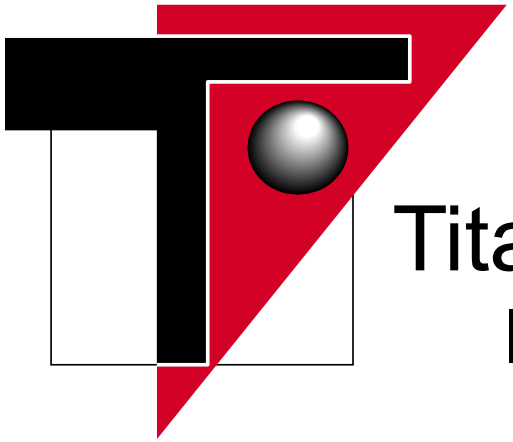


Titan Pharmaceuticals, Inc.

Innovations in Medicine™

Neuroscience 2007

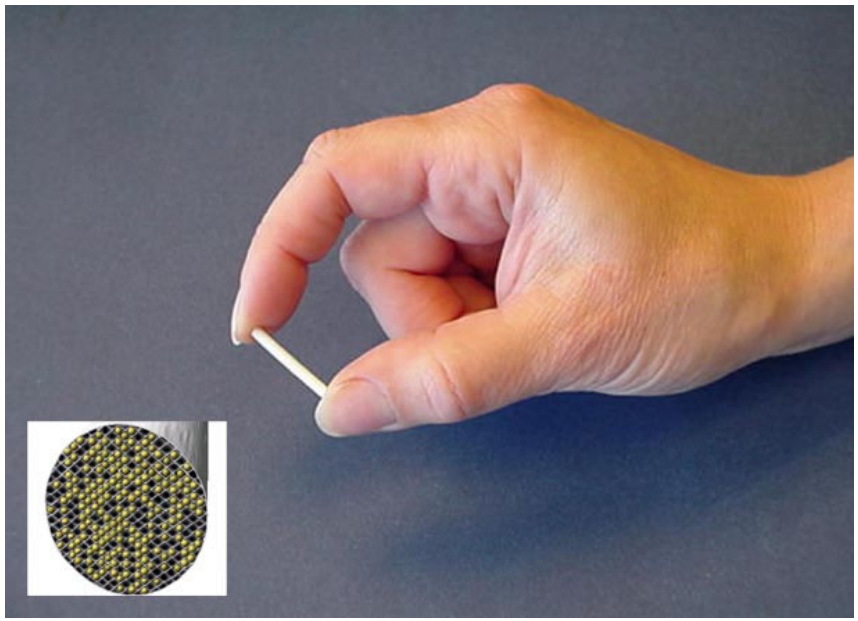
Long-term continuous delivery of the dopamine agonist lisuride with ProNeura™ subcutaneous implants

K. L. Beebe, U. F. Wirtz, R. Patel, L. Peng,
L. R. Bucalo, S. P. Sreedharan

Titan Pharmaceuticals, Inc.
South San Francisco, CA

ProNeura™ Technology

Solid Matrix Long-Term Delivery Technology



- Provides constant blood levels for six months to one year
- Inserted subcutaneously in a 15-minute office-based procedure.
- Easily removed in the office
- Simple, economical manufacturing process

Current Status

- Probuphine® – Buprenorphine-releasing implant, phase III clinic for opioid dependence
- Preclinical safety & PK obtained for other agents

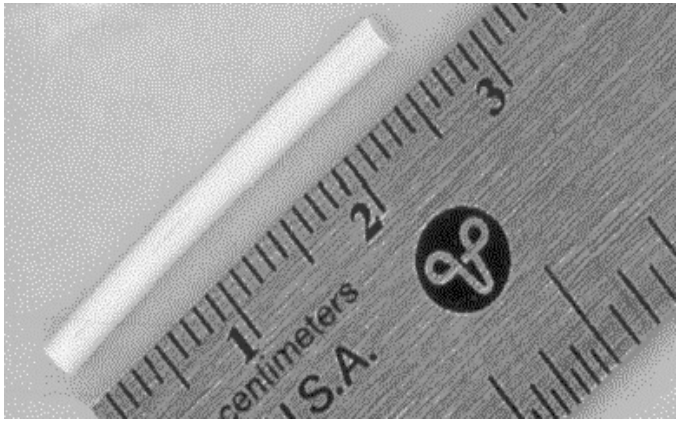
Manufacturing of ProNeura Products

Ethylene vinyl acetate (EVA) polymer
Inert component of several
approved products

+

Drug of Choice
Wide variety of drugs:
Water soluble or insoluble
High or low oral bioavailability

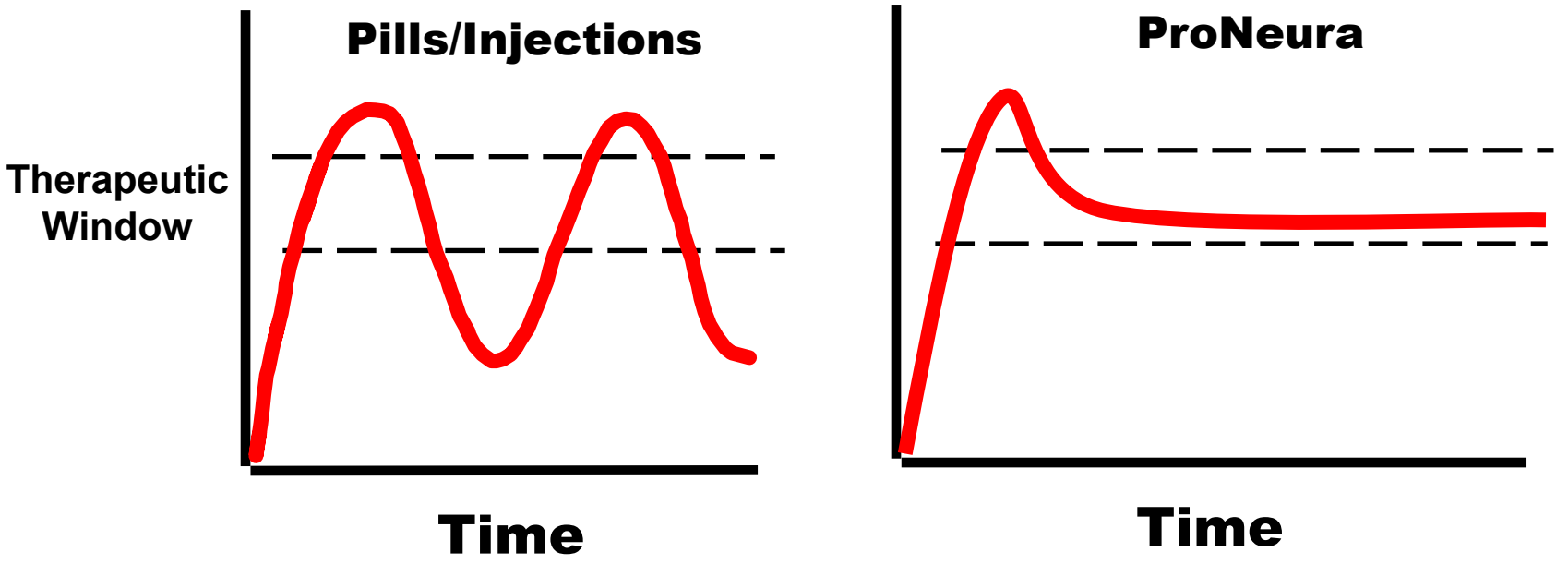
Blend and Extrude



Dimensions:

27 mm long,
2.4 mm diameter

ProNeura Maintains Stable Blood Levels

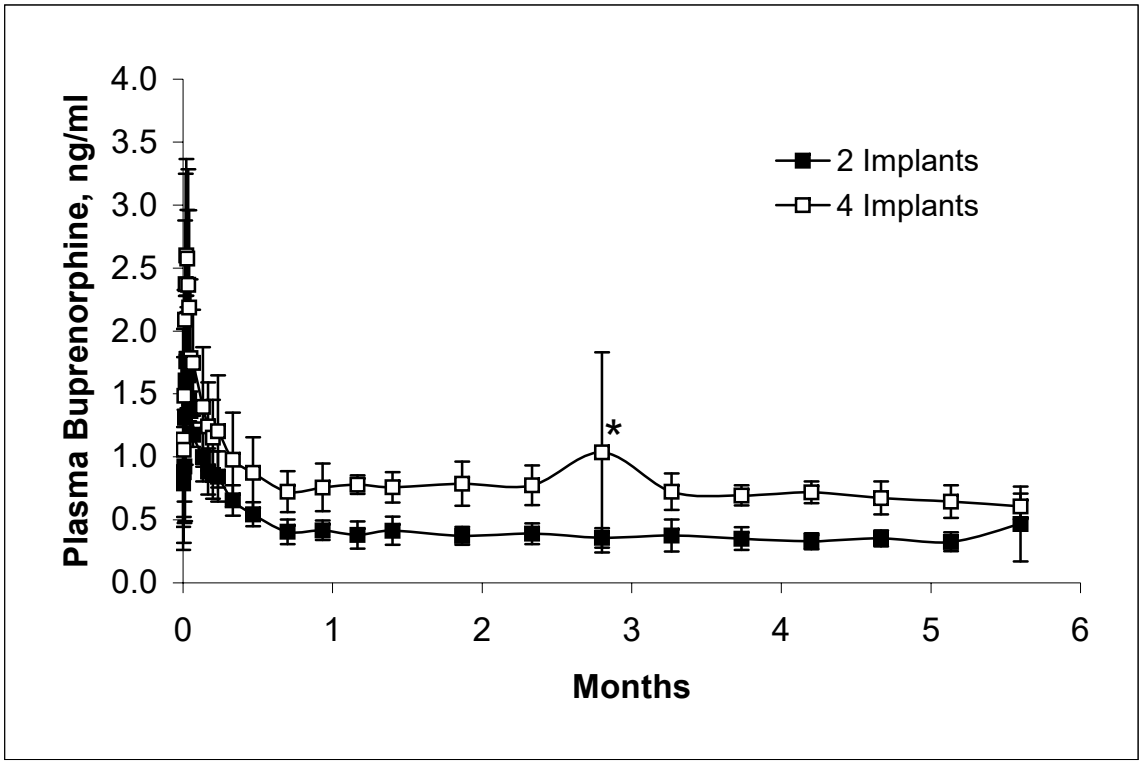


Advantages over oral dosing:

- Maintains constant blood levels of drug continuously for 6 - 12 months
- Decreases adverse effects from drug peaks/troughs
- Assures compliance

Probuphine® (Buprenorphine Implant) Clinical Pharmacokinetics

Phase I/II Study in 12 subjects with opioid dependence



Mean ± SD

J White, J Bell, J Saunders, P Williamson, M Makowska, D Lissin, A Jacobs. A Bhatnagar

University of Queensland, Australia, and Titan Pharmaceuticals, Inc., USA

Parkinson's Disease (PD) Therapy

- Dyskinesias, fluctuations & "OFF" periods associated with continued L-DOPA treatment
  - Likely due to pulsatile receptor stimulation from oral dosing
- Solution: Continuous Dopaminergic Stimulation (CDS) to prevent or delay the onset of dyskinesias

Chase TN, Baronti F, Fabbrini G, Heuser IJ, Juncos JL, Mouradian, MM. Neurology. 1989; 39(Suppl 2):7-10.

Olanow CW, Schapira AH, Rascol O. Trends Neurosci. 2000; 23(10 Suppl):S117-126.

Stocchi F, Olanow CW. Neurology. 2004; 62(1 Suppl 1):S56-63.

ProNeura Technology Can Achieve Continuous Dopaminergic Stimulation in PD

- Dopamine agonist delivery using ProNeura will potentially improved potency
  - Provides constant plasma levels for 6 months to 1 year of treatment, thus approaching true Continuous Dopaminergic Stimulation
  - Improves bioavailability over oral formulations
  - Eliminates patient non-compliance, mistiming, or missed doses

ProNeura – Apomorphine Implants

- PULSATILE STIMULATION:

MPTP-lesioned, L-DOPA-naïve cynomolgus monkeys (n=3) received daily injections of 0.2 mg/kg apomorphine (minimally-effective dose to turn animal ON).

- RESULT: All animals were ON for approximately 90 minutes after each apomorphine injection.

- CONTINUOUS STIMULATION:

MPTP-lesioned, L-DOPA-naive cynomolgus monkeys (n=4) each received three ProNeura implants containing 100mg apomorphine per implant.

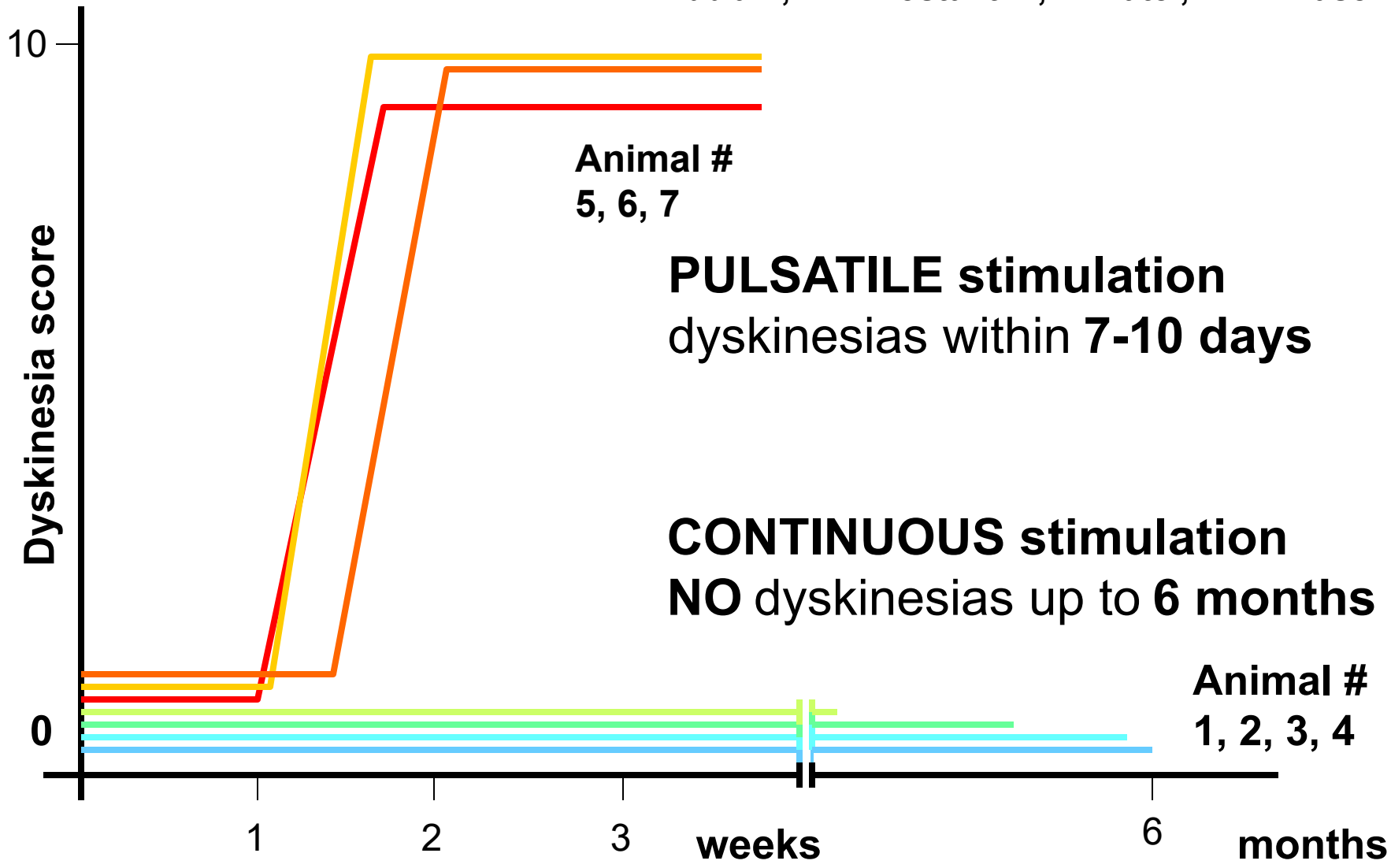
- RESULT: All ProNeura-apomorphine implanted animals were continuously ON within 1 day after implantation for up to 6 months.

F. Bibbiani, L.C. Costantini, R. Patel, T.N. Chase

Experimental Therapeutics Branch, NINDS, National Institutes of Health, USA; Titan Pharmaceuticals, Inc., South San Francisco, USA

Dyskinesias

F. Bibbiani, L.C. Costantini, R. Patel, T.N. Chase



Lisuride is Ideal for ProNeura Platform

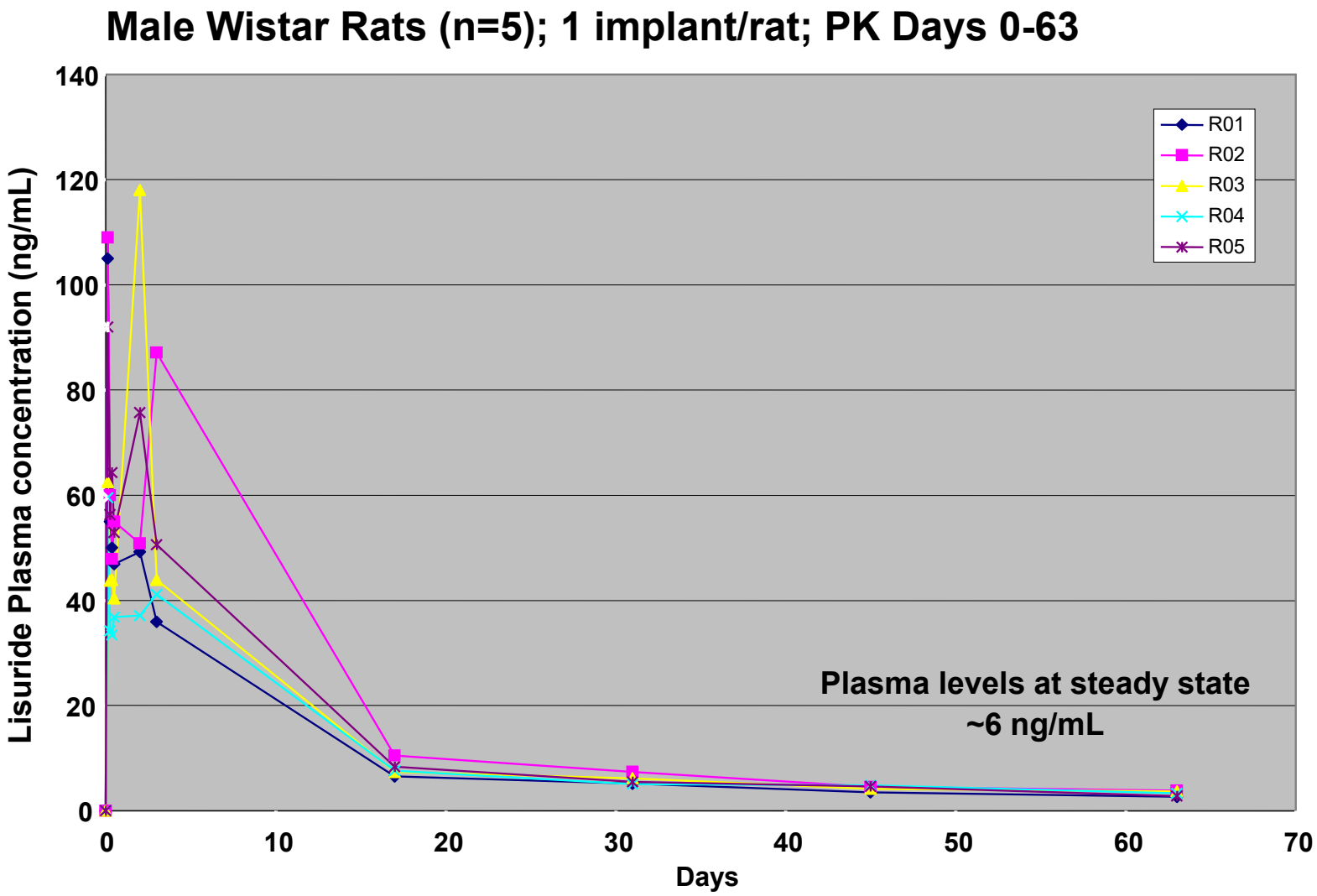
- Lisuride is a potent dopamine receptor agonist
  - Stimulates postsynaptic D2 receptors with a high potency
  - Clinically proven to be safe and effective for PD therapy
  - Approved for treatment of PD in Europe in tablet form

- Continuous delivery of lisuride is superior to pulsatile dosing
  - **Prospective randomized trial of lisuride infusion versus oral levodopa.** ***Stocchi et al. Brain. 2002;125(Pt 9):2058-66***
  - **Efficacy of a low-dose subcutaneous lisuride infusion.** ***Hayashi et al. Intern Med. 1998; 37(5):444-8***
  - **Apomorphine and lisuride infusion. A comparative chronic study.** ***Stocchi et al. Adv Neurol. 1993; 60:653-5***
  - **Effect of chronic subcutaneous minipump infusion of lisuride upon locomotor activity of rats.** ***Wachtel et al. J Neural Transm. 1988; 27(Suppl):177-83***

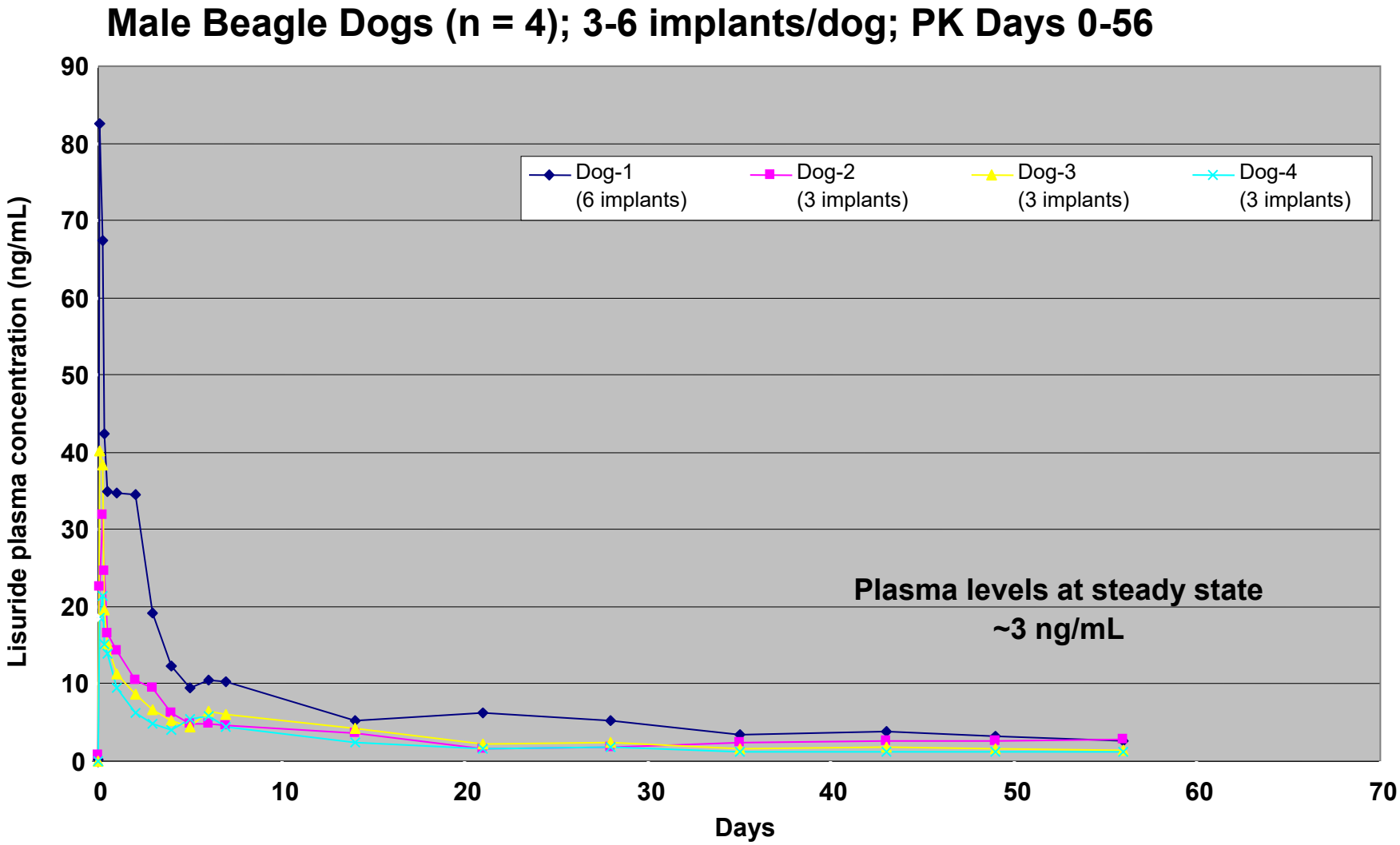
Current Lisuride Formulations

- Dopergin tablets (Schering AG)
  - 0.6 – 2 mg daily divided dose
  - Approved in European Union, Australia, New Zealand
  - Variable and unpredictable drug metabolism
  - Not suitable for achieving Continuous Dopaminergic Stimulation
- Lisparin sc. for infusions (Neurobiotec)
  - Phase III in Europe – daily injection
  - Not suitable for achieving Continuous Dopaminergic Stimulation
- Transdermal Lisuride patch (Neurobiotec/Prestwick)
  - Phase II in US, Europe – 48 hour treatment
  - Potential for patient noncompliance
  - Does not achieve true Continuous Dopaminergic Stimulation

Pharmacokinetics of Lisuride Release in Rats



Pharmacokinetics of Lisuride Release in Dogs



ProNeura-Lisuride Implants
Results from Feasibility Study

- The release rate of lisuride from ProNeura implants at steady state was:
  - **0.09 mg/day/implant in rats**
  - **0.17 mg/day/implant in dogs**

- Lisuride oral dose in PD = 0.2 - 2 mg/day
  Lisuride oral bioavailability = 21%
  Effective oral lisuride dose = 0.042 - 0.42 mg/day

- Number of Proneura-Lisuride implants required to deliver effective oral lisuride dose in humans (based on release rate in dogs) = **~0.5 - 2 rods**

- At study termination (~2 months after implantation), residual content analysis of explanted rods indicated about 25% of the starting lisuride content (58.7 mg) was released from each implant
  - **A ProNeura product releasing lisuride continuously for 6 months or longer, within the therapeutic window for treating PD, is feasible**

- **NO local skin irritation observed in implanted rats and dogs**

ProNeura™ Summary

- Stable Plasma Drug Levels for up to 6 - 12 Months
- Simple to Administer – 15-Minute Office-Based Procedure
- Easily Removed in the Office when Needed
- Proof of Principle Established with Several Agents
- Solid Matrix Technology – No Liquid Components, No Risk of Drug Dumping
- Simple Manufacturing Process
- Strong Interest from Key Opinion Leaders