

## **FDA ADVISORY COMMITTEE BRIEFING DOCUMENT**

### **MNK-812 (oxycodone hydrochloride) immediate-release tablets**

#### **JOINT MEETING OF THE ANESTHETIC AND ANALGESIC DRUG PRODUCTS ADVISORY COMMITTEE AND DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE**

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**ADVISORY COMMITTEE BRIEFING MATERIALS:  
AVAILABLE FOR PUBLIC RELEASE**

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<b>List of Abbreviations and Definitions of Terms</b>	
<b>ADF</b>	Abuse-deterrent formulation
<b>ADP</b>	Adenosine diphosphate
<b>AE</b>	Adverse event
<b>API</b>	Active pharmaceutical ingredient
<b>ATP</b>	Adenosine triphosphate
<b>AUC</b>	Area under the plasma concentration-time curve
<b>CDC</b>	Centers for Disease Control and Prevention
<b>CI</b>	Confidence interval
<b>C<sub>max</sub></b>	Maximum plasma concentration
<b>DAAAP</b>	Division of Anesthesia, Analgesia, and Addiction Products
<b>E<sub>max</sub></b>	Maximum effect
<b>ER</b>	Extended-release
<b>FDA</b>	United States Food and Drug Administration
<b>GRAS</b>	Generally regarded as safe
<b>HAP</b>	Human abuse potential
<b>HCl</b>	Hydrochloride
<b>HIV</b>	Human immunodeficiency virus
<b>HMW</b>	High molecular weight
<b>IN</b>	Intranasal
<b>IR</b>	Immediate-release
<b>IV</b>	Intravenous
<b>LS</b>	Least squares
<b>NDA</b>	New Drug Application
<b>PD</b>	Pharmacodynamic(s)
<b>PEO</b>	Polyethylene oxide
<b>PK</b>	Pharmacokinetic(s)
<b>PRP</b>	Platelet rich plasma
<b>RADARS</b>	Researched Abuse, Diversion and Addiction-Related Surveillance
<b>REMS</b>	Risk Evaluation and Mitigation Strategy
<b>SD</b>	Standard deviation
<b>SE</b>	Single-entity
<b>TE<sub>max</sub></b>	Time to maximum effect
<b>t<sub>1/2</sub></b>	Half-life
<b>T<sub>max</sub></b>	Time to maximum plasma concentration
<b>TPP</b>	Thrombocytopenic purpura

## 1 EXECUTIVE SUMMARY

MNK-812 is an investigational abuse-deterrent, immediate-release (IR), single-entity (SE) oxycodone hydrochloride (HCl) tablet with a proposed indication for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. MNK-812 has been formulated in five strengths of oxycodone HCl (5, 10, 15, 20, and 30 mg) to be administered orally every 4 to 6 hours. SpecGx LLC, a business unit of Mallinckrodt Pharmaceuticals, submitted a New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) in January 2018 requesting approval of MNK-812. In consultation with the FDA's Division of Anesthesia, Analgesia, and Addiction Products (DAAAP), MNK-812 was developed under the 505(b)(2) regulatory pathway where approval is based, in part, on demonstration of bioequivalence to Roxicodone®, an IR SE oxycodone HCl tablet without abuse-deterrent properties.

MNK-812 tablets incorporate Mallinckrodt's proprietary IR abuse-deterrent technology which is formulated with physical/chemical barriers to impart meaningful deterrence to intranasal (IN) and intravenous (IV) abuse while providing bioequivalence to Roxicodone:

- MNK-812 is a hard, non-brittle tablet that resists particle size reduction, making it more difficult to render into an abusable form for IN or IV routes of administration.
- MNK-812 tablets contain aversive agents that cause nasal irritation when insufflated to discourage IN abuse. In an IN human abuse potential (HAP) study, recreational opioid users had significantly lower willingness to take drug again and overall drug liking for IN MNK-812 than IN Roxicodone.
- MNK-812 produces a viscous solution that is difficult to syringe when an intact or manipulated tablet is dissolved in small volumes of aqueous solvents.

The pre-market studies to evaluate the abuse-deterrent properties of MNK-812 were designed based on the FDA Guidance Document "*Abuse-Deterrent Opioids – Evaluation and Labeling: Guidance for Industry*" (2015) as well as direct consultation with the FDA and experts in the design and conduct of abuse-deterrent studies.

This briefing document summarizes the findings of the MNK-812 development program, which support approval of this IR opioid analgesic with labeling as an abuse-deterrent product by the IN and IV routes of abuse. Mallinckrodt is seeking approval of MNK-812 as an abuse-deterrent replacement for branded and generic IR SE oxycodone tablets sold by Mallinckrodt. **Since it is intended as a replacement for currently-marketed products, MNK-812 will be referred to as "ADF Replacement" throughout the remainder of this briefing document.** If approved, the ADF Replacement would have the same indication and labeling as Roxicodone with the exception of additional abuse-deterrent designations. Since Mallinckrodt currently manufactures approximately 15% of the IR SE oxycodone tablets prescribed in the US (approximately 2.8 million prescriptions per year) (IQVIA 2018), this planned replacement has the potential to transition a substantial number of IR SE oxycodone medications to a product with meaningful abuse-deterrent properties.

Mallinckrodt is committed to fulfilling its post-approval requirements consistent with the company's involvement in existing opioid analgesic Risk Evaluation and Mitigation Strategy (REMS) and post-market approval requirements. At a minimum, this will require having a medication guide, providing REMS assessments to the FDA, establishing Elements to Assure Safe Use, and conducting Category 4 studies to evaluate whether the ADF Replacement is having its intended public health impact.

### **Public Health Need for Abuse-Deterrent IR Opioid Medications**

Opioid analgesic medications remain an essential treatment for the management of moderate to severe acute pain when non-opioid alternatives do not provide sufficient pain relief. However, the ongoing crisis of opioid diversion, abuse, and overdose demands that steps be taken to mitigate the risk to public health posed by the misuse of prescription opioid medications. While appropriate prescribing practices are the essential first step, other important strategies include patient and physician education, REMS, prescription drug monitoring programs, safe storage and disposal programs, revised prescribing guidelines, ensuring access to substance abuse treatment, and the broader availability of ADFs.

Immediate-release ADFs are a harm reduction strategy aimed at reducing non-oral (ie, IN and IV) routes of prescription opioid abuse for which each exposure carries additional risk beyond oral ingestion for disease transmission, injury, overdose, and death. ADFs cannot be expected to stop an individual with opioid use disorder from abusing opioids in general or to stop a determined individual from overcoming abuse-deterrent mechanisms with sufficient time, effort, and knowledge. Despite their limitations, abuse-deterrent technologies have the potential to deter the initiation and overall incidence of more dangerous routes of opioid abuse and to make diversion less attractive.

The FDA has supported the development and advancement of opioid medications with meaningful abuse-deterrent properties as one component of the public health strategy to reduce the harms of opioid abuse (FDA 2015, 2017). According to a recent FDA statement, “Transitioning from the current market, dominated by conventional opioids, to one in which most opioids have abuse-deterrent properties, holds significant promise for a meaningful public health benefit” (FDA 2017).

In 2017, all prescriptions for IR SE oxycodone were non-ADF products, and 99.9% of these were dispensed as generic products (IQVIA 2018). There is only one IR SE oxycodone product, RoxyBond™ (Inspirin Delivery Sciences), that has abuse-deterrent labeling consistent with the current FDA Guidance. Thus, the replacement of IR SE oxycodone tablet medications manufactured by Mallinckrodt with a product having meaningful abuse-deterrent properties would help to further the FDA's goal of transitioning the market of opioid medications to ADFs.

### **Abuse of IR SE Oxycodone Products**

Epidemiologic data from the Research and Abuse, Diversion and Addiction-Related Surveillance (RADARS®) System support that IR opioids are a common target for abuse. The rate of IR opioid intentional abuse is approximately 5-fold higher than extended-release (ER) opioids. This finding is not surprising since IR opioids are more commonly prescribed and the majority of individuals who abuse prescription opioid medications report preferring IR opioids over ER opioids for the immediacy of the high and ease of use for non-oral routes of abuse (Cicero et al 2017). Furthermore, individuals commonly begin their abuse patterns with IR products (Budman et al 2009; Lankenau et al 2012).

Oxycodone medications are common targets of abuse. According to data from drug treatment centers, the rate of abuse for IR SE oxycodone is approximately twice that of ER oxycodone (Inflexxion 2018). In a large sample of individuals entering drug treatment who reported abusing IR SE oxycodone products in the last 30 days (N=2,630; Inflexxion 2018):

- 50.2% reported abuse by the oral route,
- 49.9% reported abuse by the IN route, and
- 24.6% reported abuse by the IV route.

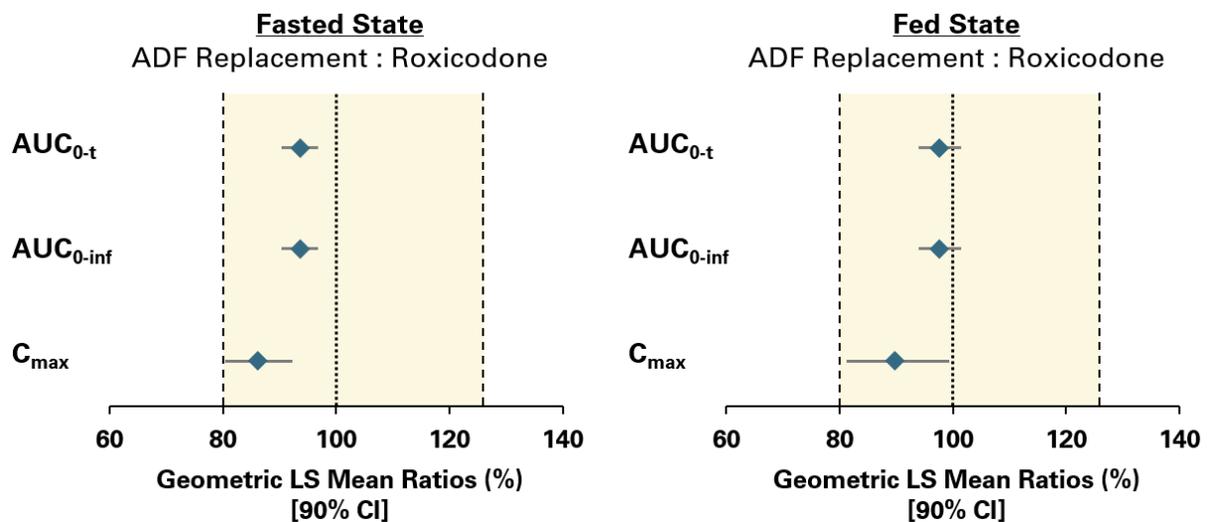
Given that non-oral routes of abuse are associated with more than twice the risk of overdose, death, or other major effects compared with the oral route (Green et al 2017), the replacement of conventional IR SE oxycodone products that can be easily insufflated or injected with medications that have meaningful abuse-deterrent properties is a potentially important harm reduction strategy.

**Bioequivalence of ADF Replacement to Roxicodone Supports Approval for Proposed Indication**

Mallinckrodt’s ADF Replacement was developed in consultation with the FDA using the 505(b)2 regulatory pathway. This approach allows the FDA to use their prior findings of safety and efficacy to approve a new product if it is found to be bioequivalent to an approved product with the same active pharmaceutical ingredient (API), dosage form, indication, and route of administration. The development program for the ADF Replacement included relative bioavailability studies to demonstrate bioequivalence to Roxicodone in the fed and fasted states per the FDA Guidance document for oxycodone IR tablets (FDA 2009). Phase 3 efficacy or safety studies have not been required by the FDA.

Mallinckrodt performed two pivotal bioequivalence studies – one in the fasted state (N=32) and the other in the fed state (N=49). In both studies, the 90% confidence intervals (CI) for the geometric least squares (LS) mean ratios of the exposure through end of study ( $AUC_{0-t}$ ), exposure from zero to infinity ( $AUC_{0-inf}$ ), and maximum plasma concentration ( $C_{max}$ ) of ADF Replacement 15 mg tablets and Roxicodone 15 mg tablets were within the pre-specified bioequivalence bounds (Figure 1).

**Figure 1: Bioequivalence of ADF Replacement to Roxicodone 15 mg Tablets in Fasted and Fed States**



Note: Yellow shaded area indicates pre-specified bioequivalence bounds of 80% to 125%.

In the fasted study, the median (range) time to maximum concentration ( $T_{max}$ ) values were:

- 1.5 hours (0.8 – 2.2) for the ADF Replacement, and
- 1.0 hours (0.5 – 2.0) for Roxicodone.

In the fed study, the median (range)  $T_{max}$  values were:

- 3.0 hours (0.3 – 8.0) for the ADF Replacement, and
- 2.0 hours (0.5 – 4.0) for Roxicodone.

Three participants had  $T_{max}$  values in the fed state with the ADF Replacement of 6 to 8 hours (ie, two subjects with a  $T_{max}$  of 6 hours and one subject with a  $T_{max}$  of 8 hours). Inspection of the plasma oxycodone concentration-time curves for these individuals showed that they had oxycodone concentrations similar to their respective  $C_{max}$  values by 4 hours (ie, the earliest time point within the 4-to-6-hour dosing interval). Thus, the observed  $T_{max}$  values in these subjects were not indicative of a clinically meaningful effect of food (see [Section 4.3](#) for details).

Overall, the results of the relative bioavailability studies demonstrate that the ADF Replacement is therapeutically equivalent to Roxicodone.

### **Category 1 (In Vitro) Abuse-Deterrent Studies**

Since the ADF Replacement is intended to replace non-abuse-deterrent IR SE oxycodone tablets manufactured by Mallinckrodt, Roxicodone – a non-ADF IR SE oxycodone product manufactured by Mallinckrodt – was selected as the comparator. RoxyBond, a FDA-approved abuse-deterrent IR SE oxycodone product, was not marketed prior to the NDA submission for the ADF Replacement, so the relative abuse-deterrent properties of RoxyBond and the ADF Replacement have not been evaluated.

#### Particle Size Reduction

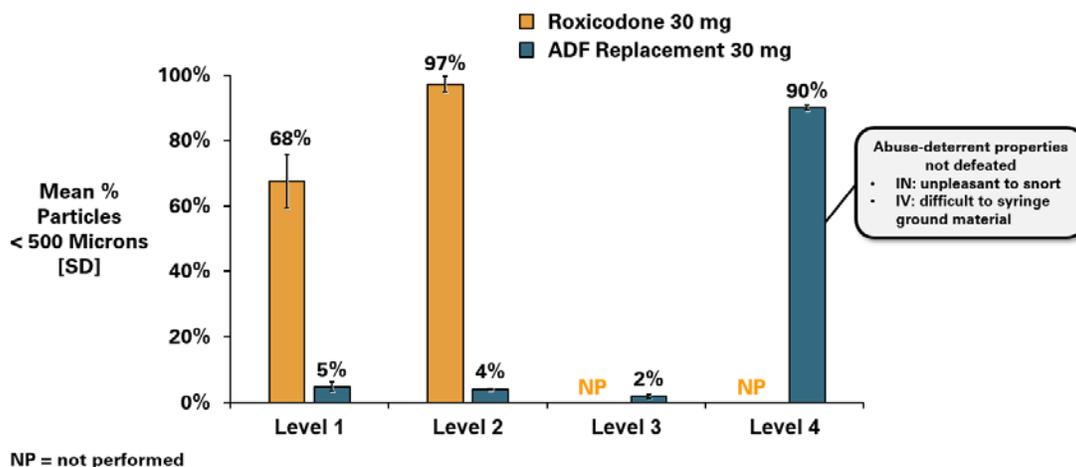
Unlike ER opioids, which have an intrinsic time-release mechanism, whereby reducing particle size can speed drug release, particle size reduction for an IR opioid does not meaningfully change its release profile. The rationale for reducing the particle size of an IR opioid product is to render the product into an abusable form for IN or IV abuse.

Particle size reduction tests were performed on Roxicodone and ADF Replacement 30 mg tablets using several methods of physical manipulation (eg, crushing, cutting, grinding, grating, milling). The four levels of manipulation that were selected for formal evaluation were based on initial testing with a larger number of tools that were representative of various ways an individual may attempt to reduce the particle size of an opioid product. In these tests, higher levels of manipulation represent more sophistication and intensity.

[Figure 2](#) displays the mean percentage of small particles achieved with each level of manipulation for Roxicodone and the ADF Replacement. (Note: particles smaller than 500 microns are considered amenable for snorting.) Roxicodone was easily reduced into small particles using the two lowest levels of manipulation, so testing with more advanced tools was not performed. In contrast, only the highest level of manipulation achieved a high yield of small particles for the ADF Replacement.

Importantly, while a tool was identified that reduced the ADF Replacement to small particles, this did not defeat the product's abuse-deterrent properties. In terms of IN abuse, the aversive agents made the ground ADF Replacement unpleasant to snort (see [Section 7.5](#)); and, in terms of IV abuse, ground ADF Replacement tablets were difficult to syringe in injectable volumes of various solvents (see [Section 5.5](#)).

**Figure 2: Mean Percentage of Particles < 500 Microns after Particle Size Reduction**



Tablet Thermal Stressing Conditions to Selectively Degrade the Nasal Irritant

ADF Replacement tablets contain tartaric acid, which serves a dual purpose as both a disintegrant to facilitate its immediate release when taken orally as intended and as a nasal irritant to deter IN abuse. Once the IN abuse-deterrent properties of ADF Replacement tablets are known, individuals may attempt to thermally stress tablets to selectively degrade the nasal irritant to allow for insufflation without experiencing aversive nasal effects. Due to the potential for the thermal stressing conditions to degrade oxycodone HCl as well as tartaric acid, the recovery of both ingredients was quantitatively determined.

Twenty-eight thermal stressing conditions were evaluated with ADF Replacement 30mg tablets. None of the thermal stressing conditions were able to eliminate tartaric acid from ADF Replacement tablets. The tablet thermal stressing conditions that produced the greatest degradation of the nasal irritant (76-83%) also degraded a substantial amount of oxycodone HCl (33-73%), which would not be a desirable result for IN abuse. Pre-clinical studies have shown that the aversive effects of tartaric acid are dose related; therefore, insufflation of thermally-stressed tablets would still be expected to cause unpleasant effects because tartaric acid could not be eliminated.

Small Volume Extraction and Syringeability

Mallinckrodt evaluated 1,836 combinations of solvents, volumes, temperatures, agitation, needle gauges, extraction times, and pretreatments to thoroughly evaluate the IV abuse potential of ground and intact ADF Replacement and Roxicodone 30 mg tablets. Small volume extraction and syringeability testing can be broadly characterized in two ways:

- **Common Methods for IV Abuse:** 288 combinations of conditions were evaluated for both the ADF Replacement and Roxicodone to determine the feasibility of preparing IV solutions without the additional time or effort of pretreatment in the most frequently-used solvent for IV abuse.
- **Advanced Methods for IV Abuse:** 1,548 combinations of conditions with various pretreatments and with other directly-injectable solvents were evaluated for the ADF Replacement. Roxicodone was not evaluated in these tests since it was easily syringeable with a high yield of oxycodone without pretreatment in the most frequently-used solvent for IV abuse.

Since ADF opioid medications must be bioavailable to treat pain, the abuse-deterrent properties of any ADF can be overcome with sufficient time, effort, materials, and knowledge. Given that any ADF can only be abuse-deterrent and not abuse-proof, the goal of the small volume extraction and syringeability testing was to determine the extent of the work required to overcome the abuse-deterrent properties of the ADF Replacement and whether these barriers could be expected to deter individuals from IV abuse relative to the non-ADF products it is intended to replace. With that goal in mind, Mallinckrodt used knowledge of the composition of ADF Replacement tablets to select conditions and advanced techniques to challenge the abuse-deterrent properties. Please note throughout the remainder of this briefing document oxycodone HCl recovery and syringeable oxycodone HCl is noted as oxycodone recovery and syringeable oxycodone.

#### *Small Volume Extraction and Syringeability Testing with Common Methods*

The gelling properties of the ADF Replacement provided substantial resistance to extraction and syringeability.

- The yield of syringeable oxycodone from intact tablets without pretreatment was very low (< 10%) across all conditions for the ADF Replacement and was variable for Roxicodone (ie, yields of syringeable oxycodone from Roxicodone were generally higher with longer extraction times).
- **Table 1** summarizes the common methods for IV abuse with ground tablets. High yields of injectable oxycodone were recovered from ground Roxicodone tablets in most conditions, however no condition yielded appreciable oxycodone recovery from ground ADF Replacement tablets.

<b>Table 1: Oxycodone Recovery from Ground ADF Replacement and Roxicodone Tablets across Small Volume Extraction and Syringeability Tests with Common Methods</b>		
Yield of Syringeable Oxycodone	n (%) of Conditions	
	ADF Replacement 30 mg (N = 144 Conditions)	Roxicodone 30 mg (N = 144 Conditions)
0% to 5%	141 (98)	0
> 5% to 10%	2 (1)	0
> 10% to 20%	1 (<1)	0
> 20% to 40%	0	15 (10)
> 40% to 60%	0	73 (51)
> 60% to 100%	0	56 (39)

#### *Small Volume Extraction and Syringeability Testing with Advanced Methods*

In order to further evaluate the abuse-deterrent properties of the ADF Replacement, additional testing was performed with four types of pretreatment known to be used by individuals to overcome IV abuse-deterrent properties based on drug abuse websites (eg, bluelight.org). In these studies, ADF Replacement tablets were tested across a range of solvent volumes, needle gauges, agitation, temperature elevation, and extraction times with the most frequently-used solvent for IV abuse. **Table 2** provides the key results and interpretations from these studies.

**Table 2: Summary of Small Volume Extraction and Syringeability Tests with Advanced Methods Using Most Frequently-Used Solvent for IV Abuse**

IV Pre-treatment	N Conditions Tested	Median (Range) Oxycodone Recovery (%)	Interpretation
1	288	0 (0 – 18)	<ul style="list-style-type: none"> <li>IV Pretreatment 1 did not meaningfully increase the feasibility of preparing IV solutions of the ADF Replacement.</li> </ul>
2	288	0 (0 – 9)	<ul style="list-style-type: none"> <li>IV Pretreatment 2 did not meaningfully increase the feasibility of preparing IV solutions of the ADF Replacement.</li> </ul>
3	216	1 (0 – 35)	<ul style="list-style-type: none"> <li>IV Pretreatment 3 did not increase the median yield of syringeable oxycodone; the maximum yield was 35%.</li> <li>The conditions required for maximum recovery required advanced conditions: ground tablets, largest injection volume, largest needle, the longest extraction time point, and elevated temperature throughout the extraction.</li> </ul>
4	216	10 (0 – 60)	<ul style="list-style-type: none"> <li>IV Pretreatment 4 increased the yield of syringeable oxycodone (median 10%, maximum 60%).</li> <li>The set of conditions required for the highest yields of oxycodone with Pretreatment 4 were extensive: ground tablets, large injection volumes, large needles, the longest extraction time point, and elevated temperature throughout the extraction.</li> <li>Sets of conditions that provided the highest yield of syringeable oxycodone would take an individual over an hour to perform.</li> </ul>

The use of other directly-injectable solvents for extraction did not increase the maximum yield of syringeable oxycodone relative to experiments conducted with the most frequently-used solvent for IV abuse.

In summary, the ADF Replacement provided substantial barriers to preparation for IV injection. The yield of syringeable oxycodone was low in all but a small number of conditions, which required a time-consuming pretreatment, large extraction volumes that are not preferred for IV abuse, large needles not commonly used for IV abuse, and elevated temperature throughout the extraction for a process that would take over an hour to perform. The results of the extensive testing demonstrate that the ADF Replacement has physicochemical properties expected to make abuse via injection more difficult than the non-abuse-deterrent IR SE oxycodone products it is intended to replace.

### ***In Vitro and In Vivo Excipient Safety Studies***

Epidemiologic data from the Centers for Disease Control and Prevention (CDC) identified an association between IV abuse of Opana® ER, an ER oxymorphone product, and the incidence of thrombotic thrombocytopenic purpura-like symptoms (TPP), a rare, serious blood disorder characterized by microangiopathic hemolytic anemia and thrombocytopenia (CDC 2013). Subsequent mechanistic investigations in animals confirmed that repeated IV injection of the high molecular weight polyethylene oxide (HMW PEO) that was the primary excipient in Opana® ER could result in hemolysis, retinal damage, and thrombotic microangiopathy (Hunt et al 2017).

While ADF Replacement tablets do not include any of the HMW PEO associated with the safety issues observed with Opana ER, Mallinckrodt evaluated the potential safety risks of IV injection of ADF Replacement extracts in general toxicology studies.

The yield of syringeable oxycodone was low for the ADF Replacement using all common conditions for IV abuse. Therefore, the ADF Replacement test articles (Test Article 1 and 2) for the general toxicology studies were selected based on results from the advanced conditions that achieved the highest yields of syringeable oxycodone using the two most frequently-cited IV pretreatments on drug abuse websites (eg, bluelight.org). Prior to initiating the excipient safety studies, the FDA provided feedback to Mallinckrodt on elements of the protocols, which were incorporated. Key results from these studies are provided below. A full description of study results is provided in [Section 6](#).

- *In Vitro* Hemolytic Potential, Plasma Compatibility, and Platelet Aggregation Studies
  - Test articles did not exhibit hemolysis in whole human blood.
  - Test articles did not exhibit any evidence of human plasma incompatibility.
  - Test articles did not induce platelet aggregation when mixed with human plasma or platelet rich plasma (PRP).
- *In Vivo* Multiple-dose IV Toxicity Study in Rabbits
  - No evidence of overt toxicity or tissue damage was observed with test articles.
  - Test articles were not associated with signs or symptoms of thrombotic microangiopathy, acute kidney injury, or eye ischemia or injury.
  - A statistically significant increase in fibrinogen with Test Article 2 was not considered adverse in the absence of other correlations of inflammation or coagulation and because fibrinogen levels were within the laboratory's normal historical ranges.
  - A statistically significant increase in spleen weight with Test Article 2 was not considered adverse due to a lack of tissue damage.
  - Minimal to slight microscopic pathology findings were observed with the test articles, but the independent pathologist did not consider the changes in organs to be adverse in the context of the study findings.

Overall, the extracts in pretreated ADF Replacement tablets were not associated with signs or symptoms of thrombotic microangiopathy, overt toxicity, or tissue damage. However, it should be acknowledged that IV injection of *any* solid oral dosage form – whether ADF or non-ADF – is not safe due to the risk for overdose and the inclusion of excipients that are not intended for IV use.

**Category 2 / Category 3 Intranasal (IN) Human Abuse Potential (HAP) Study**

The IN HAP study was a randomized, double-blind, double-dummy study in non-dependent recreational opioid users with experience using opioids via the IN route. The study included four treatments: IN ADF Replacement 30 mg, IN Roxycodone 30 mg, oral ADF Replacement 30 mg (ie, dosing via the intended route of administration), and placebo, with a 72-hour washout between each treatment period. The primary analysis population was comprised of 38 participants who completed the study.

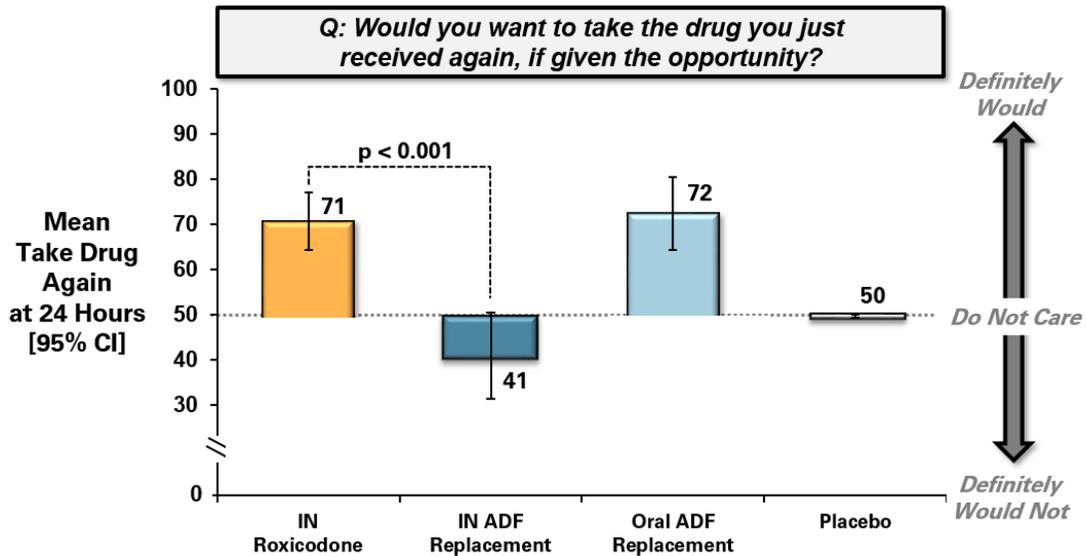
Pharmacodynamic (PD) endpoints for intranasal HAP studies can be classified in three ways:

- **“Positive effects”** are assessed by endpoints such as Drug Liking and Drug High that are measured several times after study drug administration. For these endpoints, it is common to look at the trends in effects over time as well as the maximum effect regardless of time ( $E_{max}$ ). Importantly, the maximum positive effects of an IR opioid are similar for IN and oral administration; the rationale for insufflating an IR opioid is to achieve positive effects faster than oral administration.
- **“Negative effects”** are assessed by endpoints such as Ease of Snorting and the Nasal Effects Assessment. Ease of Snorting is measured immediately after insufflation. The Nasal Effects Assessment is measured several times after study drug administration to assess the degree of adverse sensations like nasal pain and burning.
- **“Overall experience”** is assessed by endpoints such as Take Drug Again and Overall Drug Liking. Both endpoints are measured 12 and 24 hours after study drug administration when the psychoactive effects of the study drug have dissipated to understand how subjects integrated the “positive” and “negative” effects of the drug-taking experience in their memory and to gauge future behavior.

The key PD findings reflected the primary mechanism of IN abuse deterrence for the ADF Replacement, namely to create “negative effects” with aversive agents to discourage abuse.

- In terms of “positive effects,” Drug Liking  $E_{max}$  and Drug High  $E_{max}$  were similar between the active IN and oral treatments. For the primary Drug Liking  $E_{max}$  comparison, IN ADF Replacement did not reach the pre-specified superiority margin of 10% compared with IN Roxycodone (77 vs. 83;  $p = 0.223$ ). While  $E_{max}$  scores were similar, IN ADF Replacement was associated with significantly lower Drug Liking and Drug High scores than IN Roxycodone over the first hour after dosing, which paralleled the delay in oxycodone absorption with IN ADF Replacement compared with IN Roxycodone.
- In terms of “negative effects,” the ADF Replacement was rated as significantly more difficult to insufflate than IN Roxycodone ( $p < 0.001$ ). The ADF Replacement also caused significantly more unpleasant nasal effects than IN Roxycodone. The percentage of subjects reporting an adverse nasal effect was 95% for IN ADF Replacement compared with 32% for IN Roxycodone; nasal effects that were considered moderate or severe were reported in 79% of subjects for IN ADF Replacement compared with 3% for IN Roxycodone.
- In terms of “overall experience,” subjects expressed substantial willingness to take IN Roxycodone or the oral ADF Replacement again, but not IN ADF Replacement (**Figure 3**). Take Drug Again and Overall Drug Liking scores were significantly lower for IN ADF Replacement than the other active treatments and similar to placebo at 24 hours post dose.

**Figure 3: Take Drug Again Assessment in IN HAP Study at 24 Hours Post Dose**



**Conclusions**

The development program for the ADF Replacement demonstrates that it can be expected to provide the same therapeutic benefit as Roxicodone with the added benefit of meaningful IN and IV abuse-deterrent properties. For IV abuse, the ADF Replacement was difficult to prepare for injection based on more than 1,800 common and advanced preparation conditions. For IN abuse, compared to the products it is intended to replace, the ADF Replacement delayed oxycodone absorption, reduced Drug Liking and Drug High at early time points, and created unpleasant nasal effects that led individuals to report no greater Overall Drug Liking or willingness to take again than placebo.

## 2 PUBLIC HEALTH NEED FOR ABUSE-DETERRENT IR OPIOID MEDICATIONS

### Summary

- IR opioid analgesics remain essential medications for the treatment of pain when alternative, non-opioid treatment options are inadequate.
- Epidemiologic data suggest that the abuse rate of IR SE oxycodone is more than twice as high as ER oxycodone.
- A substantial percentage of individuals entering drug treatment report recent IN or IV abuse of IR SE oxycodone (50% and 25%, respectively).
- ADFs have been identified as one of several public health interventions advocated by FDA in response to prescription opioid abuse in the US.
- Current ADF technologies cannot prevent the most common form of abuse via the oral route by overconsumption of tablets since the medication must be bioavailable to treat pain. ADFs are intended as harm reduction measures to deter intranasal (IN) and intravenous (IV) abuse, which carry additional health risks beyond the oral route.

### 2.1 Background on IR Opioid Medications

Immediate-release prescription opioid analgesics are one of the common options for the treatment of moderate-to-severe acute pain. While non-opioid (eg, nonsteroidal anti-inflammatory drugs, acetaminophen, local anesthetics, physical therapy) and multimodal treatment options are often able to effectively manage acute pain either with no or reduced use of opioids, these clinical situations tend to be cases where pain is less severe, of short duration, or more localized. There remain, however, many clinical situations where opioid analgesics are essential for the adequate management of pain. In cases when alternative treatments are inadequate, prescription opioids should be used at the lowest effective dose for the shortest appropriate duration (CDC 2018).

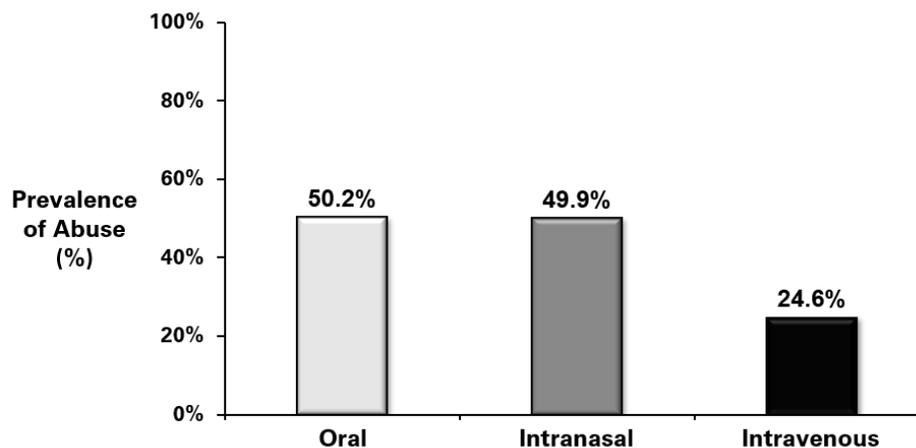
### 2.2 Epidemiology of IR SE Oxycodone Abuse

Abuse of prescription IR opioids is a substantial public health challenge in the US. The most recent data from 2017 suggests that IR SE oxycodone products are abused at more than twice the rate of ER oxycodone (5.2 vs 2.5 cases per 100 treatment center admissions; Inflexxion 2018). The relatively high rates of IR SE oxycodone abuse may be due to several factors:

- IR SE oxycodone is prescribed more commonly than ER oxycodone. In 2017, there were 17.4 million IR SE oxycodone prescriptions dispensed from outpatient retail pharmacies compared with 3.5 million ER oxycodone prescriptions (IQVIA 2018).
- Individuals who abuse prescriptions opioids frequently initiate abuse with IR opioids (Budman et al 2009; Lankenau et al 2012), likely due to their higher availability.
- Survey data suggest that individuals who abuse opioids prefer IR over ER formulations. In a large sample of 8,304 individuals entering treatment for opioid use disorder, 66% expressed a preference for IR opioids, 4% preferred ER opioids, and 30% had no preference. The preference for IR opioids was primarily due to the perceived immediacy and quality of the high and ease of IN and IV abuse (Cicero et al 2017).

The reported preference for IR opioids for non-oral routes of abuse is consistent with abuse patterns in the community. Among a large sample of individuals assessed for drug treatment in 2017 who had abused IR SE oxycodone in the last 30 days (N=2,630), approximately half of individuals reported oral and IN abuse; nearly one in four reported IV abuse ([Inflexxion 2018](#); [Figure 4](#)). (Note: the percentages do not add to 100% since individuals could report abuse by more than one route.)

**Figure 4: Prevalence of IR SE Oxycodone Abuse by Route in NAVIPPRO Database (2017)**



The high rates of IN and IV abuse of IR SE oxycodone are particularly concerning since non-oral abuse exposures are associated with a higher likelihood of a serious adverse health outcome than exposures to oral ingestion. National surveillance data from US Poison Centers suggest that the relative risk of death or a major effect (eg, overdose) is 2.2 times greater for an exposure to IN abuse and 2.6 times greater for an exposure to IV abuse compared with oral abuse ([Green et al 2017](#)).

Abuse via the IV route, in particular, is associated with additional health consequences beyond the immediate risks of overdose or death. In 2016, 6% of new human immunodeficiency virus (HIV) diagnoses and 9% of new acquired immune deficiency syndrome (AIDS) diagnoses in the US were linked to injecting drug use ([CDC 2017](#)). IV drug use is also associated with transmission of other bloodborne infections like hepatitis C ([Liang & Ward 2018](#)) as well as injuries and diseases such as endocarditis, sepsis, bone and joint infections, and thrombosis and emboli ([Larney et al 2017](#)).

## 2.3 Addressing Opioid Abuse in the US

### 2.3.1 Overview of Strategies to Address Opioid Abuse

The ongoing crisis of opioid diversion, abuse, and overdose demands that steps be taken to protect patients and the public health from the harms of the misuse of prescription opioid medications. It is well recognized that an effective solution to curb the opioid crisis must be multifaceted. The most prominent elements of the overall public health strategy include appropriate prescribing practices, patient and physician education, the Opioid Analgesic REMS, prescription drug monitoring programs, safe storage and disposal programs, effective law enforcement practices, ensuring access to substance abuse treatment, and ADFs.

### 2.3.2 Goals of Abuse-Deterrent Technologies

The FDA has supported the development and advancement of opioid medications with meaningful abuse-deterrent properties as one component of the public health strategy to reduce the harms of opioid abuse (FDA 2015, 2017). According to a recent FDA statement: “Transitioning from the current market, dominated by conventional opioids, to one in which most opioids have abuse-deterrent properties, holds significant promise for a meaningful public health benefit” (FDA 2017).

According to the FDA, the goal of ADFs is “to make manipulation more difficult or to make abuse of the manipulated product less attractive or less rewarding” (FDA 2015). The FDA further clarifies that ADFs are intended to be abuse-*deterrent*, and not abuse-*proof*. “The fact that a product has abuse-deterrent properties does not mean that there is no risk of abuse. It means, rather, that the risk of abuse is lower than it would be without such properties. Because opioid products must in the end be able to deliver the opioid to the patient, there must always be some abuse of these products.” No technology has yet been successful at deterring abuse by swallowing intact capsules or tablets.

Thus, IR ADFs are a harm reduction strategy aimed at reducing non-oral routes of prescription opioid abuse for which each exposure carries additional risk beyond oral ingestion for disease transmission, injury, overdose, and death. ADFs cannot be expected to stop an individual with opioid use disorder from abusing opioids in general or to stop a determined individual from overcoming abuse-deterrent mechanisms with sufficient time, effort, and knowledge. However, despite the limitations, abuse-deterrent technologies have the potential to make diversion of prescription opioids less attractive, deter novice/recreational users from initiating abuse via non-oral routes, and to reduce the harms associated with IN and IV abuse.

### 2.3.3 Mallinckrodt’s Plan to Replace IR SE Oxycodone Tablets with ADF Replacement

In alignment with the goals of the FDA to transition the opioid market to ADFs, if approved, Mallinckrodt will implement plans to cease production of its current branded and generic formulations of non-ADF IR SE oxycodone tablets and replace them with the ADF Replacement. Since Mallinckrodt tablets currently represent approximately 15% of the market for IR SE oxycodone tablets (approximately 2.8 million prescriptions per year) (IQVIA 2018), the ADF Replacement has the potential to transition a sizable proportion of the IR SE oxycodone market to a medication with meaningful abuse-deterrent properties.

### 3 ADF REPLACEMENT DEVELOPMENT PROGRAM

#### Summary

- Mallinckrodt's ADF Replacement is an IR SE oxycodone HCl tablet with the proposed indication for the management of pain severe enough to require an opioid analgesic and for which alternative treatment options are inadequate.
- Mallinckrodt developed the ADF Replacement under the 505(b)2 regulatory pathway where approval is based, in part, on demonstration of bioequivalence to Roxicodone, an FDA-approved non-ADF IR SE oxycodone tablet.
- The ADF Replacement incorporates Mallinckrodt's proprietary abuse-deterrent technology for IR solid oral dosage forms.
- In accordance with FDA guidance documents and advice from the Agency, Mallinckrodt has performed a comprehensive evaluation of the ADF Replacement's IN and IV abuse-deterrent properties.
- Mallinckrodt has performed *in vitro* and *in vivo* excipient safety studies to evaluate the potential safety risks of IV administration of ADF Replacement extracts.

#### 3.1 Mallinckrodt ADF Replacement and Abuse-Deterrent Technology

ADF Replacement tablets are IR SE oxycodone HCl tablets intended for oral administration for the management of pain severe enough to require an opioid analgesic and for which alternative treatment options are inadequate. The proposed indication for the ADF Replacement is the same as the current indication for Roxicodone, which is a non-abuse-deterrent IR SE oxycodone HCl tablet.

The ADF Replacement is differentiated from Roxicodone in that it is formulated with physical and chemical barriers and aversive agents to deter IN and IV abuse. Mallinckrodt is proposing that the ADF Replacement be labeled as an abuse-deterrent product via the IN and IV routes of abuse, consistent with the results of the abuse-deterrent studies.

#### 3.2 Formulation

Mallinckrodt's ADF Replacement tablets are formulated in five strengths: 5 mg, 10 mg, 15 mg, 20 mg, and 30 mg for oral administration every 4-6 hours as needed for the management of pain. The dosage forms appear as modified-oval shaped, film-coated tablets that are similar in size and shape to an oblong Advil® 200 mg tablet. All tablets have a non-functional coating that varies in color according to strength and are debossed with the strengths on one side to identify different strengths visually. ADF Replacement tablets are manufactured using a simple, conventional process of blending, compression, color coating, and curing.

**Table 3** provides an overview of the formulation components and proposed function. The relative composition across tablet strengths is similar, with the only notable exception being the amount of oxycodone HCl (range 5 – 30 mg). All excipients in ADF Replacement tablets are either generally regarded as safe (GRAS) or are used in other FDA-approved oral drug products as listed in the Inactive Ingredient Database.

**Table 3: Components and Proposed Function of ADF Replacement Tablets**

Proposed Function	Component
Active pharmaceutical ingredient (API)	Oxycodone HCl
Abuse Deterrence	Tartaric acid*
	Citric acid
	Effersoda*
	Polyethylene glycol
	Polyethylene oxide
	Glucosmannan
	Sodium carboxymethyl cellulose
	Hydroxypropylmethyl cellulose
Other	Xanthan gum
	Butylated hydroxytoluene
	Magnesium stearate
	Opadry® coating materials

\* Also serves as tablet disintegrant

PEO is an important pharmaceutical excipient in many marketed ADFs to impart physical hardness and gelling properties that are intended to deter IN and IV abuse. The molecular weight and amounts of PEO vary between products. For example, Opana® ER was primarily composed of high molecular weight (HMW) PEO with a molecular weight of approximately 7,000,000 (Hunt et al 2017). The currently-marketed formulation of OxyContin® is primarily composed of HMW PEO with a molecular weight of approximately 4,000,000 (FDA 2009).

Recent data has suggested that repeated IV injections of the HMW PEO in Opana® ER with a molecular weight of 7,000,000 can elicit thrombotic microangiopathy (Hunt et al 2017). While ADF Replacement tablets do not contain any PEO with a molecular weight of 7,000,000 or greater, Mallinckrodt performed *in vitro* and *in vivo* excipient safety studies in order to evaluate the safety of all excipients in ADF Replacement tablets for IV injection. The results of these general toxicology studies can be found in Section 6.

### 3.3 Overview of Development Program

Mallinckrodt developed the ADF Replacement under the 505(b)2 regulatory pathway where approval is based, in part, on demonstration of bioequivalence to Roxycodone. Bioequivalence implies that two products are biologically equivalent in terms of the rate and extent to which the API becomes available at the site of drug action when administered at the same dose under similar conditions.

To support abuse-deterrent label claims, the FDA Guidance (2015) for the development of ADFs outlines that sponsors should conduct a variety of studies, which fall into 4 categories:

- Category 1 – Laboratory Manipulation and Extraction Studies
- Category 2 – Pharmacokinetic Studies
- Category 3 – Clinical Abuse Potential Studies
- Category 4 – Post-market Studies

Mallinckrodt has performed the comprehensive set of Category 1, 2, and 3 studies in accordance with the FDA Guidance “*Abuse Deterrent Opioids - Evaluation and Labeling: Guidance for Industry*” (2015). In addition, the FDA provided additional input on study designs and protocols throughout the development of the ADF Replacement, including:

- Experimental conditions for the Category 1 abuse-deterrent studies
- Statistical analyses on PD endpoints in the Category 2/3 IN HAP study
- Preclinical safety studies to evaluate the safety of injection of ADF Replacement extracts

The following sections provide an overview of the key studies in the development program.

### 3.3.1 Clinical Pharmacokinetic Studies

Mallinckrodt performed two pivotal clinical pharmacokinetic (PK) studies comparing the relative bioavailability of ADF Replacement 15 mg tablets to Roxycodone 15 mg tablets in the fed and fasted states. In the fasted PK study, study drug was administered after an overnight fast of at least 10 hours. In the fed PK study, study drug was administered following consumption of a standard high-fat breakfast. Both PK studies were open-label, randomized, 2-period, crossover studies in healthy subjects under a naltrexone blockade (Table 4).

<b>Table 4: Overview of Clinical Pharmacokinetic Studies in Healthy Volunteers</b>			
<b>Study</b>	<b>Purpose</b>	<b>N Subjects</b>	<b>Treatments</b>
1004	Evaluate bioequivalence in fasted state	32	ADF Replacement 15 mg (fasted) Roxycodone 15 mg (fasted)
1005	Evaluate bioequivalence in fed state	49	ADF Replacement 15 mg (fed) Roxycodone 15 mg (fed)

### 3.3.2 Category 1 *In Vitro* Studies

The goal of Category 1 studies is to test the limitations of the physical and chemical abuse-deterrent properties of an ADF. The abuse-deterrent barriers of any formulation can be overcome with sufficient time, effort, and knowledge. Therefore, the primary goals of Category 1 testing are to identify the extent of the effort and procedures needed to overcome the physical/chemical barriers and to determine whether those barriers can be expected to meaningfully deter abuse by a particular route.

Mallinckrodt performed the full set of *in vitro* studies outlined in FDA’s Guidance document for the development and evaluation of ADFs. Category 1 studies were performed in an iterative fashion based on feedback from the Agency. Specifically, after the majority of an initial battery of tests were completed, Mallinckrodt performed additional testing based on advice from the FDA to ensure that the abuse-deterrent features of the ADF Replacement had been thoroughly characterized. Except where noted, all Category 1 testing was performed with Roxycodone as the non-ADF comparator. (Note: RoxyBond, an FDA-approved abuse-deterrent IR SE oxycodone product, was not marketed prior to the NDA submission for the ADF Replacement. As such, the relative abuse-deterrent properties of RoxyBond and the ADF Replacement have not been evaluated.)

The following Category 1 evaluations were performed:

- **Particle size reduction studies** evaluated the feasibility of various tools to crush, cut, grate, grind, or mill Roxycodone and ADF Replacement tablets.
- **Tablet thermal stressing studies** evaluated the feasibility of selective degradation of the primary nasal irritant in ADF Replacement tablets.
- **Large volume extraction studies** evaluated the ability to differentially solubilize and extract oxycodone in large volumes of representative solvents.
- **Small volume extraction and syringeability studies** evaluated the feasibility of preparing Roxycodone and the ADF Replacement for IV abuse in injectable volumes of solvents representing 1,836 different combinations of common and advanced methods.

### 3.3.3 *In Vitro* Hemolytic Potential, Plasma Compatibility, and Platelet Aggregation Studies

To assess the safety of ADF Replacement extracts if injected via the IV route, Mallinckrodt performed a series of general toxicology studies to assess the hemolytic potential of the ADF Replacement extracts in whole human blood, to evaluate plasma compatibility, and to quantify platelet aggregation and adenosine triphosphate (ATP) release in PRP. The *in vitro* and *in vivo* studies used the combination of experimental conditions that provided the highest amount of syringeable oxycodone using the two most frequently-cited IV pretreatments for abuse-deterrent opioids on drug abuse websites (eg, [bluelight.org](http://bluelight.org)).

### 3.3.4 *In Vivo* Multiple-Dose IV Toxicity Study

To further evaluate the local and systemic effects of ADF Replacement extracts following IV injection, Mallinckrodt performed a multiple-dose IV general toxicity study in rabbits. The study was designed in consultation with the FDA to evaluate the potential for local and systemic effects of IV injection of ADF Replacement extracts, including hematologic effects, thrombotic microangiopathy, overt toxicity, and tissue damage. The study was performed in accordance with the US FDA Good Laboratory Practice for Nonclinical Laboratory Studies, the Animal Welfare Act, the Guide for the Care and Use of Laboratory Animals, and the Office of Laboratory Animal Welfare.

### 3.3.5 Category 2/3 Intranasal Human Abuse Potential Study

Mallinckrodt performed a combined Category 2/3 IN HAP study, to evaluate the PK and PD of IN ADF Replacement 30 mg relative to IN Roxycodone 30 mg, oral ADF Replacement 30 mg (ie, intended route of administration), and placebo.

The IN HAP study was a randomized, double-blind, double-dummy, placebo-controlled, 4-period crossover study. The study enrolled nondependent, recreational opioid users with recent experience insufflating opioid products. Forty-three (43) subjects entered the treatment phase and 40 subjects completed the treatment phase. A total of 38 subjects completed the study and did not experience emesis within 1 hour of study drug administration and comprised the primary analysis population. (Note: early emesis would be expected to confound the PK and PD findings.)

## 4 BIOEQUIVALENCE

### Summary

- For an NDA submitted under the 505(b)2 pathway, approval is based, in part, on demonstrating bioequivalence to an approved product to establish therapeutic equivalence.
- Mallinckrodt performed two pivotal bioequivalence studies, which demonstrated that ADF Replacement 15 mg tablets were bioequivalent to Roxycodone 15 mg tablets in the fed and fasted states. Thus, the ADF Replacement is therapeutically equivalent to Roxycodone.
- No Phase 3 efficacy or safety studies have been required by the FDA.

### 4.1 Bioequivalence for Regulatory Approval

The ADF Replacement was developed in consultation with the FDA using the 505(b)2 regulatory pathway. This approach allows the FDA to use prior findings of safety and efficacy to approve a new drug product if it is found to be bioequivalent to an approved product with the same API, dosage form, indication, and route of administration. Bioequivalence of the ADF Replacement to Roxycodone, which does not have dosing instructions with regard to food, was evaluated in relative bioavailability studies in the fed and fasted states per the FDA Guidance document for oxycodone IR tablets (FDA 2009).

The FDA does not typically require new products submitted under the 505(b)2 pathway to conduct Phase 3 efficacy or safety studies unless potentially clinically meaningful differences between the new product and reference product are identified (eg, food effects). Rather, PK studies demonstrating bioequivalence of the new drug to the reference drug are typically sufficient to provide scientifically valid evidence for regulatory approval. The FDA has not required Phase 3 efficacy or safety studies for the ADF Replacement.

### 4.2 Bioequivalence of the ADF Replacement to Roxycodone in the Fasted State

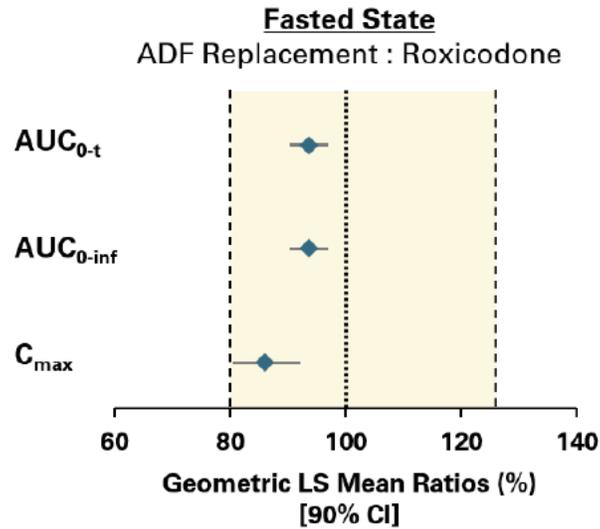
Study 1004 was an open-label, randomized, 2-period, crossover study comparing the relative bioavailability of ADF Replacement 15 mg tablets with Roxycodone 15 mg tablets in 32 healthy volunteers in the fasted state. All subjects received naltrexone prior to study drug administration to block the PD effects of oxycodone as a safety measure in healthy subjects.

The three primary PK parameters to determine bioequivalence –  $C_{max}$ ,  $AUC_{0-t}$ , and  $AUC_{0-inf}$  – as well as  $T_{max}$  and half-life ( $t_{1/2}$ ) are shown in Table 5.

Parameter	ADF Replacement 15 mg (fasted) (N = 32)	Roxycodone 15 mg (fasted) (N = 32)
$C_{max}$ (ng/mL), mean (SD)	26.3 (7.8)	30.8 (10.6)
$AUC_{0-t}$ (ng·h/mL), mean (SD)	144.6 (39.1)	152.8 (38.0)
$AUC_{0-inf}$ (ng·h/mL), mean (SD)	145.6 (39.2)	153.8 (38.1)
$T_{max}$ (hours), median (range)	1.5 (0.8 – 2.2)	1.0 (0.5 – 2.0)
$t_{1/2}$ (hours), mean (SD)	4.0 (0.7)	4.1 (0.7)

Figure 5 illustrates that the 90% CI for the geometric LS mean ratios between the ADF Replacement and Roxycodone were all contained within the pre-specified bounds, meeting the criteria for bioequivalence. Overall, the results demonstrate that the ADF Replacement is therapeutically equivalent to Roxycodone in the fasted state.

**Figure 5: Bioequivalence of ADF Replacement to Roxicodone 15 mg Tablets in the Fasted State**



Note: Yellow shaded area indicates bioequivalence bounds of 80% to 125%.

#### 4.3 Bioequivalence of the ADF Replacement to Roxicodone in the Fed State

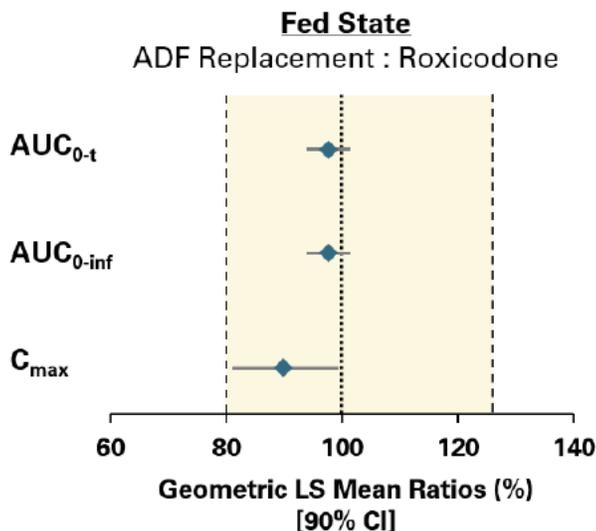
Study 1005 was an open-label, randomized, 2-period, crossover study comparing the relative bioavailability of ADF Replacement 15 mg tablets with Roxicodone 15 mg tablets in 49 healthy volunteers in the fed state. All subjects received naltrexone to block PD effects of oxycodone as a safety measure for healthy subjects.

A summary of PK parameters is provided in [Table 6](#) and the bioequivalence analysis is shown in [Figure 6](#). The ADF Replacement was bioequivalent to Roxicodone on all PK parameters, which means that the ADF Replacement is therapeutically equivalent to Roxicodone in the fed state.

**Table 6: Summary of PK Parameters for ADF Replacement and Roxicodone 15 mg in the Fed State**

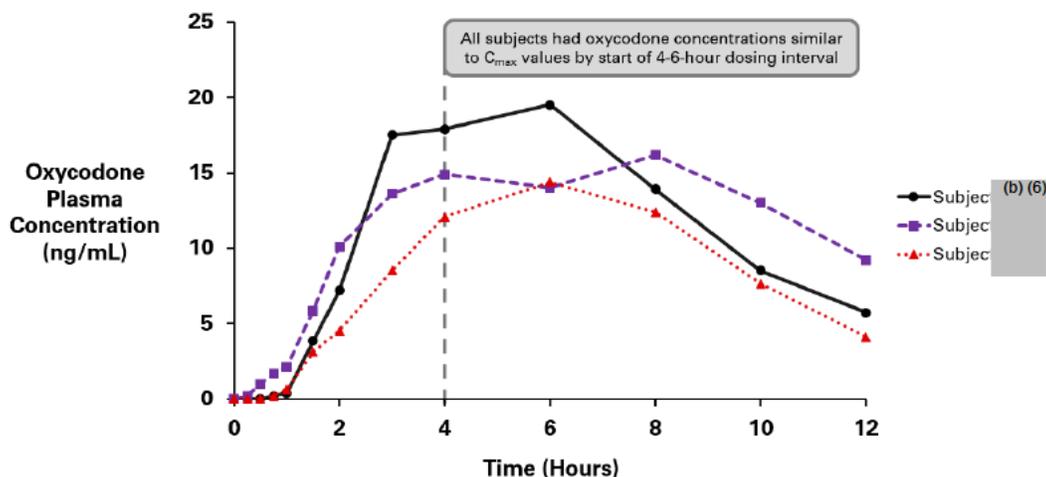
Parameter	ADF Replacement 15 mg (fed) (N = 49)	Roxicodone 15 mg (fed) (N = 49)
C <sub>max</sub> (ng/mL), mean (SD)	29.7 (15.1)	31.0 (9.0)
AUC <sub>0-t</sub> (ng·h/mL), mean (SD)	169.4 (38.8)	173.5 (40.2)
AUC <sub>0-inf</sub> (ng·h/mL), mean (SD)	170.4 (38.9)	174.6 (40.4)
T <sub>max</sub> (hours), median (range)	3.0 (0.3 – 8.0)	2.0 (0.5 – 4.0)
t <sub>1/2</sub> (hours), mean (SD)	4.1 (0.8)	4.0 (0.7)

**Figure 6: Bioequivalence of ADF Replacement to Roxicodone 15 mg Tablets in the Fed State**



The  $T_{max}$  range of the ADF Replacement (0.3 to 8 hours) was higher than the range observed with Roxicodone in this study (0.5 to 4 hours). Three participants had  $T_{max}$  values with the ADF Replacement of 6 to 8 hours in the fed state (ie, two subjects with a  $T_{max}$  of 6 hours and one subject with a  $T_{max}$  of 8 hours). Inspection of the plasma oxycodone concentration-time curves for these individuals showed that they had oxycodone concentrations similar to their respective  $C_{max}$  values by 4 hours, which is the earliest time point within the 4-to-6-hour dosing interval (Figure 7). Thus, the observed  $T_{max}$  values in these subjects were not indicative of a clinically meaningful effect of food.

**Figure 7: Oxycodone Plasma Concentrations for 3 Subjects with  $T_{max}$  Values of 6-8 Hours in Fed Bioequivalence Study Following Administration of ADF Replacement 15 mg Tablets**



Overall, the results of the bioequivalence studies in the fed and fasted states demonstrate that the ADF Replacement is therapeutically equivalent to Roxicodone, which does not have dosing instructions with regard to food.

## 5 CATEGORY 1 STUDIES

### Summary

#### Particle Size Reduction Studies

- Unlike ER opioids, the release profile of an IR opioid is not substantively affected by particle size reduction. The rationale for particle size reduction of an IR opioid is to render the product into an abusable form for IN or IV abuse.
- The particle size of Roxycodone was easily reduced by the two lowest levels of manipulation. Only the highest level of manipulation achieved a high yield of small ADF Replacement particles. The ADF Replacement retains abuse-deterrent properties with particle size reduction, since tablets contain aversive agents to make IN abuse unpleasant and gelling agents to make IV abuse difficult.

#### Tablet Thermal Stressing Studies

- An individual may attempt to selectively degrade the nasal irritant in the ADF Replacement, tartaric acid, to decrease the aversive effects of IN abuse.
- None of the thermal stressing conditions were able to eliminate the nasal irritant. The conditions that produced the greatest degradation of the nasal irritant also degraded oxycodone, which would not be a desirable result for IN abuse. The aversive effects of tartaric acid are dose related, so thermally-treated ADF Replacement tablets would still be expected to impart unpleasant effects when insufflated since tartaric acid could not be eliminated.

#### Small Volume Extraction and Syringeability Studies

- Mallinckrodt performed 1,836 combinations of extraction solvents, volumes, agitations, temperatures, needle gauges, pretreatments, tablet manipulations, and extraction times to evaluate the IV abuse-deterrent properties of the ADF Replacement. Most tests were performed using the most frequently-used solvent for IV abuse.
- Common Methods for IV Abuse
  - The yield of syringeable oxycodone from intact tablets without pretreatment was low (< 10%) across all conditions for the ADF Replacement and variable for Roxycodone.
  - With ground tablets, high yields of syringeable oxycodone were recovered in most conditions from Roxycodone. No conditions yielded an appreciable oxycodone recovery from the ADF Replacement.
- Advanced Methods for IV Abuse
  - IV Pretreatments 1 and 2 did not increase the feasibility of preparing IV solutions of the ADF Replacement (highest oxycodone yields were 18% and 9%, respectively).
  - IV Pretreatment 3 increased the maximum yield to 35%, but required a largest injection volume, the largest needle, longest extraction time, and elevated temperature throughout the extraction.
  - IV Pretreatment 4 increased the yield of syringeable oxycodone with a maximum 60% recovery, but required an hour-long procedure of pretreatment, large injection volume, large needles, longest extraction time, and elevated temperature throughout the extraction.
  - The use of other directly-injectable solvents did not increase the maximum yield of syringeable oxycodone relative to the most frequently-used solvent for IV abuse.

### 5.1 Overview

Mallinckrodt performed the full set of laboratory-based *in vitro* manipulation and extraction studies outlined in the FDA Guidance “Abuse-deterrent Opioids – Evaluation and Labeling: Guidance for Industry” (2015) to evaluate the physical and chemical abuse-deterrent properties of the ADF Replacement.

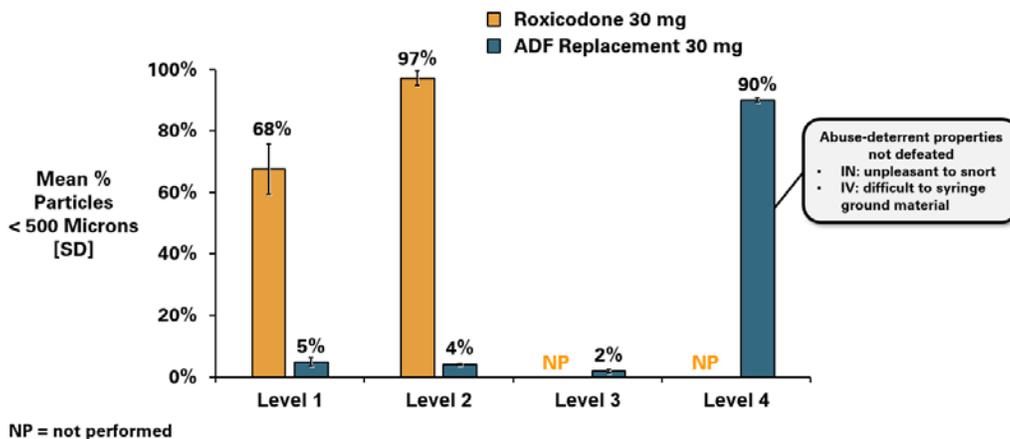
The purpose of Category 1 studies is to evaluate common methods of physical and chemical manipulation as well as advanced methods that would require substantial time, laboratory equipment, and chemistry knowledge. While some of the advanced methods employed may go beyond what individuals are known to attempt in the real world, the rationale for using sophisticated laboratory techniques is to challenge the ADF to its limits with the understanding that any abuse-deterrent mechanism can be overcome with sufficient time, effort, and knowledge. The key Category 1 studies used the highest dosage strength of the ADF Replacement (30 mg) for all testing with Roxicodone as the non-ADF comparator, where appropriate.

## 5.2 Particle Size Reduction

The rationale for particle size reduction is distinct for IR and ER opioids. For ER opioids, particle size reduction compromises the controlled-release of the drug product by altering an extended release of the drug to an immediate release (ie, “dose-dumping”). Since IR products are designed to release the drug rapidly, particle size reduction does not have a meaningful impact on drug release. However, particle size reduction does allow both IR and ER products to be abused via the IN and IV routes, which provide a faster onset of effects than the oral route.

Following an exploratory stage with a larger set of mechanical and electrical tools that were representative of the way an individual may attempt to reduce particle size (eg, crushing, cutting, grinding, grating, milling), four levels of manipulation were brought forward for formal evaluation. Higher levels of manipulation represent more sophistication and intensity. Figure 8 illustrates the yield of particles < 500 microns (ie, a common threshold for particles amenable to snorting) for each method. The two lowest levels of manipulation produced a high yield of small particles for Roxicodone, but not the ADF Replacement. Since Level 2 manipulation reduced 97% of Roxicodone particles to < 500 microns, higher levels were not evaluated. Only the highest level of manipulation was able to achieve a high yield of small particles for the ADF Replacement, which is consistent with the manipulation required to defeat the physical hardness of hard-to-crush ADF products.

**Figure 8: Mean Percentage of Particles < 500 Microns after Particle Size Reduction**



The particle size reduction procedure for the ADF Replacement was subsequently optimized with Level 4 manipulation to ensure the highest yield of small particles and to prevent the tool from breaking while performing the manipulation. Importantly, particle size reduction does not defeat the abuse-deterrent properties of the ADF Replacement, since tablets contain aversive agents that cause unpleasant effects when manipulated tablets are insufflated and gelling agents that make IV abuse difficult.

### 5.3 Tablet Thermal Stressing to Selectively Degrade the Nasal Irritant

ADF Replacement tablets contain tartaric acid, which serves two purposes:

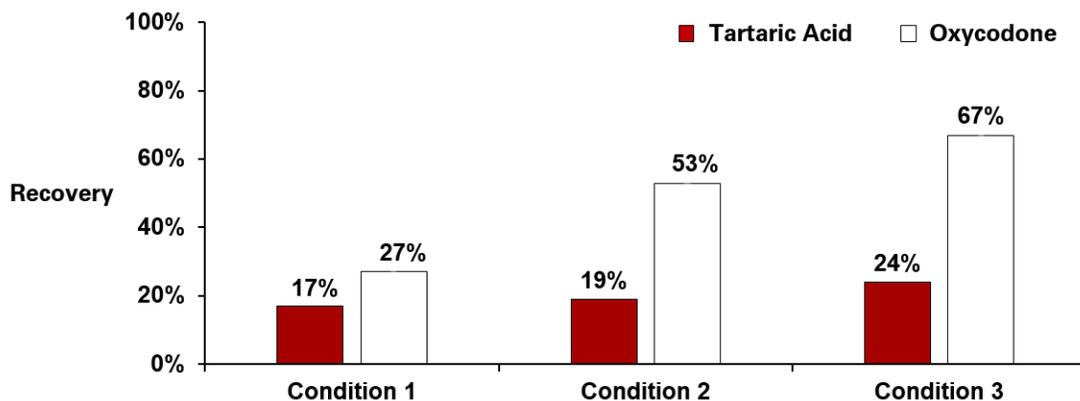
- Disintegrant to facilitate immediate release when taken orally as intended
- Nasal irritant to deter IN abuse

The amount of tartaric acid in ADF Replacement tablets was driven primarily for its function as a disintegrant and is higher than the amount needed to cause nasal irritation. Once the IN aversive characteristics of the ADF Replacement are known, a dedicated individual may attempt to thermally stress the tablet in an attempt to selectively degrade or eliminate tartaric acid.

Mallinckrodt evaluated 28 thermal stressing conditions on ADF Replacement 30 mg tablets to evaluate the feasibility of various approaches for selective degradation. The temperatures and times for the respective conditions were selected based on the known physical properties of tartaric acid and oxycodone HCl in an attempt to selectively degrade tartaric acid. Due to the potential for the thermal stressing conditions to degrade oxycodone as well as tartaric acid, the recoveries of both ingredients were quantitatively determined. Since Roxycodone does not include any agents to discourage IN abuse, it was not evaluated in this study.

Figure 9 illustrates the recovery of tartaric acid and oxycodone from the three most effective thermal stressing conditions. None of the thermal stressing conditions were able to eliminate tartaric acid from ADF Replacement tablets. The conditions that produced the greatest degradation of the nasal irritant (76-83%) also degraded a substantial amount of oxycodone (33-73%), which would not be a desirable result for IN abuse. Pre-clinical studies suggest that the degree of aversive effects is related to the dose of the nasal irritant. Thus, insufflation of thermally-stressed tablets would still be expected to cause unpleasant sensations (eg, pain, burning) since tartaric acid remained in all conditions.

**Figure 9: Most Effective Thermal Stressing Conditions at Degrading Tartaric Acid from ADF Replacement Tablets**



### 5.4 Large Volume Extraction

The rationale for large volume extraction of an opioid product is to either (1) obtain a drinkable, liquid solution with a high amount of extracted opioid or (2) to differentially solubilize the opioid from other excipients such as gelling agents. Extraction in large volumes is a concern for oral abuse of ER opioid products, since they are subject to “dose dumping” and defeat of the time-release mechanism. In contrast, there is minimal incentive for an individual to attempt extraction of an IR opioid for oral abuse which are rapidly bioavailable by design when taken orally intact. In fact, the FDA requires an IR SE

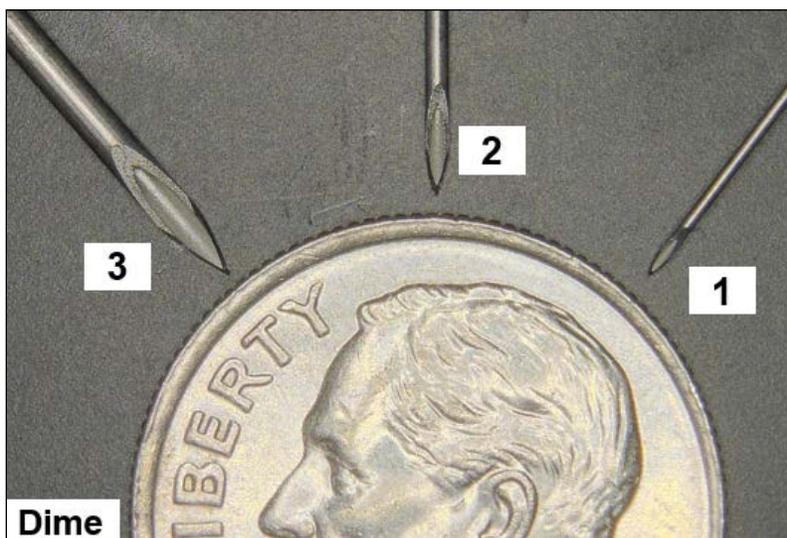
oxycodone tablet have a dissolution profile showing at least 85% release of the active drug within 15 minutes (FDA 2015).

Mallinckrodt performed large volume extraction studies in representative solvents with varying pH and polarity in accordance with the FDA Guidance document on abuse-deterrent testing (FDA 2015). As expected with any IR formulation, the rate of release of oxycodone HCl was rapid in most aqueous solvents under most conditions with both the ADF Replacement and Roxicodone. Importantly, due to the fact that the ADF Replacement has several different gelling polymers, none of the solvents were able to differentially solubilize oxycodone from the gelling excipients.

### 5.5 Small Volume Extraction and Syringeability

The rationale for small volume extraction of an opioid is to obtain an injectable amount of solution with a high yield of the opioid that can be syringed for IV injection. A typical condition for IV abuse would be to extract oxycodone HCl in 1-2 mL of an injectable solvent for less than one minute and syringe and inject the solution using a small needle (eg, Needle 1; Figure 10).

**Figure 10: Needle Gauges Evaluated for Syringeability**



Given the importance of robust IV abuse-deterrent properties, Mallinckrodt performed 1,836 separate combinations of small volume extraction and syringeability test conditions. These tests included simple methods for IV abuse as well as more extensive combinations with high solvent volumes, large needles, agitation, elevated temperature, long extraction times, and pretreatments in an attempt to overcome the gelling properties of the ADF Replacement. Following the initial battery of tests, additional pretreatment conditions were evaluated in consultation with FDA to ensure that the IV abuse deterrence of the ADF Replacement had been fully characterized. Due to the iterative nature of the testing, the tests were aggregated for summary in two categories:

- **Common Methods for IV Abuse:** 288 combinations of conditions were evaluated for both intact and ground ADF Replacement and Roxicodone 30 mg tablets to determine the feasibility of preparing IV solutions without the additional time and effort of pretreatment in the most frequently-used solvent for IV abuse.
- **Advanced Methods for IV Abuse:** 1,548 combinations of conditions with various pretreatments and other directly-injectable solvents were evaluated for the ADF Replacement only, since Roxicodone could be easily prepared for injection using common methods.

Since ADF opioid medications must be bioavailable to treat pain, the abuse-deterrent properties of any ADF can be overcome with sufficient time, effort, materials, and knowledge. Given that any ADF can only be abuse-deterrent and not abuse-proof, the goal of the small volume extraction and syringeability testing was to determine the extent of the work required to overcome the abuse-deterrent properties and whether these barriers would be sufficient to deter individuals from IV abuse of the product. With that goal in mind, Mallinckrodt used knowledge of the composition of ADF Replacement tablets to select pretreatment conditions and advanced techniques to challenge the abuse-deterrent properties.

#### 5.5.1 Common Methods for IV Abuse with ADF Replacement and Roxicodone

The yield of syringeable oxycodone from intact tablets in the most frequently-used solvent without pretreatment was low (< 10%) across all conditions for the ADF Replacement and was variable for Roxicodone. In general, yields from Roxicodone were higher with longer extraction times.

A summary of the more relevant testing conditions using ground tablets without pretreatment (across solvent volumes, temperatures, agitation conditions, needle gauges, and extraction times) is provided in [Table 7](#). While Roxicodone provided a high yield of syringeable oxycodone in most conditions, no conditions yielded an appreciable oxycodone recovery from the ADF Replacement.

<b>Table 7: Oxycodone Recovery from Ground ADF Replacement and Roxicodone Tablets across Small Volume Extraction and Syringeability Tests with Common Methods</b>		
Yield of Syringeable Oxycodone	n (%) of Conditions	
	ADF Replacement 30 mg (N = 144 Conditions)	Roxicodone 30 mg (N = 144 Conditions)
< 5%	141 (98)	0
> 5% to 10%	2 (1)	0
> 10% to 20%	1 (<1)	0
> 20% to 40%	0	15 (10)
> 40% to 60%	0	73 (51)
> 60% to 100%	0	56 (39)

### 5.5.2 Advanced Methods for IV Abuse with ADF Replacement

The ADF Replacement was further evaluated using methods of pretreatment known to be used by individuals in an attempt to overcome IV abuse-deterrent properties. These additional studies evaluated a broad range of solvent volumes, needle gauges, agitation conditions, elevated temperatures, and extraction times with pretreated ADF Replacement tablets. **Table 8** provides the key results and interpretations from the studies using IV pretreatments. In general, the yield of syringeable oxycodone was low in all but a small number of advanced conditions.

<b>Table 8: Summary of Small Volume Extraction and Syringeability Tests with Advanced Methods Using Most Frequently-Used Solvent for IV Abuse</b>			
<b>IV Pre-treatment</b>	<b>N Conditions Tested</b>	<b>Median (Range) Oxycodone Recovery (%)</b>	<b>Interpretation</b>
1	288	0 (0 – 18)	<ul style="list-style-type: none"> <li>IV Pretreatment 1 did not meaningfully increase the feasibility of preparing IV solutions of the ADF Replacement.</li> </ul>
2	288	0 (0 – 9)	<ul style="list-style-type: none"> <li>IV Pretreatment 2 did not meaningfully increase the feasibility of preparing IV solutions of the ADF Replacement.</li> </ul>
3	216	1 (0 – 35)	<ul style="list-style-type: none"> <li>IV Pretreatment 3 did not increase the median yield of syringeable oxycodone; the maximum yield was 35%.</li> <li>The conditions required for maximum recovery required advanced conditions: ground tablets, largest injection volume, largest needle, the longest extraction time point, and elevated temperature throughout the extraction.</li> </ul>
4	216	10 (0 – 60)	<ul style="list-style-type: none"> <li>IV Pretreatment 4 increased the yield of syringeable oxycodone (median 10%, maximum 60%).</li> <li>The set of conditions required for the highest yields of oxycodone with Pretreatment 4 were extensive: ground tablets, large injection volumes, large needles, the longest extraction time point, and elevated temperature throughout the extraction.</li> <li>Sets of conditions that provided the highest yield of syringeable oxycodone would take an individual over an hour to perform.</li> </ul>

The use of other directly-injectable solvents for extraction did not increase the maximum yield of syringeable oxycodone relative to experiments conducted with the most frequently-used solvent for IV abuse.

### 5.5.3 Conclusions of Small Volume Extraction and Syringeability Studies

Overall, the ADF Replacement provided substantial barriers to preparation for IV injection. The yield of syringeable oxycodone was low in all but a small set of advanced conditions which would require at least an hour-long process involving a time-consuming pretreatment, high extraction volumes, needles 2-4 times larger than those preferred for IV abuse, and an elevated temperature maintained throughout the extraction. The results demonstrate that the ADF Replacement can be expected to make abuse via injection more difficult than the non-ADF IR SE oxycodone tablets that it is intended to replace.

## 6 IN VITRO AND IN VIVO EXCIPIENT SAFETY STUDIES

### Summary

- Epidemiologic data and mechanistic data in animals identified a rare, but serious risk that repeated IV injection of the HMW PEO that was the primary excipient in Opana ER could cause thrombotic microangiopathy, acute kidney injury, and retinal damage.
- The ADF Replacement does not contain any of the type of HMW PEO that was used in Opana ER.
- Mallinckrodt performed *in vitro* and *in vivo* excipient safety studies to evaluate the safety of IV injection of ADF Replacement extracts. The test articles were selected based on the advanced sets of conditions that achieved the highest yields of syringeable oxycodone using the two most frequently-cited IV pretreatment methods on drug abuse websites.
- FDA provided advice to Mallinckrodt on these study designs, which were implemented.

### In Vitro Hemolytic Potential, Plasma Compatibility, and Platelet Aggregation Studies

- Test articles did not exhibit hemolysis in whole human blood.
- Test articles did not exhibit any evidence of human plasma incompatibility.
- Test articles did not induce platelet aggregation when mixed with human plasma or PRP.

### In Vivo Multiple-dose IV Toxicity Study

- No evidence of overt toxicity or tissue damage was observed with the test articles.
- Test articles were not associated with signs or symptoms of thrombotic microangiopathy, acute kidney injury, or eye ischemia or injury.
- A statistically significant increase in fibrinogen with Test Article 2 was not considered adverse in the absence of other correlates of inflammation or coagulation and because fibrinogen levels were within the laboratory's normal historical ranges.
- A statistically significant increase in spleen weight with Test Article 2 was not considered adverse due to a lack of tissue damage.
- Minimal to slight microscopic pathology findings were observed, but the independent pathologist did not consider the changes in organs to be adverse in the context of the study findings.

### 6.1 Rationale for Studying Safety of Excipients for IV Injection

Epidemiologic data from the Centers for Disease Control and Prevention (CDC) identified an association between IV abuse of Opana® ER, an ER oxymorphone product, and the incidence of TTP-like symptoms, a rare, serious blood disorder characterized by microangiopathic hemolytic anemia and thrombocytopenia (CDC 2013). Subsequent mechanistic investigations in animals confirmed that repeated IV injection of the specific type of HMW PEO, which was the primary excipient in Opana ER, could result in hemolysis, retinal damage, and thrombotic microangiopathy (Hunt et al 2017).

While ADF Replacement tablets do not include any of the HMW PEO associated with the safety issues observed with Opana ER, Mallinckrodt evaluated the potential safety risks of IV injection of ADF Replacement extracts in general toxicology studies. In all studies, the sets of experimental conditions that achieved the highest yield of syringeable oxycodone using the two most frequently-cited pretreatment methods for IV abuse on drug abuse websites (eg, bluelight.org) were used as Test Article 1 and Test Article 2, respectively. The FDA provided feedback and recommendations on design elements of these safety studies, which were implemented. All studies were performed by an independent, third-party laboratory.

## 6.2 *In Vitro* Hemolytic Potential, Plasma Compatibility, and Platelet Aggregation Studies

The *in vitro* studies evaluated whether the ADF Replacement extracts had the potential to cause hemolysis (ie, destruction of erythrocytes) when mixed with whole human blood, whether ADF Replacement extracts were compatible with human plasma, and whether ADF Replacement extracts caused platelet aggregation in human plasma.

### 6.2.1 Hemolytic Potential Study

To evaluate hemolytic potential, the two ADF Replacement test articles were compared to a negative control and a positive control. (The positive control was a substance known to lyse erythrocytes.) Each mixture was incubated in a test tube for 40 to 45 minutes at approximately 37°C. After incubation, the tubes were centrifuged (set to maintain 2 to 8°C) and the supernatant was harvested. A hemoglobin index, which approximates the amount of hemoglobin in mg/dL, was determined for the supernatant of each tube. A positive result for this assay was considered to be a hemoglobin concentration of 500 mg/dL more than the negative control.

As shown in [Table 9](#), neither ADF Replacement test article exhibited *in vitro* hemolytic potential.

<b>Table 9: Results of <i>In Vitro</i> Hemolytic Potential Study</b>		
<b>Condition in Human Blood</b>	<b>Hemoglobin (mg/dL)</b>	<b>Result of Hemolysis Assay</b>
Negative control	5	-
Test Article 1	9	Negative
Test Article 2	1	Negative
Positive control	5895	Positive

### 6.2.2 Plasma Compatibility Study

To evaluate plasma compatibility, both test articles were introduced into human plasma and compared to a negative control. Compatibility with human plasma was evaluated by adding 0.5 mL of Test Article 1 and Test Article 2 into tubes containing human plasma. The contents of each tube were examined macroscopically to record changes in color or clarity relative to the negative control as well as the presence of flocculation or precipitation. Microscopic examinations were conducted for all mixtures.

Test Article 1 did not cause macroscopic changes compared with the negative control, and there was no evidence of protein flocculation. Test Article 2 in plasma resulted in a cloudy appearance compared with the negative control, and there was no evidence of protein flocculation microscopically. The cloudy appearance of plasma when mixed with Test Article 2 was likely due to the presence of finely suspended particles that were noted prior to introduction into the plasma. There was no visual evidence of platelet aggregation with either test article.

### 6.2.3 Platelet Aggregation Study

To quantify platelet aggregation and ATP release, 45 µL of Test Article 1, Test Article 2, or buffer were added into 405 µL of platelet rich plasma (PRP) and were compared to 450 µL PRP as a negative control. PRP was derived by centrifuging whole blood collected into 3.2% citrate that was collected from a volunteer blood donor with a normal platelet aggregation response. The extent of platelet aggregation was quantified in the absence of an agonist and in response to 3 different agonists. Results were compared to the negative control obtained from the donor PRP and historical values.

The addition of Test Article 1 or Test Article 2 to PRP did not increase platelet aggregation or impact ATP release. Observed percent platelet aggregation and platelet adenosine diphosphate (ADP) responses when drug was added to PRP were similar to that observed with addition of the buffer. Test Article 1, Test Article 2, and the buffer all produced results that were similar to the negative control and were within the normal reference range for healthy blood donors.

### **6.3 In Vivo Multiple-dose IV Toxicity Study**

The *in vivo* multiple-dose IV toxicity study was conducted to evaluate the local and systemic effects of pretreated ADF Replacement extracts, which contain oxycodone and various excipients, after repeated IV injection. At the request of the FDA, the study was designed to evaluate the potential for local effects, hematological effects, thrombotic microangiopathy, overt toxicity, and tissue damage.

In this study, 12 New Zealand White female rabbits, aged 17 to 19 weeks and weighing 2.0 to 3.5 kg at the initiation of dosing, were randomized to one of 3 dosing groups:

- Test Article 1, N=4
- Test Article 2, N=4
- Negative control (0.9% saline), N=4

Animals in the Test Article groups were administered 1 mL/kg of the ADF Replacement extract IV at a nominal concentration of either 2.0 mg oxycodone/mL (Test Article 1) or 2.8 mg oxycodone/mL (Test Article 2). Doses were administered once daily for three days via slow bolus IV injection into a marginal ear vein (alternated each dosing day). Injection sites were marked and maintained for collection at necropsy. Negative control animals were administered 1 mL/kg of 0.9% saline for injection via the same dosage route.

Each animal was monitored at least twice daily (a.m. and p.m.) where abnormal findings were to be recorded as observed for mortality, abnormalities, and signs of pain or distress. Food consumption was monitored throughout the pre-dose and dosing phases. Body weight was monitored, at a minimum, during the pre-dose phase, before dosing on Day 1 of the dosing phase, and on the day of scheduled sacrifice. Abnormal findings were recorded if they were observed.

Dermal observations at the dosing sites (both ears) were scored and graded according to a standardized technique in the pre-dose phase, prior to dosing on each day of the dosing phase, as well as 2-4 hours post-dose on dosing days

On the day of scheduled sacrifice, blood was collected for all animals via a jugular vein and urine was collected via cystocentesis at the time of necropsy. A full panel of clinical pathology tests was performed including hematology, coagulation, clinical chemistry, and urinalysis ([Table 10](#)).

**Table 10: Clinical Pathology Tests in IV Toxicity Study**

<b>Hematology</b>	
Red blood cell (erythrocyte) count	Platelet count
Hemoglobin	White blood cell (leukocyte) count
Hematocrit	Absolute neutrophil count
Mean corpuscular volume	Absolute lymphocyte count
Mean corpuscular hemoglobin	Absolute monocyte count
Mean corpuscular hemoglobin concentration	Absolute eosinophil count
Red cell distribution width	Absolute basophil count
Absolute reticulocyte count	Absolute large unstained cell count
Blood smear	
<b>Coagulation</b>	
Prothrombin time	Activated partial thromboplastin time
Fibrinogen	
<b>Clinical Chemistry</b>	
Glucose	Aspartate aminotransferase
Urea nitrogen	Alanine aminotransferase
Creatinine	Alkaline phosphatase
Total protein	Gamma glutamyltransferase
Albumin	Creatine kinase
Globulin	Calcium
Albumin/globulin ratio	Inorganic phosphorus
Total cholesterol	Sodium
Triglycerides	Potassium
Total bilirubin	Chloride
<b>Urinalysis</b>	
Appearance (clarity and color)	Glucose
Volume	Ketones
Specific gravity	Bilirubin
pH	Blood
Protein	

At necropsy, the external features of the carcass; external body orifices; abdominal, thoracic, and cranial cavities; organs; and tissues were examined, organs were weighed, and macroscopic observations were recorded. Tissues were fixed in 10% neutral buffered formalin or modified Davidson's fixative (eyes, optic nerve) prior to being embedded in paraffin. The following tissues were processed to slide, stained with hematoxylin and eosin, and evaluated microscopically by a veterinary pathologist: the injection site(s), heart, kidneys, lungs, spleen, and uterus. An additional section was taken from the kidney and stained with Jones Silver stain.

This study was performed in accordance with the US FDA Good Laboratory Practice for Nonclinical Laboratory Studies, the Animal Welfare Act, the Guide for the Care and Use of Laboratory Animals, and the Office of Laboratory Animal Welfare. The study design is based on the principles of the FDA CDER/International Conference on Harmonisation (ICH) Harmonised Tripartite Guidelines ICH-M3(R2), Nonclinical Safety Studies for the conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals (FDA 2010).

The *in vivo* study used a standard grading scale that was used by the independent pathologist to characterize the microscopic/histopathology findings:

- 1 (Minimal) – describes inconspicuous changes
- 2 (Slight) – referring to a noticeable, but not a prominent feature
- 3 (Moderate) – a prominent feature
- 4 (Marked) – a dominant, but not overwhelming feature
- 5 (Severe) – implies an overwhelming condition

The key findings from the *in vivo* study are provided in [Table 11](#). Overall, the study found no evidence of overt toxicity or tissue damage that would be associated with thrombotic microangiopathy, retinal damage, or acute kidney injury.

<b>Table 11: Summary of Findings from Multiple-dose <i>In Vivo</i> Toxicity Study</b>			
<b>Evaluation</b>	<b>Negative Control</b>	<b>Test Article 1</b>	<b>Test Article 2</b>
<b>Injection site</b>	Mild, procedure-related	Mild, procedure-related	Mild, procedure-related
<b>Coagulation</b>	Normal	Normal	Normal
<b>Urinalysis</b>	Normal	Normal	Normal
<b>Hematology</b>	Normal	Normal	2-fold increase in reticulocytes*, otherwise normal
<b>Clinical chemistry</b>	Normal	Normal	1.5-fold increase in fibrinogen
<b>Macroscopic</b>	No findings	No findings	No findings
<b>Organ weight</b>	No change	No change	50% increase in spleen weight
<b>Microscopic (Histopathology)</b>	Eye, infiltrates, minimal [1/4] Lung, infiltrates, minimal [1/4] Spleen, congestion [0/4]	Eye, infiltrates [0/4] Lung, infiltrates, slight [4/4] Spleen, congestion [0/4]	Eye, infiltrates, minimal [3/4] Lung, infiltrates, slight [4/4] Spleen, congestion, slight [2/4]

\* Within normal historical range and not statistically or biologically significant

Mild, procedure-related injection site reactions were observed in all groups. No effects were observed for coagulation or in urinalysis. All findings were normal with regard to hematology with the exception of a two-fold increase in reticulocytes for Test Article 2 that was not biologically or statistically significantly different from the negative control. All findings were normal with regard to clinical chemistry with the exception of a statistically significant 1.5-fold increase in fibrinogen for Test Article 2 relative to the negative control. The increase in fibrinogen was not considered adverse due to a lack of changes in other correlates of inflammation or coagulation and due to the fact that fibrinogen levels were within the laboratory's normal historical ranges. No macroscopic findings were noted in any of the groups. A statistically significant 50% increase in spleen weight was observed with Test Article 2 that was not considered adverse due to a lack of tissue damage; the increase in spleen weight was considered to be related to the clearance of oxycodone, excipients, or both.

In terms of microscopic findings, minimal infiltrates were observed in the eye and lung in one animal in the negative control group. With Test Article 1, slight lung infiltrates were observed in all 4 animals. With Test Article 2, minimal eye infiltrates were observed in 3 animals, slight lung infiltrates in all 4 animals, and slight spleen congestion in 2 animals. The independent pathologist did not consider the minimal to slight changes in these animals to be adverse in the context of the study findings.

#### **6.4 Conclusions from *In Vitro* and *In Vivo* Excipient Safety Studies**

The *in vitro* studies did not identify an association between the extracts in pretreated ADF Replacement tablets with hemolysis of red blood cells, flocculation of proteins, or aggregation of human platelets. Furthermore, the extracts in pretreated ADF Replacement tablets evaluated in the *in vivo* study were not associated with signs or symptoms of thrombotic microangiopathy, overt toxicity, or tissue damage that had been previously observed in mechanistic studies with a particular type of HMW PEO that is not present in the ADF Replacement. However, it should be acknowledged that IV injection of any solid oral dosage form – whether ADF or non-ADF – is not safe due to the risk for overdose and the inclusion of excipients to facilitate the intended oral route of administration, which are not intended for IV use.

## 7 CATEGORY 2 AND CATEGORY 3 INTRANASAL HUMAN ABUSE POTENTIAL STUDY

### Summary

- The IN HAP Study evaluated the PK and PD of IN ADF Replacement compared with IN Roxycodone, oral ADF Replacement, and placebo in 38 recreational, nondependent opioid users.
- Unlike most ADFs that work by decreasing “positive effects” such as Drug Liking, the primary IN abuse-deterrent mechanism of the ADF Replacement is to create “negative effects” with aversive agents to discourage abuse.
- At early time points, oxycodone plasma concentrations were significantly lower with the IN ADF Replacement than IN Roxycodone.
- PD results from “positive effects” endpoints
  - IN ADF Replacement did not meet the primary endpoint for maximum ( $E_{max}$ ) Drug Liking with a 10% superiority margin compared with IN Roxycodone ( $p = 0.223$ ).
  - Consistent with the PK results, Drug Liking scores were significantly lower for IN ADF Replacement than IN Roxycodone through the first 1.5 hours post dose, which is the most important time frame for IN abuse.
  - The average time to peak Drug Liking effect ( $TE_{max}$ ) was 0.9 hours longer for IN ADF Replacement than IN Roxycodone ( $p = 0.018$ ).
  - Similar results for maximum effects and effects over time were observed for Drug High.
- PD results from “negative effects” endpoints
  - IN ADF Replacement was significantly more difficult to snort than IN Roxycodone (84 vs 11;  $p < 0.001$ ).
  - IN ADF Replacement was associated with significantly more adverse nasal effects (eg, burning, irritation, facial pain/pressure) compared with IN Roxycodone.
- PD results from “overall experience” endpoints
  - Upon recall of the positive and negative effects 24 hours after dosing, subjects expressed less Overall Drug Liking for IN ADF Replacement than IN Roxycodone (46 vs 71;  $p < 0.001$ ), with similar overall liking to placebo (48).
  - Willingness to Take Drug Again scores 24 hours after dosing were significantly lower for IN ADF Replacement than IN Roxycodone (41 vs 71;  $p < 0.001$ ), with numerically lower willingness to take again than placebo (50).
- Overall, the study showed that while participants achieved positive psychoactive effects from all active treatments, the aversive agents in the ADF Replacement caused unpleasant sensations, including burning and pain, that led subjects to report that they were as likely to insufflate the ADF Replacement again as they were to take placebo.

### 7.1 Study Design

The IN HAP study was a randomized, double-blind, double-dummy, 4-period crossover study comparing the IN abuse potential of the ADF Replacement to Roxycodone. In accordance with FDA Guidance, the study enrolled nondependent, recreational opioid users with a recent history of IN opioid use (at least 3 times within the last year). (Note: This population is recommended by FDA because “subjects should generally not be physically dependent and should not be currently seeking or participating in treatment for drug abuse such that participating in the study could make them vulnerable to relapse (FDA 2015).”

Prior to the Treatment Phase, subjects underwent a Qualification Phase. A Naloxone Challenge Test was administered to ensure subjects were not physically dependent on opioids and a Drug Discrimination Test was administered to ensure subjects could discriminate between an IN dose of Roxycodone 15 mg and placebo. Thirty-eight (38) subjects completed all 4 study periods without emesis in the first hour (which would have confounded PK and PD findings) and comprised the primary analysis population.

In the Treatment Phase, subjects received 4 treatments in a random order with a 72-hour washout period between treatments (active treatments **bolded**):

- **IN ADF Replacement 30 mg** and oral placebo for ADF Replacement
- **IN Roxycodone 30 mg** and oral placebo for ADF Replacement
- **Oral ADF Replacement 30 mg** and IN placebo for Roxycodone
- Oral placebo for ADF Replacement and IN placebo for Roxycodone

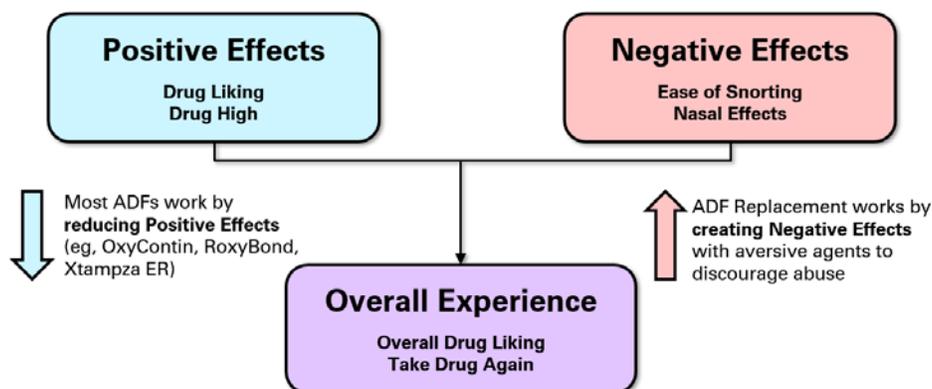
The most effective particle size reduction procedures identified in the particle size reduction studies were used to prepare Roxycodone and the ADF Replacement for IN administration in the HAP study.

## 7.2 Pharmacodynamic Endpoints

The IN HAP study evaluated the full battery of PD endpoints recommended in FDA Guidance, which can be categorized broadly in three categories (Figure 11):

- “Positive effects” are measured by endpoints such as Drug Liking and Drug High, which are evaluated at several time points through 12 hours post dose to ascertain the positive euphoric effects of the treatment.
- “Negative effects” are measured by endpoints such as Ease of Snorting (evaluated immediately post-dose) or Nasal Effects Assessment (evaluated through 12 hours post dose) to ascertain the negative aspects of the experience.
- “Overall experience” is measured by endpoints such as Overall Drug Liking and Take Drug Again, which are evaluated at 12 and 24 hours post dose, to determine how subjects integrated the positive and negative effects once the psychoactive effects have dissipated.

**Figure 11: Summary of Key Pharmacodynamic Endpoints Evaluated in IN HAP Study**



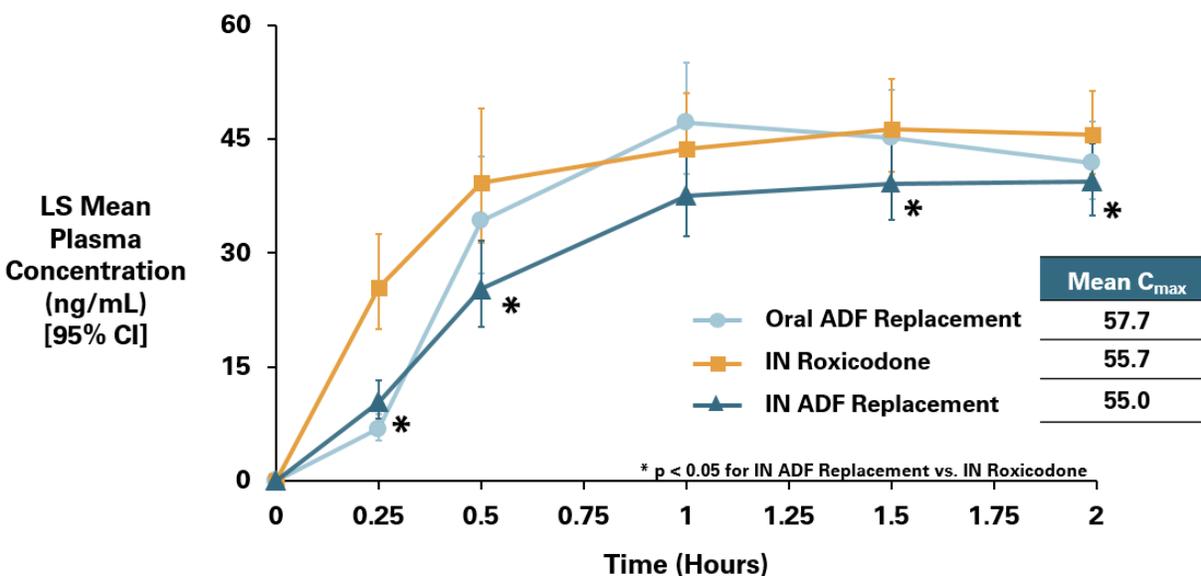
The primary mechanism of abuse deterrence for most ADFs such as OxyContin, RoxyBond, and Xtampza ER is to slow down the drug release to reduce the “positive effects” compared to a non-ADF product. The primary mechanism of abuse deterrence for the ADF Replacement is to create negative effects with aversive agents to make snorting unpleasant to increase the “negative effects” compared to a non-ADF product.

In accordance with FDA Guidance, the primary endpoint for the study was designated as Drug Liking  $E_{max}$ , or the maximum Drug Liking score regardless of time, with a superiority margin. The superiority margin for Drug Liking  $E_{max}$  was set at 10% of the absolute IN Roxicodone drug effect, whereby the estimated treatment difference between IN ADF Replacement and IN Roxicodone had to be statistically greater than the difference between IN Roxicodone and the neutral effect of 50 multiplied by 10% (approximately 3.3 points). (This is often referred to as a test for “super-superiority,” in contrast to a test for “superiority” where the difference between the treatments has to be statistically greater than 0.)

### 7.3 Pharmacokinetic Results

The oral ADF Replacement taken intact had a PK profile that would be expected for an IR SE oxycodone product, with a gradual rise in plasma concentrations (Figure 12). IN Roxicodone was associated with a substantially faster rate of rise in oxycodone concentrations at early timepoints, consistent with the IN route of administration. At early time points, IN ADF Replacement was associated with significantly lower oxycodone concentrations than IN Roxicodone that were similar to or lower than the oral intact ADF Replacement. The  $C_{max}$  values, or maximum concentrations, of oxycodone were similar for all 3 active treatments.

**Figure 12: Least Square Mean Oxycodone Plasma Concentrations through Two Hours Post Dose**



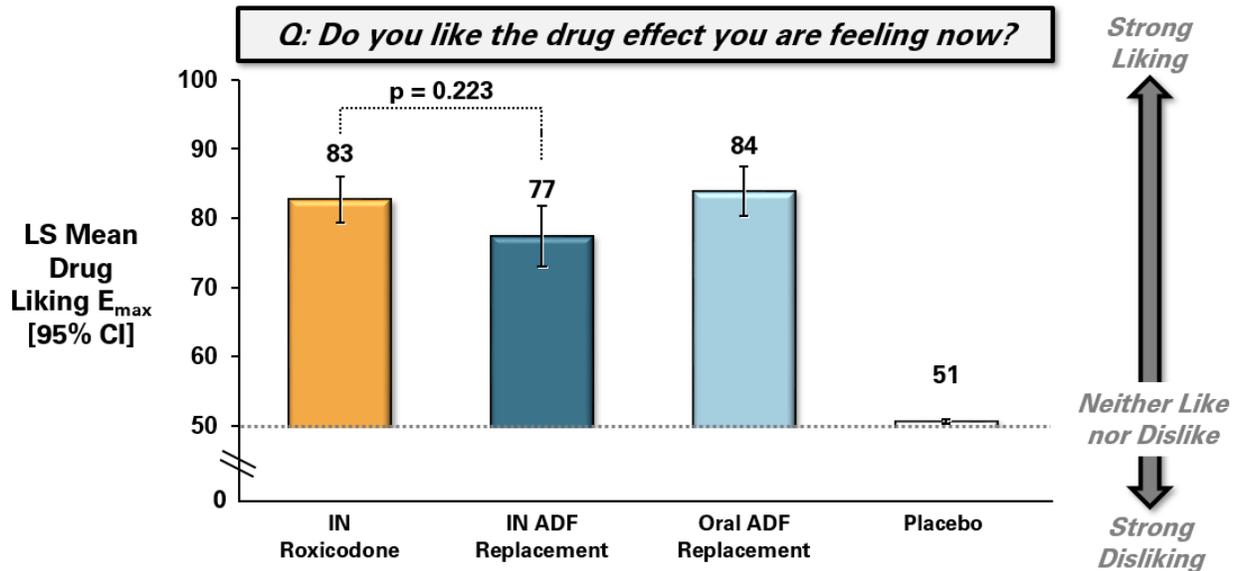
### 7.4 Pharmacodynamic Results for “Positive Effects”

#### 7.4.1 Drug Liking $E_{max}$ – Primary Endpoint

Drug Liking was assessed at regular intervals throughout the first 12 hours post dose with the question, “Do you like the drug effect you are feeling now,” which was assessed on a bipolar visual analog scale (VAS) where 0 indicates *strong disliking*, 50 indicates *neither like nor dislike*, and 100 indicates *strong liking*.

The estimated treatment difference between IN ADF Replacement and IN Roxicodone in Drug Liking  $E_{max}$  (ie, maximum Drug Liking at any time point) was -5.3 (95% CI: -10.6, 0.1), which did not achieve the pre-specified 10% superiority margin compared with Roxicodone ( $p = 0.223$ ). All active treatments were associated with positive maximum drug liking (Figure 13).

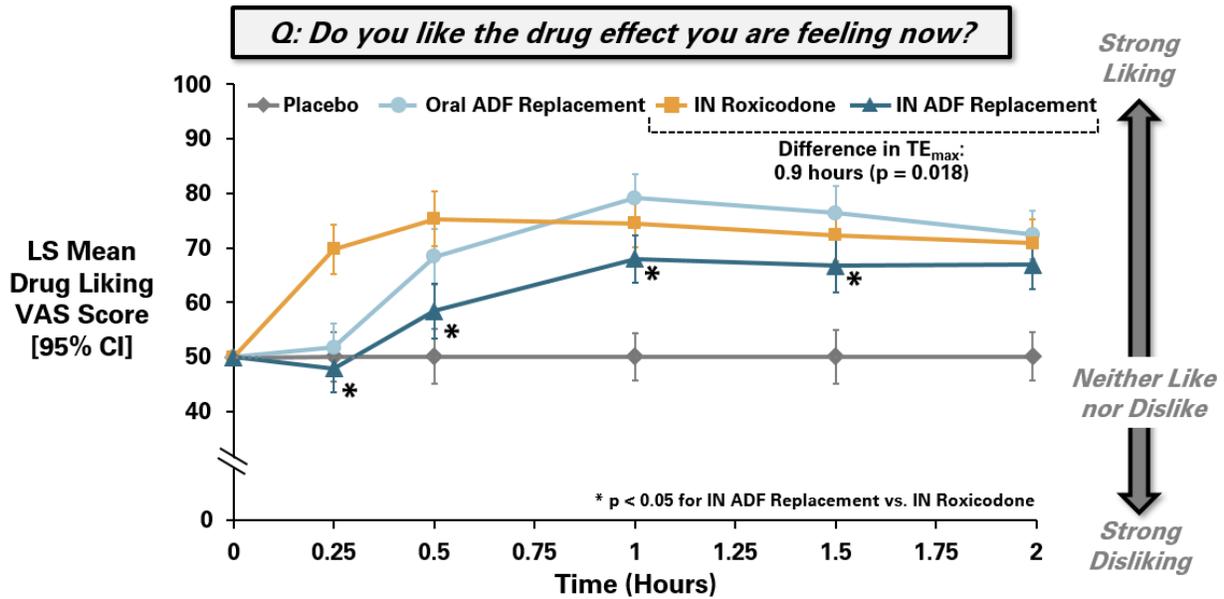
**Figure 13: Primary Endpoint – Drug Liking  $E_{max}$**



7.4.2 “At-the-Moment” Drug Liking

Figure 14 illustrates the time course in mean Drug Liking over the first two hours, which is the most relevant time frame for IN abuse. The time course results for Drug Liking were consistent with the PK results. Oral intact ADF Replacement was associated with a gradual rise in Drug Liking while IN Roxicodone had a considerably more rapid increase in Drug Liking, consistent with the faster rate of rise in oxycodone concentrations and the rationale for why individuals snort IR opioid products over oral ingestion. IN ADF Replacement delayed the average time to peak effect by 0.9 hours compared to IN Roxicodone ( $p = 0.018$ ) and was associated with significantly lower Drug Liking scores at all time points through the first hour and a half, which is the time frame individuals would expect to experience the most profound Drug Liking effects after insufflation.

**Figure 14: At-the-Moment Drug Liking through Two Hours Post Dose**

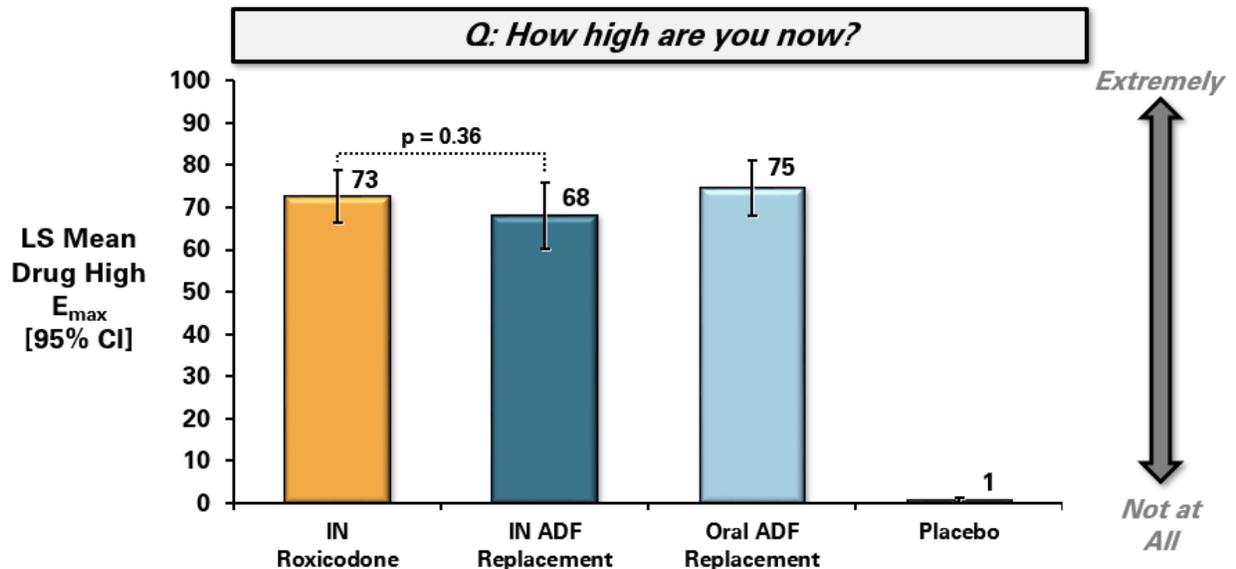


7.4.3 Drug High E<sub>max</sub>

Drug High was assessed at regular intervals throughout the first 12 hours post dose with the question, “How high are you now”, assessed on a unipolar VAS where 0 indicates *not at all* and 100 indicates *extremely*.

Results for Drug High E<sub>max</sub> were consistent with the findings for Drug Liking E<sub>max</sub>. Subjects achieved similar maximum Drug High in all active treatments (Figure 15).

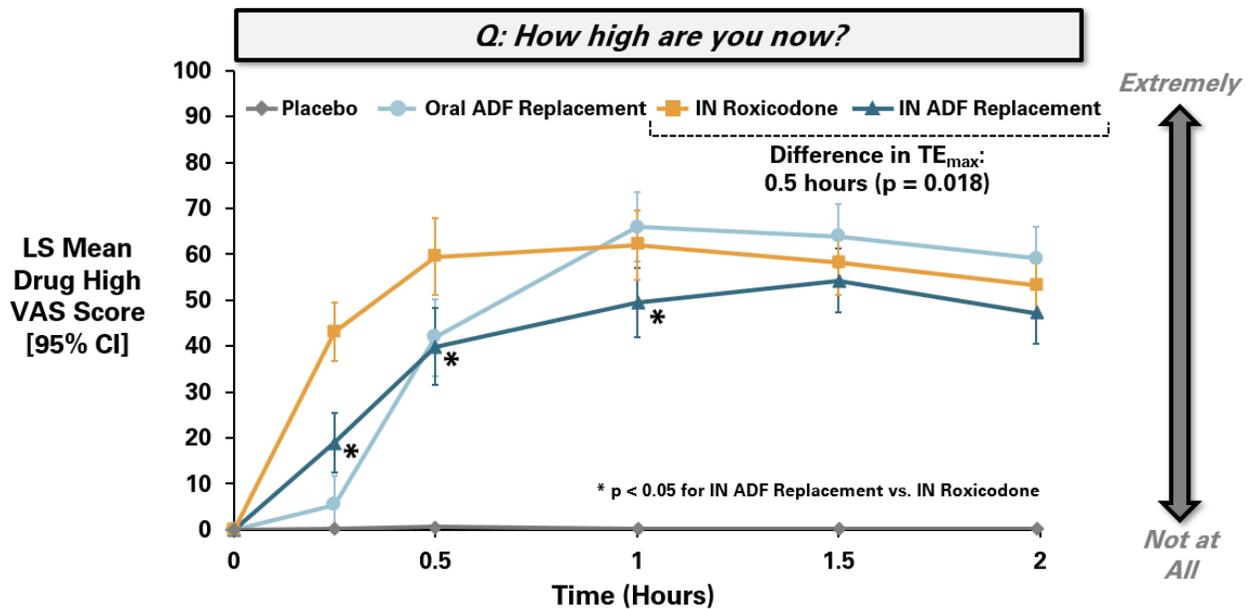
**Figure 15: Drug High E<sub>max</sub>**



#### 7.4.4 “At-the-Moment” Drug High

Results for “at-the-moment” Drug High were congruent with results for “at-the-moment” Drug Liking and PK. Oral ADF Replacement was associated with a gradual rise in Drug High, while IN Roxicodone had a considerably more rapid rise. IN ADF Replacement had a significantly delayed rise in Drug High ( $p=0.018$ ) with significantly lower mean Drug High scores than IN Roxicodone at all time points through the first hour, which is the time frame individuals would expect to feel the greatest high after insufflation (Figure 16).

**Figure 16: At-the-Moment Drug High through Two Hours Post Dose**

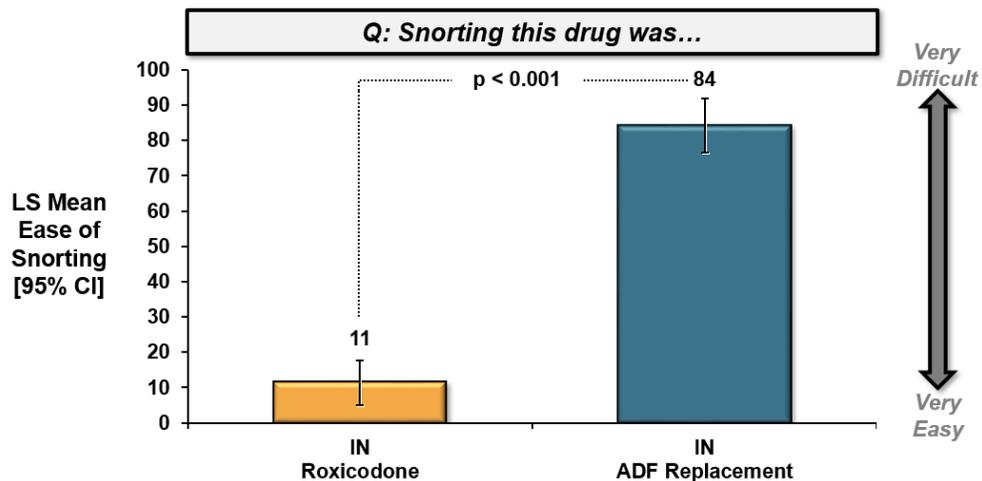


### 7.5 Pharmacodynamic Results for “Negative Effects”

#### 7.5.1 Ease of Snorting Assessment

Ease of Snorting was assessed within 5 minutes of insufflation with the question, “Snorting this drug was...,” using a unipolar VAS where 0 indicates *very easy* and 100 indicates *very difficult*. The mean ease of snorting score for IN ADF Replacement was statistically significantly higher than IN Roxicodone, indicating that subjects found the ADF Replacement much more difficult to insufflate (Figure 17).

**Figure 17: Ease of Snorting Assessment**

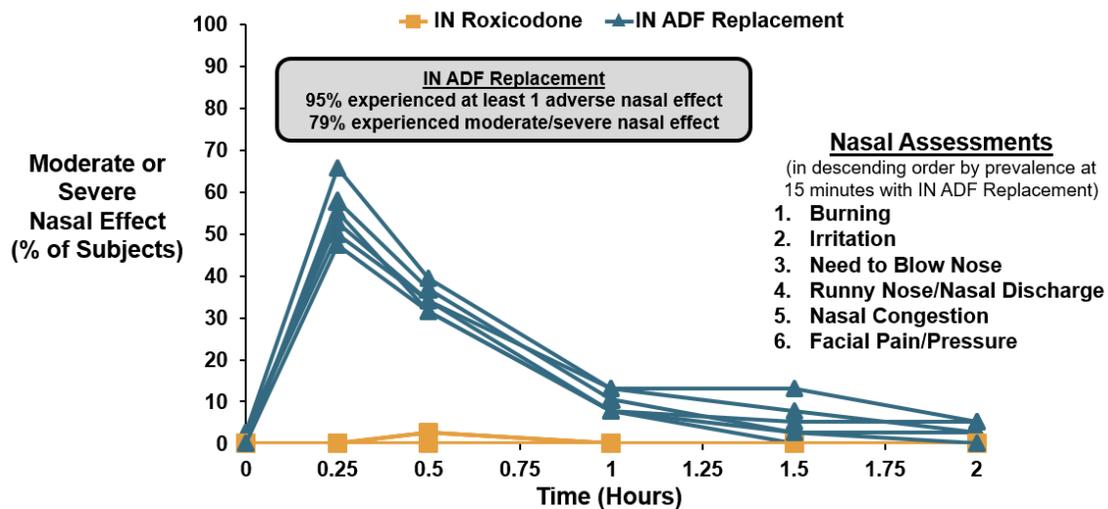


7.5.2 Nasal Effects Assessment

The Nasal Effects Assessment evaluates various negative nasal effects at regular intervals through the first 12 hours post dose, asking subjects whether each nasal assessment (ie, burning, irritation, need to blow nose, runny nose/nasal discharge, nasal congestion, and facial pain/pressure) is present on a scale of *none, mild, moderate, or severe*.

More subjects experienced adverse nasal effects after insufflating the ADF Replacement than Roxicodone. Figure 18 illustrates the prevalence of moderate/severe nasal effects (listed in descending order by prevalence at 15 minutes with the ADF Replacement) through two hours post dose. For example, at 15 minutes, 66% of subjects rated moderate or severe sensations of burning with the ADF Replacement compared with 0% of subjects for Roxicodone. Overall, 95% of subjects experienced at least one adverse nasal effect after insufflating the ADF Replacement and 79% of subjects experienced at least one adverse nasal effect that was considered moderate or severe. Most subjects experienced multiple adverse nasal effects after IN administration of the ADF Replacement.

**Figure 18: Nasal Effects Assessment – Moderate or Severe Effects through Two Hours Post Dose**



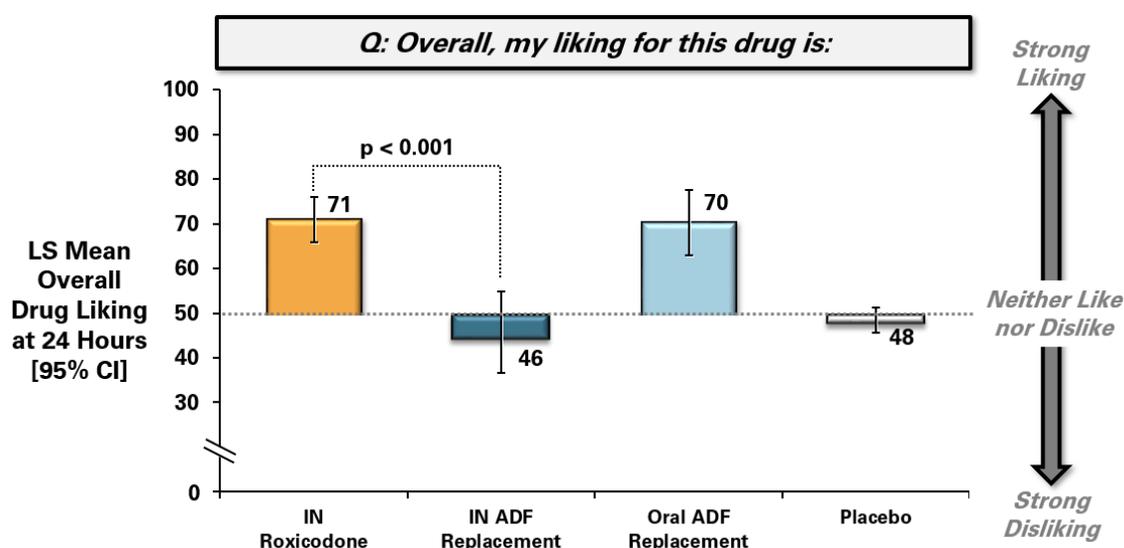
## 7.6 Pharmacodynamic Results for “Overall Experience”

### 7.6.1 Overall Drug Liking

Overall Drug Liking is assessed at 12 and 24 hours post dose with the question, “overall, my liking for this drug is,” assessed on a bipolar VAS where 0 indicates *strong disliking*, 50 indicates *neither like nor dislike*, and 100 indicates *strong liking*.

Twenty-four hours after study drug administration when subjects recalled the entire drug-taking experience, subjects only expressed positive Overall Drug Liking for IN Roxicodone and oral intact ADF Replacement. The Overall Drug Liking scores for IN ADF Replacement were significantly lower than IN Roxicodone ( $p < 0.001$ ), with similar Overall Drug Liking to placebo (Figure 19).

**Figure 19: Overall Drug Liking at 24 Hours Post Dose**



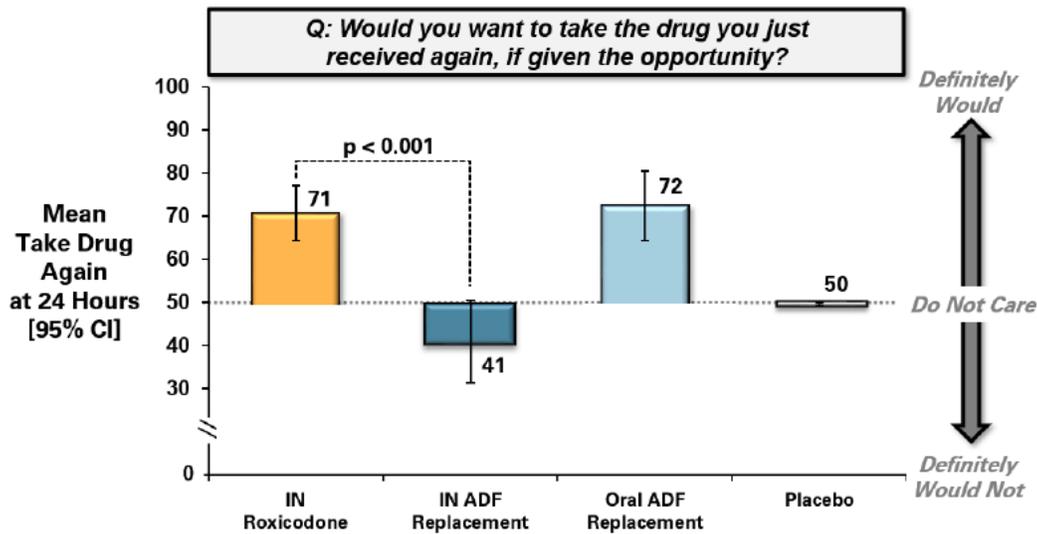
### 7.6.2 Take Drug Again Assessment

Willingness to Take Drug Again was assessed at 12 and 24 hours post dose with the question “would you want to take the drug you just received again, if given the opportunity,” measured on a bipolar VAS where 0 indicates *definitely would not*, 50 indicates *do not care*, and 100 indicates *definitely would*.

At 24 hours post dose, subjects reported high willingness to take either IN Roxicodone or oral intact ADF Replacement again (Figure 20). Willingness to take placebo again was neutral. IN ADF Replacement was associated with a significant 30-point reduction in mean Take Drug Again score compared with IN Roxicodone ( $p < 0.001$ ).

Thus, when participants had the opportunity to reflect on the overall experience and predict their future behavior, they were no more willing to snort the ADF Replacement again than they were placebo, despite experiencing maximum Drug Liking and Drug High scores that were similar to IN Roxicodone and oral ADF Replacement. This finding provides strong evidence that the “negative effects” from the aversive agents in the ADF Replacement had a meaningful deterrent effect for the IN route.

**Figure 20: Take Drug Again Assessment at 24 Hours Post Dose**



### 7.7 Treatment Emergent Adverse Events

Treatment emergent adverse events (AEs) were ascertained through spontaneous reporting by study subjects (ie, AEs were reported outside of the standardized assessments for liking or adverse nasal effects). Most AEs reported during the Treatment Phase were considered mild; no severe AEs were reported. Several subjects reported moderate AEs with IN ADF Replacement that were primarily associated with the route of administration or aversive agents, including coughing, retching, facial burning sensation, or nasal burning. Moderate AEs associated with IN Roxycodone and oral intact ADF Replacement treatments were primarily common opioid-related AEs such as pruritus, nausea, headache, and emesis.

The most common AEs during the Treatment Phase (reported in at least 10% of subjects in any group) are summarized in [Table 12](#). The two AEs with the largest difference between treatments were cough and nasal discomfort, which were higher with IN ADF Replacement. Other common AEs were expected opioid-related AEs.

<b>Table 12: Most Common Treatment Emergent Adverse Events</b>				
Adverse Event	IN Roxycodone (N=42)	IN ADF Replacement (N=40)	Oral ADF Replacement (N=41)	Placebo (N=43)
Cough	1 (2%)	11 (28%)	3 (7%)	3 (7%)
Nasal discomfort	0	10 (25%)	0	1 (2%)
Nausea	3 (7%)	2 (5%)	7 (17%)	0
Vomiting	3 (7%)	3 (8%)	4 (10%)	0
Retching	0	4 (10%)	0	0
Pruritus generalized	11 (26%)	5 (13%)	8 (20%)	0
Pruritus	1 (2%)	3 (8%)	5 (12%)	0
Euphoric mood	7 (17%)	2 (5%)	9 (22%)	2 (5%)
Headache	3 (7%)	0	4 (10%)	0

Table provides all AEs reported at a 10% rate or higher in any group.

## 7.8 Conclusions

The IN HAP study provides substantial evidence that the ADF Replacement has properties that can be expected to deter IN abuse. The PD findings were consistent with the primary mechanism of abuse deterrence.

- Maximum values for Drug Liking and Drug High were similar between all active treatments, however the absorption of oxycodone, Drug Liking, and Drug High were significantly delayed after IN administration of the ADF Reformulation compared with IN Roxycodone.
- The aversive agents made the ADF Replacement difficult to snort and caused unpleasant sensations, including burning and pain.
- Upon reflection of the overall experience and predicting future behavior, subjects reported no greater Overall Drug Liking or willingness to take the IN ADF Replacement again than placebo.

Overall, the study suggests that the ADF Replacement has properties that would make it more difficult and less attractive to abuse via the IN route compared to the products it is intended to replace.

## **8 BENEFIT-RISK EVALUATION**

### **8.1 Benefit-Risk of the ADF Replacement for its Proposed Indication as an Analgesic**

The Mallinckrodt ADF Replacement is an IR SE oxycodone product proposed for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. Clinical bioequivalence studies have demonstrated that the ADF Replacement is bioequivalent to Roxycodone in both fed and fasted states. Therefore, the ADF Replacement would be therapeutically equivalent to the non-ADF IR SE oxycodone tablets manufactured by Mallinckrodt, which it is intended to replace.

Mallinckrodt is requesting approval for 5 strengths of the ADF Replacement: 5, 10, 15, 20, and 30 mg. This flexible dose range is intended to allow prescribers to individualize patient therapy in line with consensus guidelines to use the minimum dose required to effectively manage pain (CDC 2016). For patients with moderate-to-severe pain who cannot achieve adequate pain relief with alternative treatment options, the ADF Replacement has a favorable benefit-profile for its intended use. Patients can expect the same efficacy and safety profile as currently-available IR SE oxycodone medications. The abuse-deterrent properties of the ADF Replacement are also intended to confer the added benefit of making the medication less attractive for diversion.

### **8.2 Benefit-Risk of the ADF Replacement to Replace IR SE Oxycodone Tablets Medications Manufactured by Mallinckrodt**

As recognized by FDA, ADFs are only one component of a broader strategy to address the abuse of prescription pain medications in the US. While ADFs have the potential to reduce IN and IV abuse of a specific product, make diversion less attractive, and deter initiation to non-oral routes of abuse, their limitations must also be acknowledged. An ADF cannot prevent oral abuse by overconsumption, cannot reduce IN or IV abuse of other products, and is not a treatment for opioid use disorder. Rather, ADFs are a harm reduction strategy to reduce the most dangerous forms of abuse of a specific product. Since each instance of IN or IV abuse is associated with approximately twice the likelihood of a major effect (eg, overdose) or death compared with oral abuse (Green et al 2017) as well as the additional health risks of bloodborne infections (eg, HIV, hepatitis C) associated with IV abuse, the goal of reducing non-oral routes of prescription opioid abuse is a worthwhile public health effort.

Transition of the broader opioid market to one where most medications have meaningful abuse-deterrent properties has proven difficult given the limited coverage by payers. To achieve wider uptake of ADFs, clinicians and patients will need to be able to transition from conventional non-ADF products to ADFs with fewer barriers to access. FDA has recognized the issue of cost and has advocated for the development of generic ADFs (FDA 2017). Mallinckrodt's IR SE oxycodone ADF Replacement addresses both the practical and public health concerns that have been raised about ADF products. Table 13 provides a summary of answers to the key benefit-risk questions that have been raised about ADFs by physicians, payers, and recent FDA Advisory Committees.

<b>Table 13: Benefit-Risk Considerations for Mallinckrodt's ADF Replacement</b>	
<b>Practical or Public Health Concern</b>	<b>Benefit-Risk Analysis</b>
ADFs have low uptake and will have limited public health impact	<ul style="list-style-type: none"> <li>Mallinckrodt would replace branded and generic IR SE oxycodone tablets, which currently represent approximately 15% of the IR SE oxycodone market, with the ADF Replacement.</li> </ul>
ADFs can send a false sense of security to prescribers that these medications are "safe"	<ul style="list-style-type: none"> <li>The ADF Replacement would not be promoted directly to physicians.</li> </ul>
ADFs cannot deter initiation into dangerous routes of abuse	<ul style="list-style-type: none"> <li>The ADF Replacement would be the first ADF with aversive agents to actively discourage repeat IN abuse.</li> <li>Recreational users reported that, on average, they were no more willing to snort the ADF Replacement again than placebo.</li> </ul>
ADFs should not discourage IN abuse if it pushes individuals to IV abuse	<ul style="list-style-type: none"> <li>Aversive agents strongly discourage repeat IN abuse.</li> <li>Standard methods of preparing the ADF Replacement for IV injection were not effective.</li> <li>The only combinations of conditions that provided a substantial yield of syringeable oxycodone required a process that took over an hour to complete using high extraction volumes, elevated temperatures, and large needles that are not preferred for IV abuse.</li> </ul>
ADF excipients can cause serious health consequences if injected	<ul style="list-style-type: none"> <li><i>In vitro</i> and <i>in vivo</i> studies using the sets of conditions that achieved the highest yield of syringeable oxycodone using the two most frequently-cited pretreatments for IV abuse did not suggest a clinically meaningful risk of injecting ADF Replacement extracts.</li> </ul>

Mallinckrodt is fully committed to completing its post-approval requirements consistent with the company's involvement in the existing opioid analgesic REMS and post-market requirements for other products. For the ADF Replacement, Mallinckrodt will, at a minimum, develop an appropriate medication guide, provide REMS assessments to FDA, establish Elements to Assure Safe Use, and conduct Category 4 studies to evaluate whether the ADF Replacement is having its intended public health impact in reducing IN and IV abuse in the real world.

In summary, the ADF Replacement has a favorable benefit-risk profile as a harm reduction strategy to deter IN and IV abuse. While an ADF can only provide abuse *deterrence*, and cannot be abuse-*proof*, there is substantial evidence to support labeling of the ADF Replacement with abuse-deterrent properties:

- IN abuse: recreational users from the IN HAP study reported that they were no more willing to snort the ADF Replacement again than placebo, providing strong evidence for a deterrent effect of the aversive agents.
- IV abuse: the ADF Replacement demonstrated robust physical and chemical barriers to injection across the 1,836 combinations of conditions evaluated. The maximum yield of syringeable oxycodone could only be achieved after an hour-long process with extensive IV abuse conditions. Importantly, *in vitro* and *in vivo* studies did not find evidence that injection of excipients led to hemolysis, overt toxicity, or tissue damage.

Overall, the data from the development program supports the public health benefit of replacing non-ADF IR SE oxycodone tablets manufactured by Mallinckrodt with the ADF Replacement.

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