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Prozor™ Technology & The Potential for Once-Yearly Therapies

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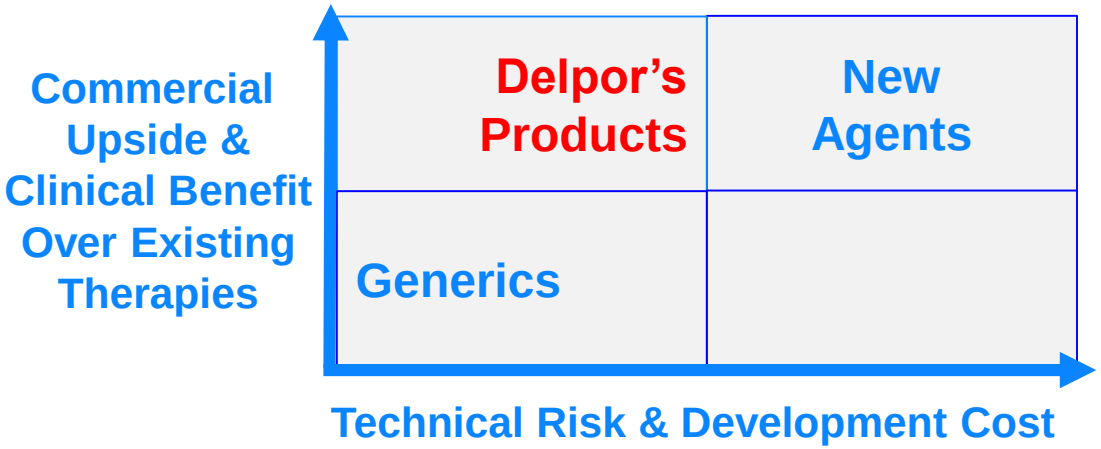
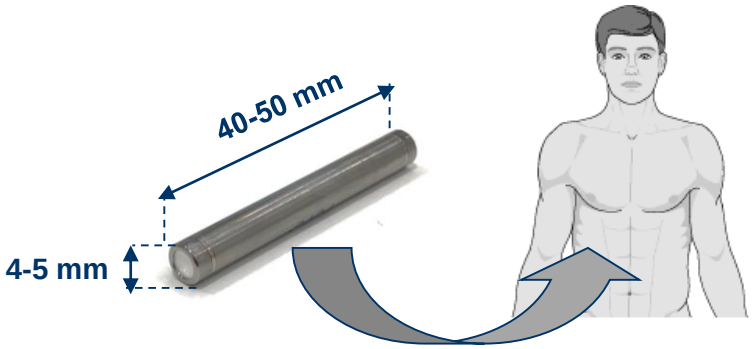
Delpor's Vision and Strategy

- **Vision: Develop Once Yearly Therapies for Chronic Conditions**
  - One Administration (10 min) = Therapy for 1 Year
- **Strategy: Create New Therapeutic Products Based on Existing Drugs – 505b2**



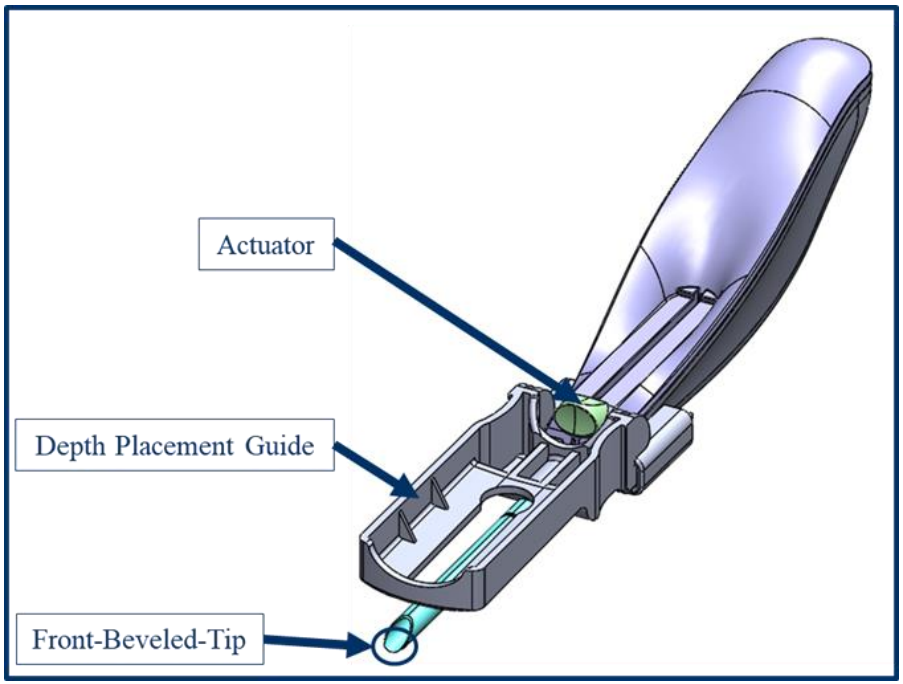
- **Innovative Drug Delivery Technologies**
  - Enable the Sustained Release of Drugs from a Matchstick Size Implant Device (Titanium)
  - Simple In-Office Outpatient Procedure (10 min)
  - Device Replaced After 6-12 Months



Implant Device and Implanter Tool

- **Implant Device and Hydration Buffer**
  - Device stored in a lyophilization vial under vacuum
  - Device is hydrated with sterile saline

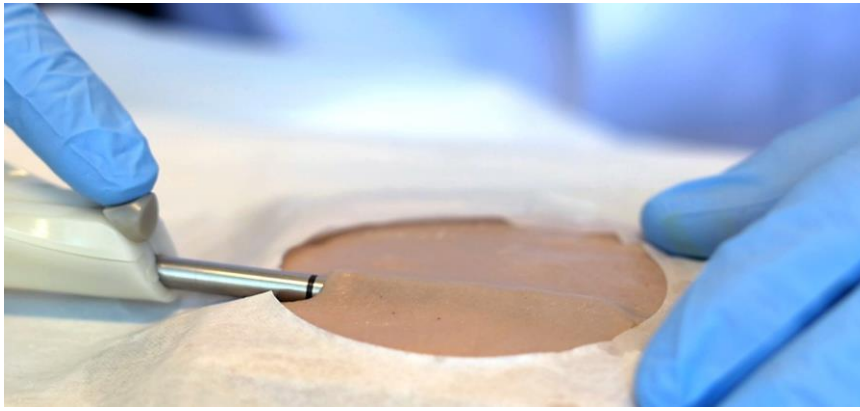
- **Implanter Tool**
  - Thermoformed tray with Tyvek® clean-peel lid



Implantation Procedure – Completed in under 10 minutes

Implant Device Hydration

Implant Insertion

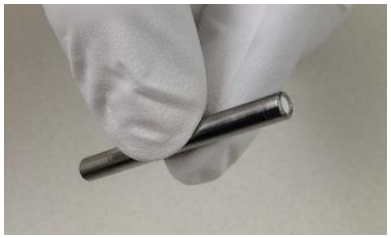


Disposable Implantation Kit

Other Implant Products and Technologies

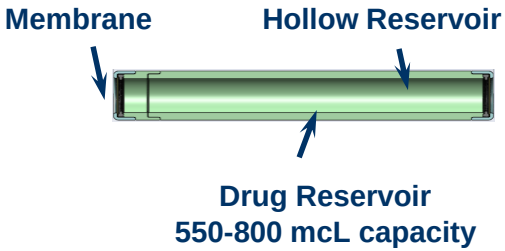
Company	Product	API / Indication	Technology	Material
Intarcia Therapeutics	ITCA 650	Exenatide Diabetes	DUROS®	Titanium
Bayer	Viadur®	Leuprolide Prostate Cancer		
Merck	Implanon®	Etonogestrel Contraception	Ethylene Vinylacetate Copolymer	Polymer/ Plastic
Endo Pharmaceuticals	Vantas®	Histerlin Prostate Cancer	Hydron® Implant Hydrogel polymers	
Endo Pharmaceuticals	Supprelin®	Histerlin CPP	Hydron® Implant Hydrogel polymers	
Titan Pharmaceuticals	Probuphine®	Buprenophine Opioid Addition	ProNeura®	

Titanium implant systems that enable zero-order release



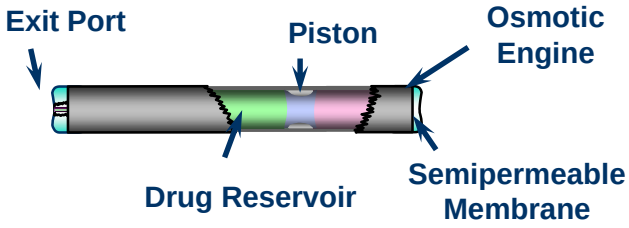
PROZOR™ Device

- Passive diffusion (no moving parts)
- Larger capacity
- Drug may be loaded in solid form



Duros® - Viadur® (leuprolide) / ITCA 650 (exenatide)

- Osmotic pump
- Part of internal volume is used by the osmotic engine
- Can be used with non-aqueous formulations



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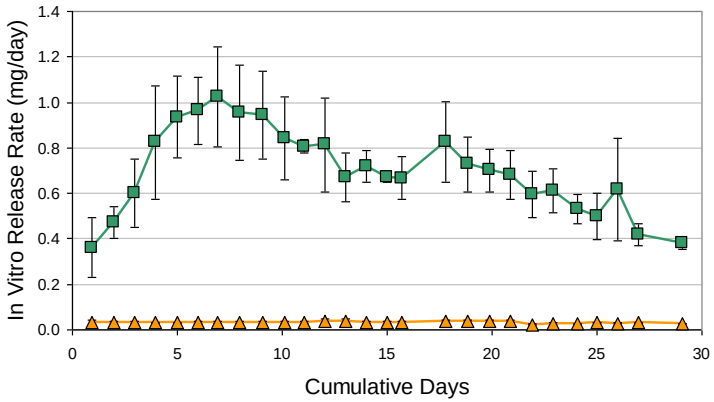
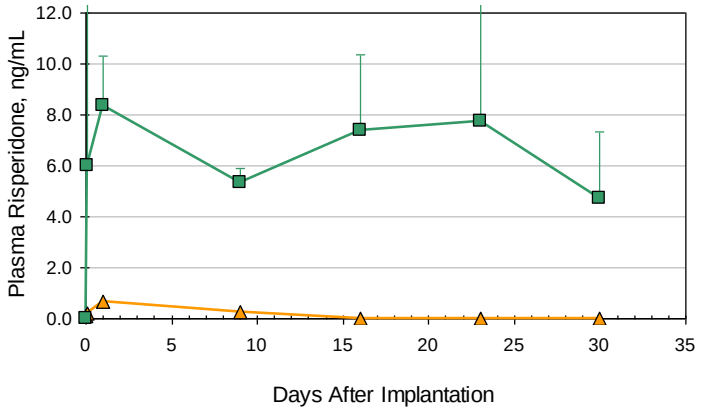
PROZOR™ Technology – Drug Release Mechanism

- Technology works with water insoluble molecules (e.g., most CNS drugs)
- Some of these drugs are weak bases and their solubility increases at lower pH
- Typical formulation is a mixture of the drug and a group of acid producing excipients designed to regulate the pH inside the device
- Acid generation improves solubility of the drug and establishes a concentration gradient sufficient to provide steady efflux
- Initial formulation used PLGA polymers as “acid generators”
- Concept works even if the excipients are separated from the drug

In Vitro Release



In Vivo (rats)



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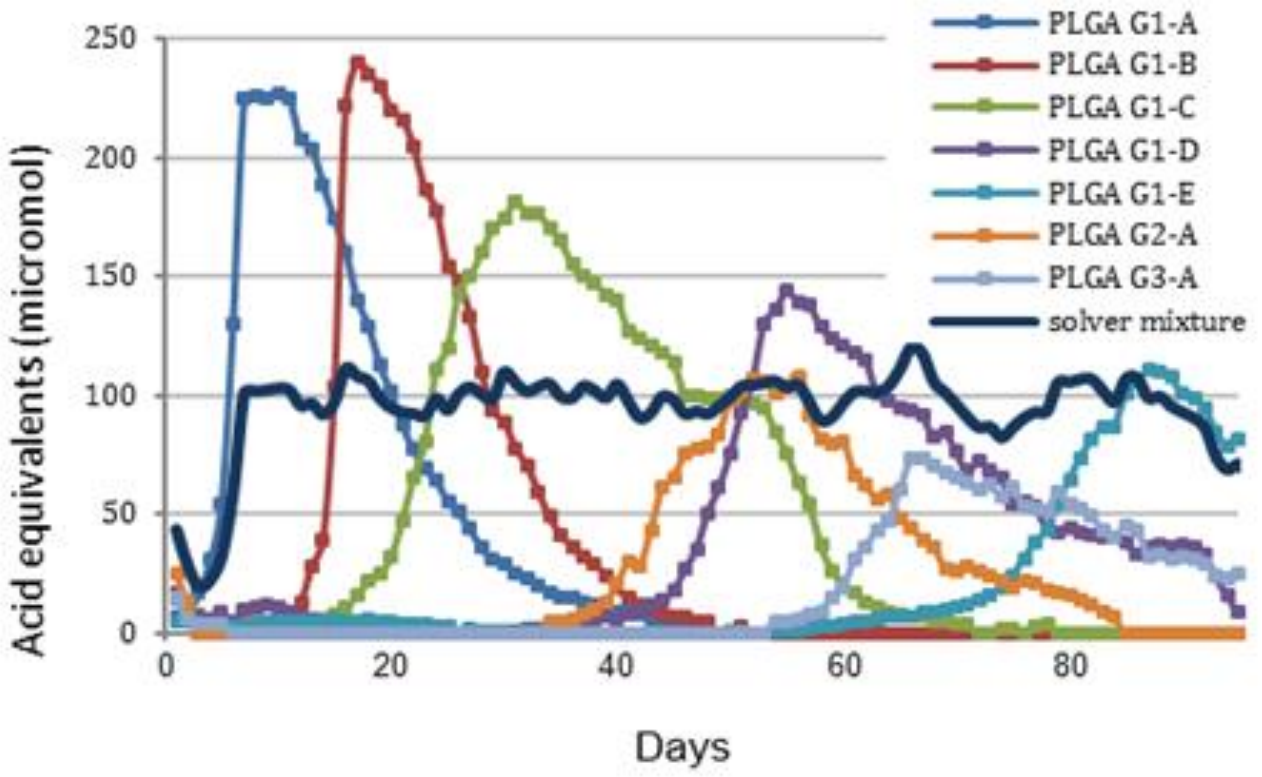
PROZOR™ Technology – Initial Formulation Approach

- Zero-order release kinetics require a steady acid production over time
- We tested the acid production profiles of several polymers covering different time windows
- We then tried to combine them in order to achieve steady acid release



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PLGA Polymer Challenges with the PROZOR™ Technology

- **Acid production of polymer mixtures is not additive due to "cross talk" among the polymers**

- **We were able to address this challenge by using certain salt forms of the drug**
  - Generated promising preclinical PK and local tolerance data

- **CMC Challenges**
  - Sensitivity to moisture
  - Sensitivity to temperature
  - Drug compounding and manufacturing challenges
  - Sensitivity to terminal sterilization methods

- **Other Challenges**
  - Sometimes we observed autocatalytic effects resulting in sudden bursts of output
  - Slowly declining kinetics
  - Duration was limited to ~6 months

PROZOR™ Technology – Current Formulation Approach

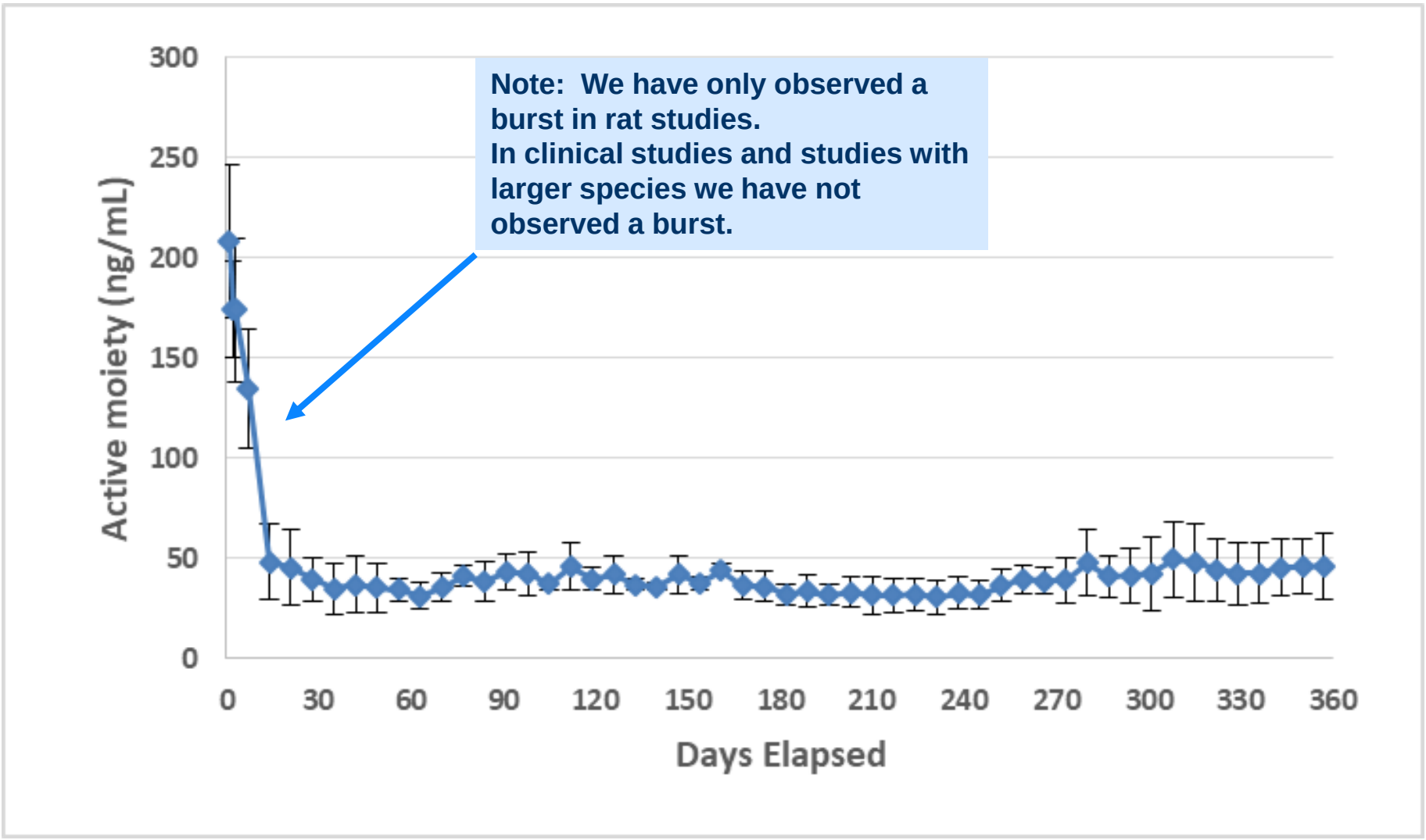
- **Switched from PLGA polymers to partially soluble acids (PSA) as the acid generating excipients**
  - e.g., small molecular weight, naturally occurring carboxylic acids
- **PSAs dissolve slowly inside the device maintaining a steady lower pH environment over several months – Typically coelute with the drug**
- **Most PSAs are safe not posing any systemic safety concerns**
- **PSAs are stable during the manufacturing process and during operation**

	Initial Formulation Approach	Current Formulation Approach
API	Risperidone	Risperidone
Acid Generating Excipient(s)	PLGA Polymers	Partially Soluble Acids

Indications and Products

Category	Products	Indications	Unmet Needs
Antipsychotics	**Risperdal (Risperidone)** Lead program (**DLP 114**)	Schizophrenia Bipolar	Low Compliance Frequent Relapses & High associated cost
	Zyprexa (Olanzapine) Invega (Paliperidone)		
Other CNS	Buprenorphine, Naltrexone	Opioid Use Disorder	Low Compliance Inferior Oral PK Frequent and Inconvenient Dosing
	Tizanidine	Spasticity	
	Escitalopram, Buspirone	MDD & Anxiety	
	Rotigotine, Ropinirole	Parkinson's	
	Rivastigmine	Alzheimer's	

Risperidone PK (rats) – Steady output without decline for 12 Months.



Research reported in this presentation was supported by the National Institute of Mental Health of the National Institutes of Health under award number R44MH094036

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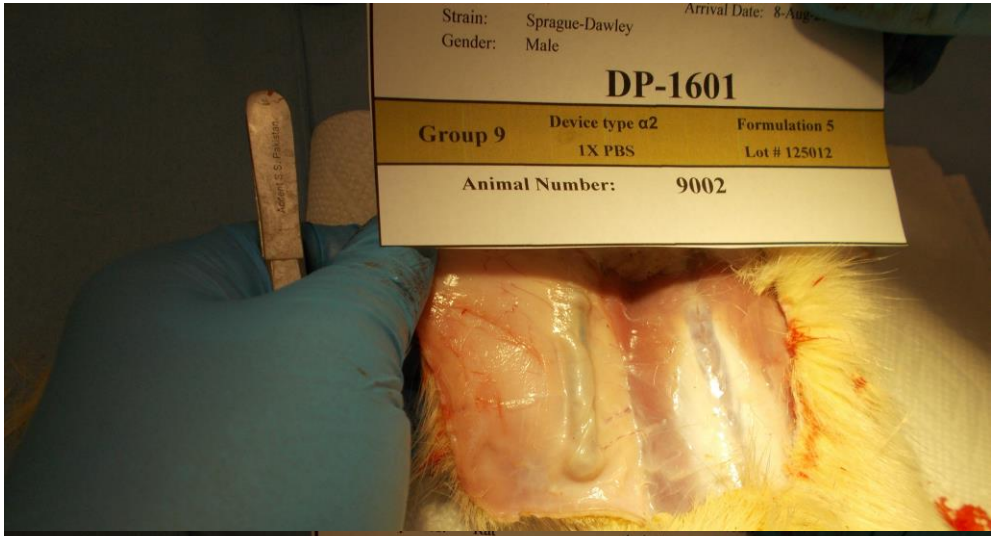
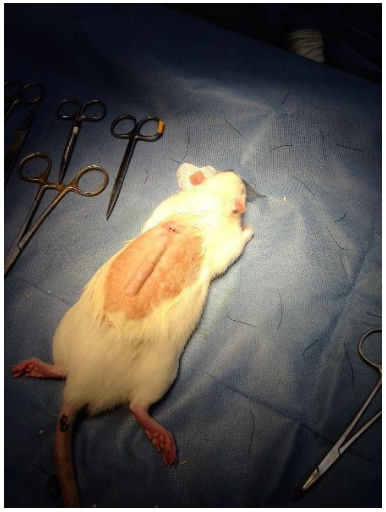
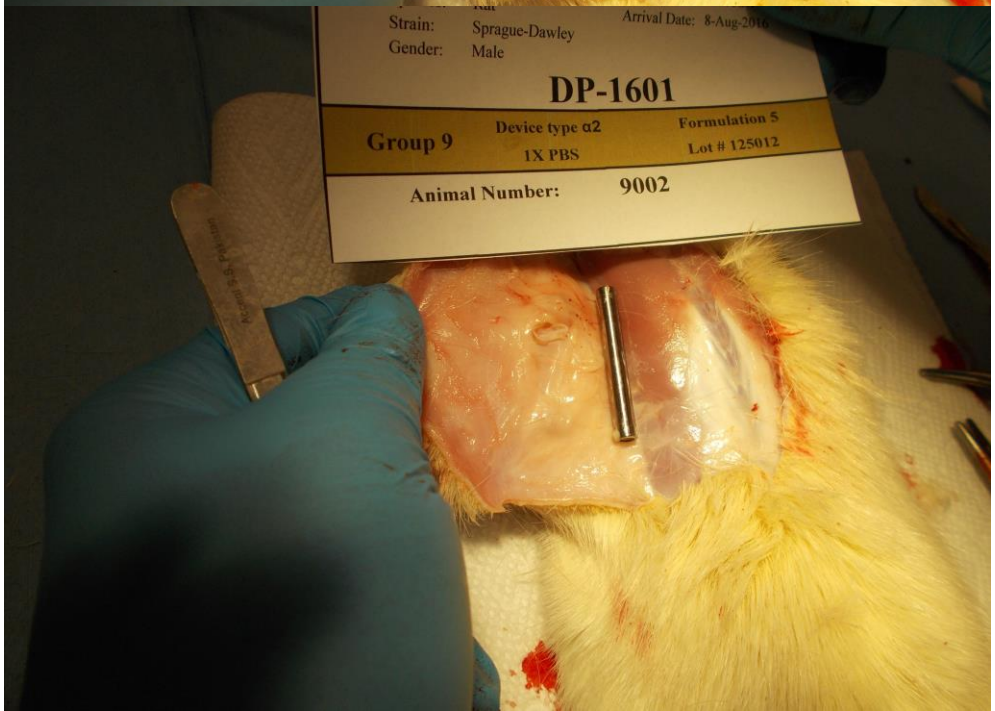
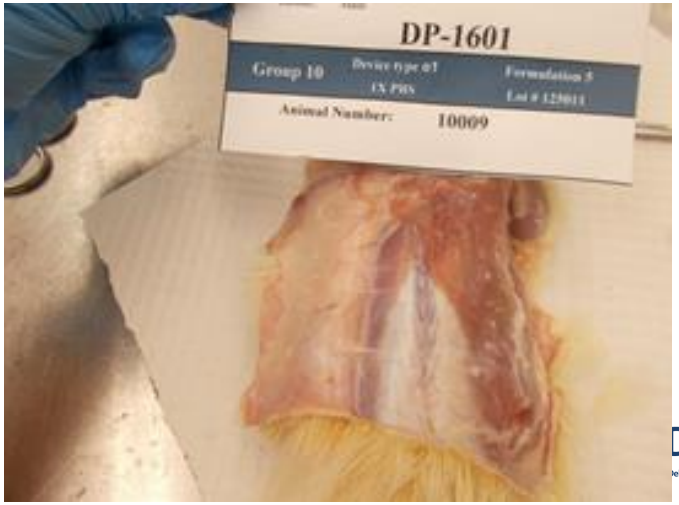
Safety and Histopathology Results Show Biocompatibility







Recovery Group shows that the capsule tissue is resorbed



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Regulatory Process – Needs to be approved as a drug and a device

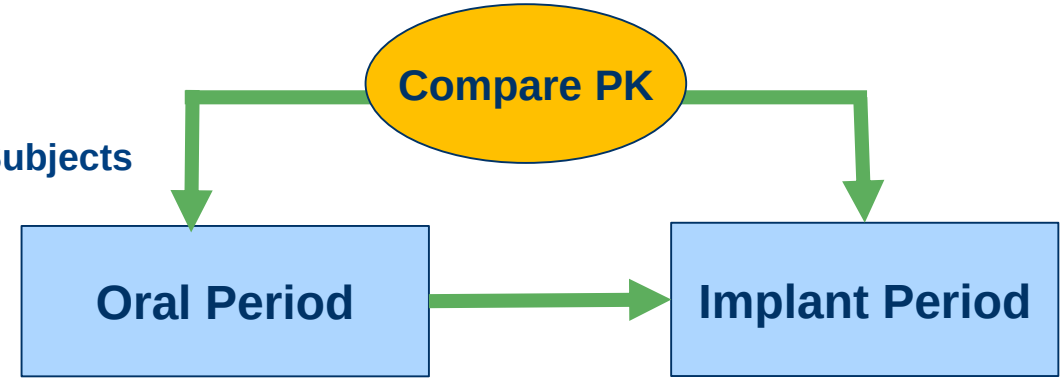
- **FDA Divisions Involved**
  - Center for Drug Evaluation and Research (CDER) – Lead
  - Center for Devices and Radiological Health (CDRH)
  - Office of Combination Products (OCP)

- **Key Areas for Product Success**
  - CMC
  - Human Factors

- **Clinical Studies**
  - Phase I study – 17 subjects completed the study with promising data
  - Phase II study expected to be launched in Q2
  - Pivotal (Phase III) study expected to be launched next year

Phase I and Phase Ib: Single sequence PK comparability study

Enrolment: 12+5 Subjects



Dose	• 1mg	• 1 device
PK Sampling	• Before oral dose on days -7 to -1 • Rich sampling (10 timepoints) on Day -1	• Rich sampling during the first 72hrs • Weekly after Day 3 and rich post-explant

Phase I Study - Demographics

Parameter	Statistic	Implant Main Study (N=12)	Implant Extension (N=5)	Implant Total (N=17)
Age (Years)				
	N	12	5	17
	Mean	31.8	30.0	31.2
	SD	7.1	9.6	7.7
	Median	32.0	25.0	31.0
	Min	20	23	20
	Max	44	46	46
Gender				
Female	n (%)	4 (33%)		4 (24%)
Male	n (%)	8 (67%)	5 (100%)	13 (76%)
Race				
Asian	n (%)	3 (25%)		3 (18%)
White	n (%)	9 (75%)	5 (100%)	14 (82%)

Phase I Study Results

- **Implant procedures lasted only 6 minutes**
- **All subjects have tolerated the device and the procedure**
- **Subjects have not experienced any clinically significant AEs**
  - 1 subject developed cellulitis after 2 months
- **All 17 Subjects have been explanted**
  - Device removal went smoothly with no visible signs of edema or erythema at the implantation site, and no tissue adherence
- **Histopathology has been completed on 2 sentinel subjects without any clinically significant findings**
- **PK shows steady output without decline (similar to animal data)**

Comparison of DLP114 to injectable products

	Risperdal® Consta®	Perseris®	Invega® Sustenna®	Invega Trinza®	DLP-114
Duration	2 Weeks	4 Weeks	4 Weeks	3 Months	6-12 Months
API	Risperidone	Risperidone	Paliperidone	Paliperidone	Risperidone
Reversibility	Not Reversible	Not Reversible	Not Reversible	Not Reversible	Reversible
Initiation Dosing & Re-Initiation When Missing a Dose	Oral Supplements For 3 weeks	No Initiation but Requires 3 Doses to reach Steady State	2 Initiation Doses Re-Initiation Needed if Dose is Missed*	4 Months Sustenna Initiation (6 doses) & Re-Initiation Needed If Dose is Missed **	No Initiation or Re-Initiation Required
Drug Accumulation/ Switching to Another Product	A few Weeks Washout	A few Weeks Washout	Several Weeks Washout	Several Months Washout***	1 Day Washout
PK	Peaks & Troughs	Peaks & Troughs	Peaks & Troughs	Peaks & Troughs	Smooth

* Requires initiation doses on Days 1 & 8 before monthly injections begin, and Re-initiation if dose is missed by 2+ weeks

** Requires Re-initiation Regimen with 2 Sustenna injections (Days 1 & 8) if Trinza dose is missed by 1-6 months
requires full Re-initiation Regimen with at least 6 Sustenna injections if Trinza dose is missed by over 6 months

*** Requires 3 tier dose escalation schedule during ~6 months for switching to oral paliperidone. No data available for switching to another drug.
Safety data involving concomitant use of Trinza with other antipsychotics is limited
Paliperidone has been detected in plasma (7% of C_{ave}) up to 18 months after a single-dose administration of Trinza

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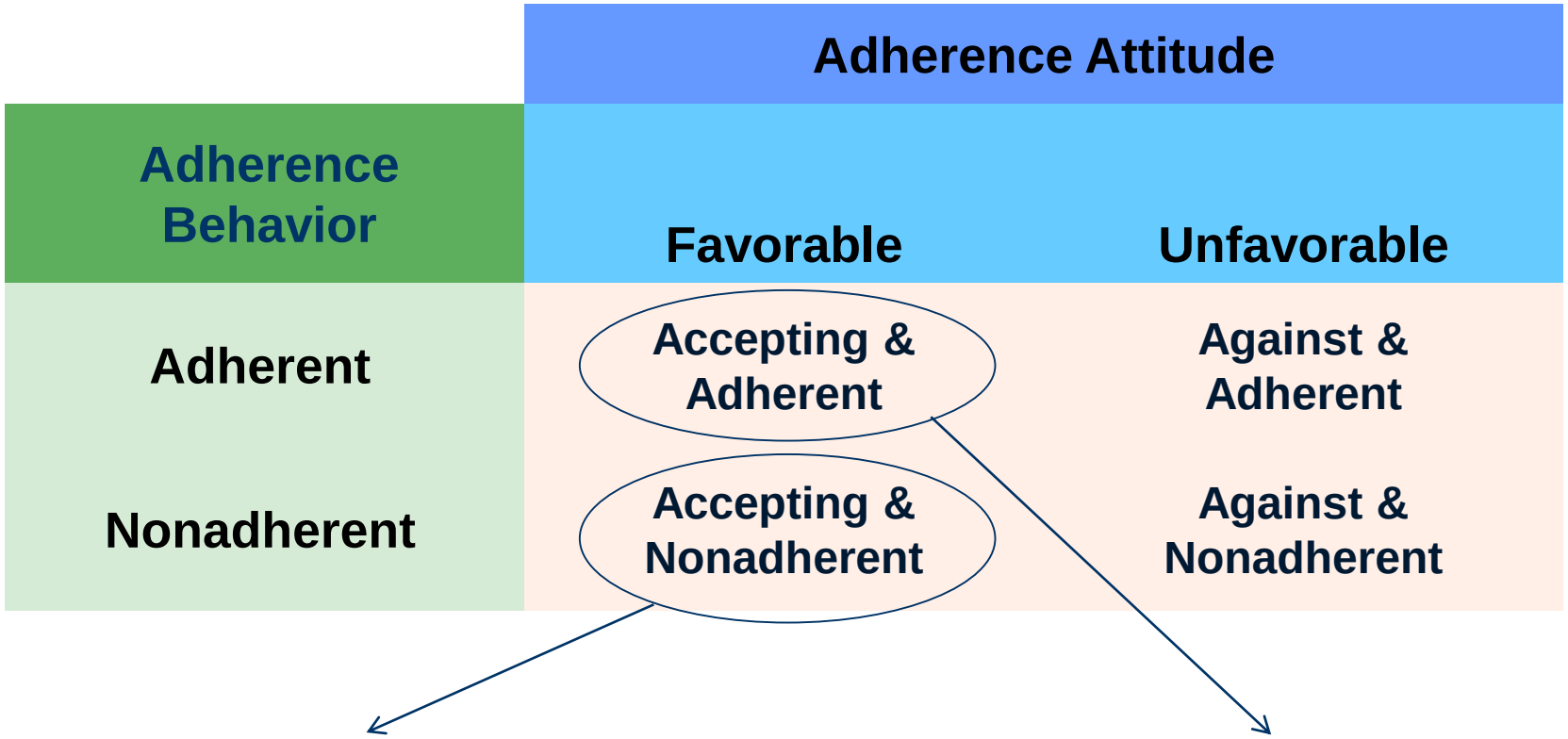
Target Patient Subsegments



Very large subsegment of the patient population

- **Patient does not possess the cognitive skills to effectively adhere to treatment**
- **Examples include, patients suffering from substance abuse, lack of motivation, apathy, etc.**

- Prevent potential future nonadherence
- Reduced peak plasma levels side effects
- Convenience
- Less stigma compared to taking pills
- Avoid medication errors and medication gaps

Adapted from Weiden, P. *J Clin Psychiatry.* 2007;68 (suppl 14):14-19.

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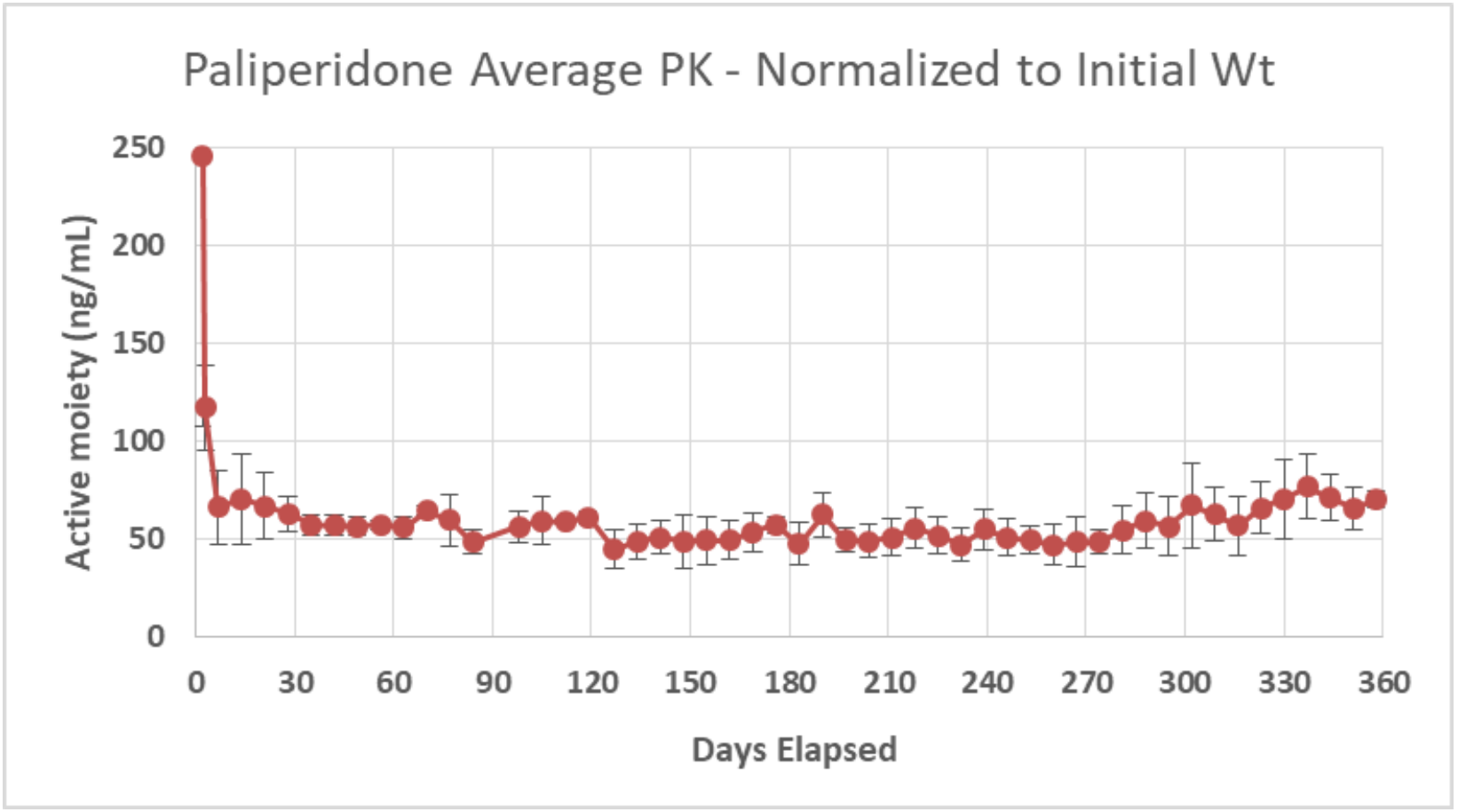
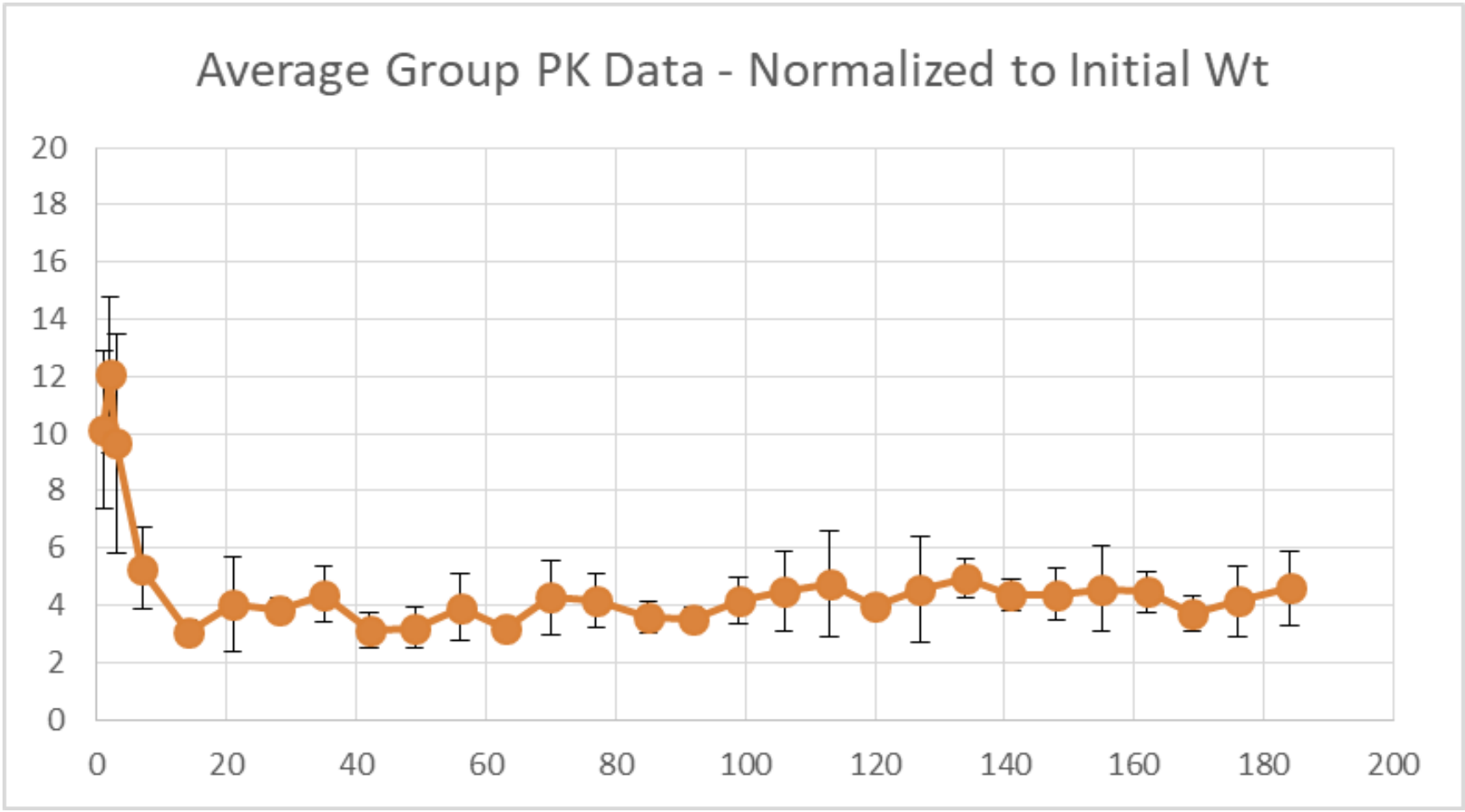
CNS programs

API	Indication	Available Products	Unmet Needs
Risperidone (Lead Program)	**Schizophrenia & Bi-polar**	**Q2W Q1M**	**Poor Adherence**
Naltrexone	Opioid Dependency	Q1M	Low Oral Bioavailability Poor Adherence
Paliperidone	Schizophrenia	Q1M and Q3M	Poor Adherence
Tizanidine	Moderate to Severe Spasticity	Oral & Baclofen IT pump	Low Oral Bioavailability Complex procedure For IT pump
Buprenorphine	Opioid Dependency	Buccal film, Q1W, Q1M 6-Month Implant	Low Oral Bioavailability Addiction, Abuse Misuse Potential
Buspirone	Depression, Anxiety	Oral	Low Oral Bioavailability Short Half Life Poor Adherence
Rotigotine	Parkinson's	Transdermal Patch	Low Oral Bioavailability Poor Adherence
Escitalopram	Depression	Oral	Poor Adherence

Preliminary Paliperidone Rat PK data (1 Year)



Preliminary Rotigotine Rat PK Data (6 months)



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