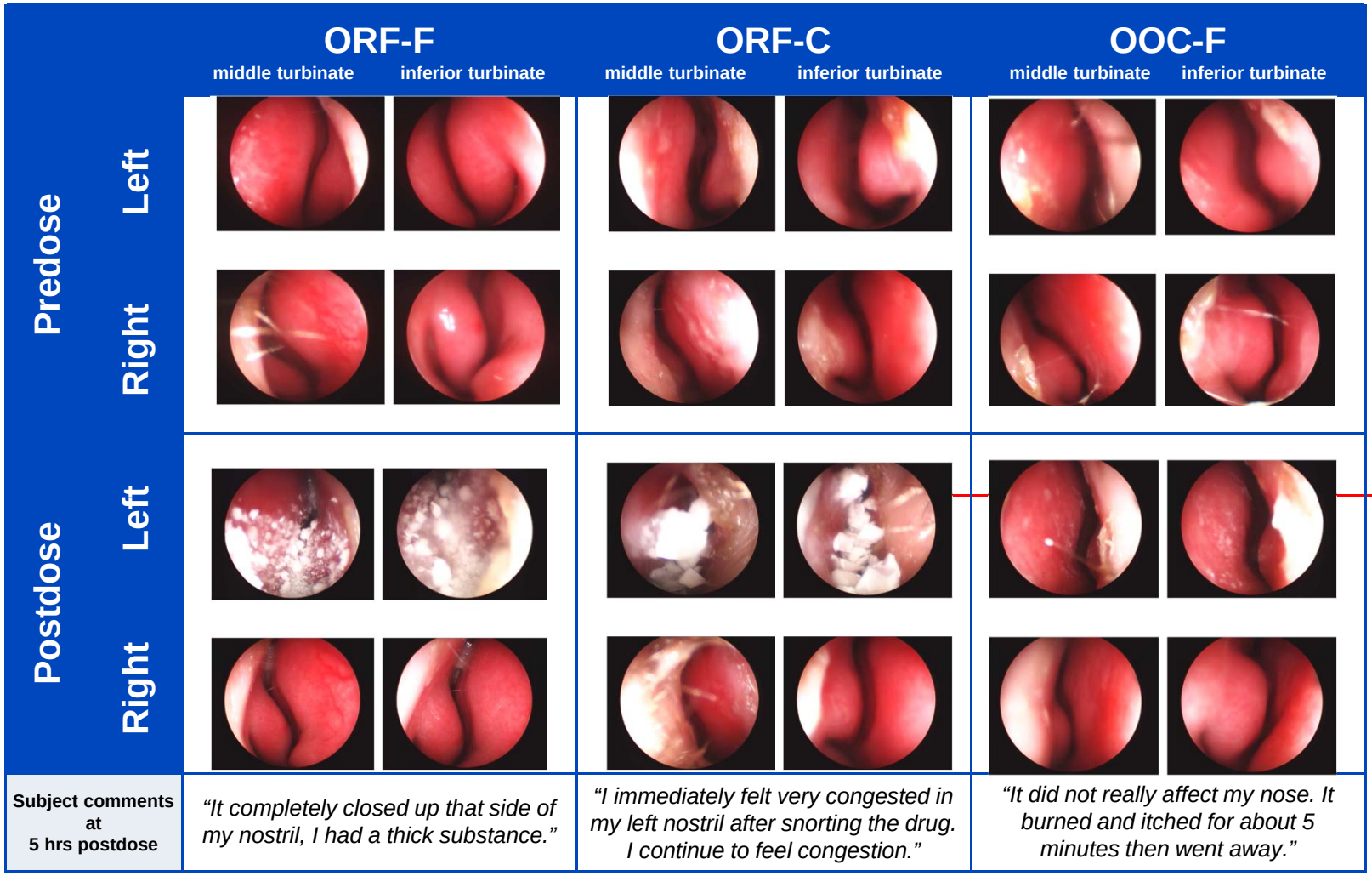
- **Internet survey** – what is done with OOC?
- **"Consumer" study** with abusers who tamper
- Pharmacokinetics after **oral** administration of tampered (chewed) Oxycontin
- **Pharmacokinetics** and local tolerability after **intra-nasal** insufflation of tampered Oxycontin
- **Pharmacodynamics and pharmacodynamics** after **intra-nasal** insufflation of tampered Oxycontin (abuse potential study)

Attractiveness of Reformulated Oxycontin Tablets: Panel Study

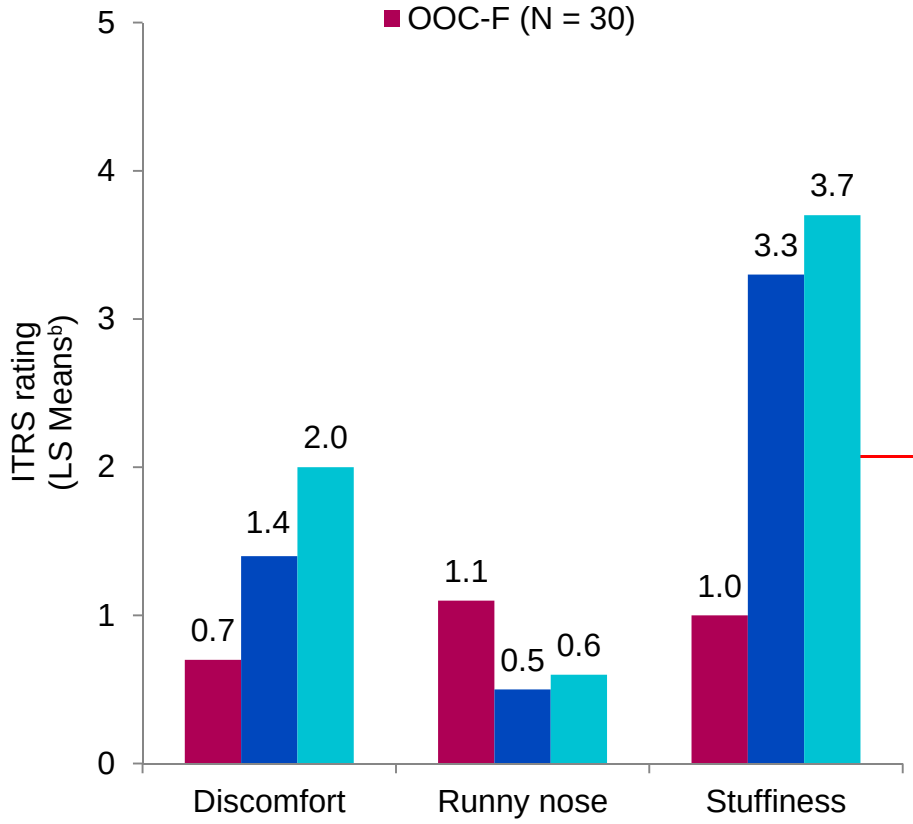


Sellers et al., J Psychopharm27:808-816;2013

Representative Examples of Subject Intranasal Endoscopies



Intranasal Tolerability Rating Scale[a]: Comparison of maximum response over time

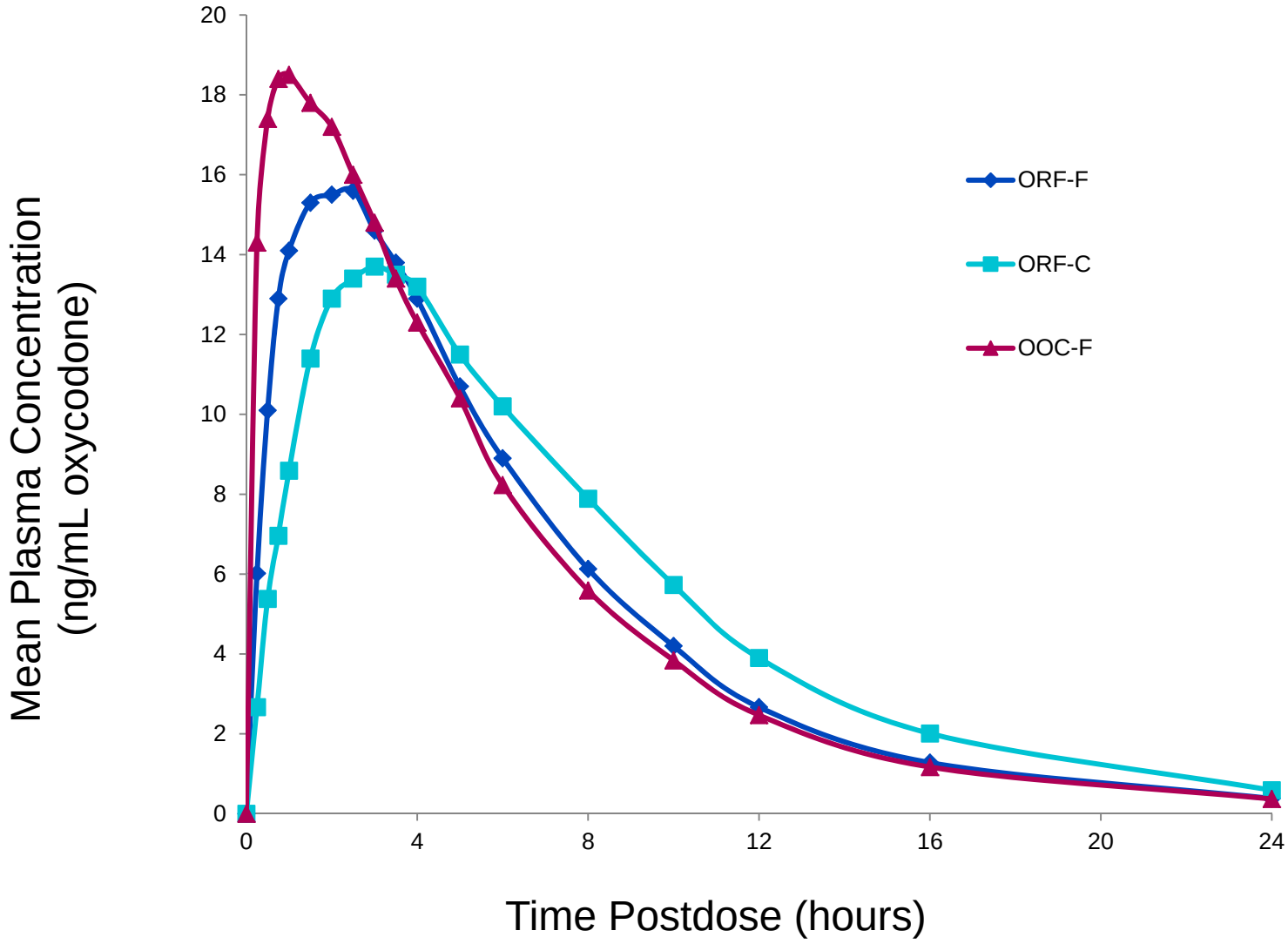


Treatment Difference Between ORF-F and OOC-F			
	Difference[c]	CI[d]	*P*[e]
Discomfort	0.7	(0.3, 1.1)	0.0030
Runny nose	-0.6	(-1.1, -0.1)	0.0363
Stuffiness	2.3	(1.4, 3.2)	<0.0001
Treatment Difference Between ORF-C and OOC-F			
	Difference[c]	CI[d]	*P*[e]
Discomfort	1.3	(0.9, 1.7)	<0.0001
Runny nose	-0.5	(-1.0, 0.0)	0.0845
Stuffiness	2.6	(1.8, 3.5)	<0.0001
Treatment Difference Between ORF-C and ORF-F			
	Difference[c]	CI[d]	*P*[e]
Discomfort	0.6	(0.2, 1.0)	0.0106
Runny nose	0.1	(-0.4, 0.6)	0.7036
Stuffiness	0.4	(-0.5, 1.2)	0.4938

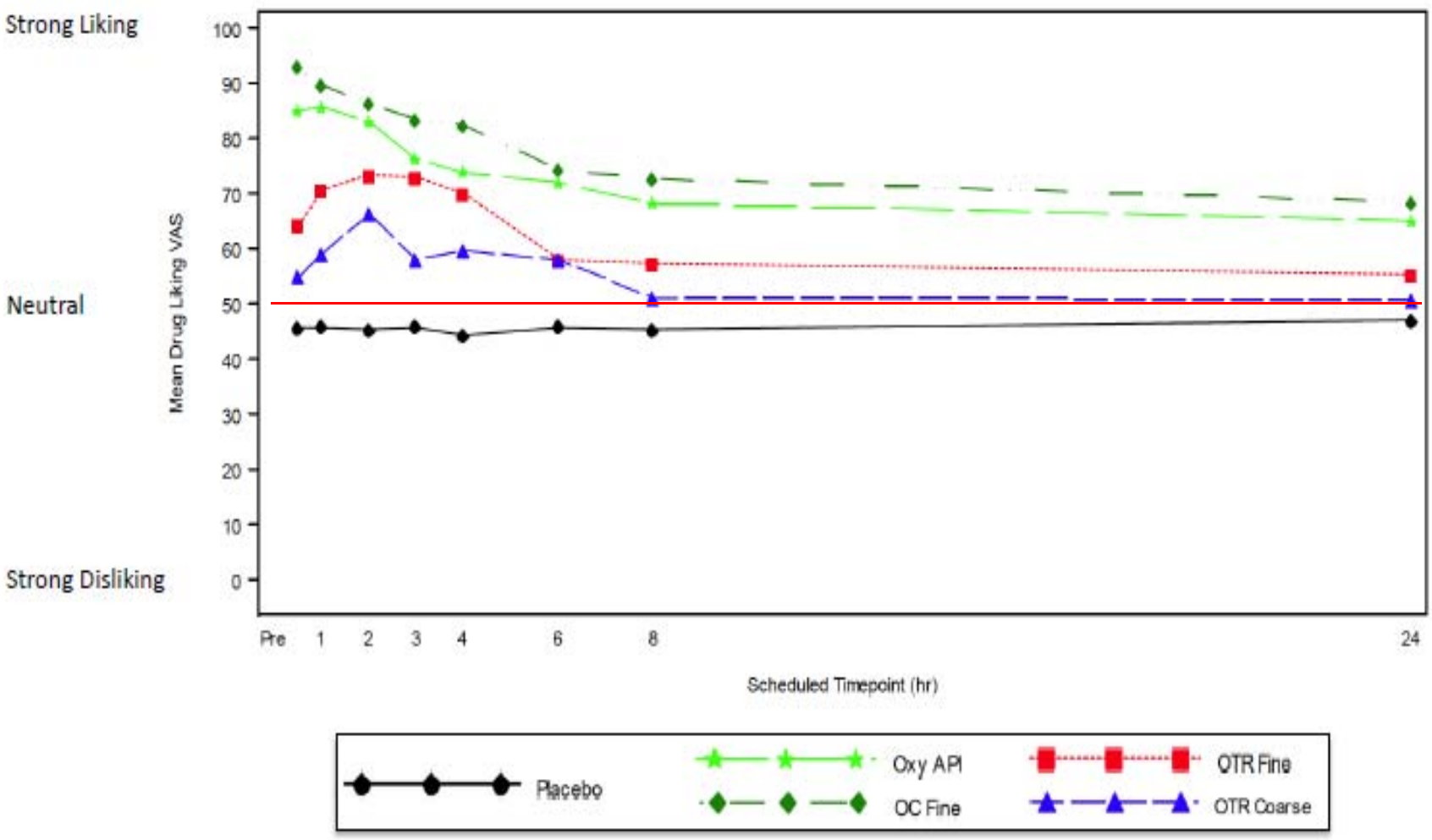
[a]Intranasal tolerability ranking scale was an 11-point scale where 0 = "none" and 10 = "worst I can imagine". [b]Least squares means from ANCOVA. [c]Difference of means between treatments from ANCOVA. [d]90% confidence interval for difference of means from ANCOVA. [e]P value for pairwise comparison between treatments from ANCOVA.

ORF-F = finely crushed 10 mg reformulated OxyContin®; ORF-C = coarsely crushed 10 mg reformulated OxyContin®; OOC-F = finely crushed 10 mg original OxyContin®.

Mean Oxycodone Concentrations Following Intranasal Dosing



Intranasal Abuse Potential of Tampered Oxycontin: Pharmacodynamics



Abuse Outcomes at 2 - 2.5 years after Reformulation of ER Oxycodone

Metric	Data Source	OxyContin Change	95% CI	P-Value
Abuse	RADARS Poison center exposures	-38%	(31-45)	<0.001
Abuse	National Poison Data System	-36%	(22-40)	<.0001
Abuse	NAVIPPRO drug treatment	-47%	(44-50)	<.0001
Abuse by non-oral routes	NAVIPPRO drug treatment	-70%	(68-72)	<.0001
Street price	RADARS Drug Diversion	-20%	(9 – 33)	0.002
Drug Diversion	RADARS Drug Diversion	-53%	(41-63)	<.001
Doctor Shopping	IMS	-40%	(35-44)	<.001
Fatalities	Adverse event reports	-62%	(49-72)	<0.001

Conclusions I: Case Study Reformulated Oxycontin

- All of the post-marketing observations were correctly anticipated by the pre-market studies **taken together**
- Oxycontin provides a **unique** case study opportunity – however the post-marketing data and "clinical importance" are **only relevant to a point in time; one product and one opiate**
- **A comprehensive suite of pre-market studies** are necessary to merit an explicit Tier 1 or 2 (?Tier 3) claim
- Such claims **require post-marketing** study, monitoring or surveillance and may merit a Tier 3(?) claim in due course

Conclusions II: Case Study Reformulated Oxycontin

- In that post-marketing epidemiological studies are so challenging to do (scientifically / logistically / cost / duration) **Tier 3 claims may be very hard to achieve for future products since the size of effects will get successively smaller and smaller- in due course will only have pre-market studies**
- For ER oxycodone products and potentially for selected studies of other opiates **Oxycontin is a useful reference comparator**
- Oxycontin has **set a benchmark** for Study Types and Labeling and Claims with respect to **"clinically important differences"**