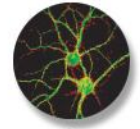


dipraglurant in Parkinson's disease

broad potential for a novel mechanism

January 2012



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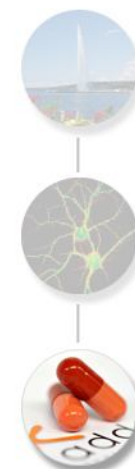


dipraglurant (ADX48621) overview

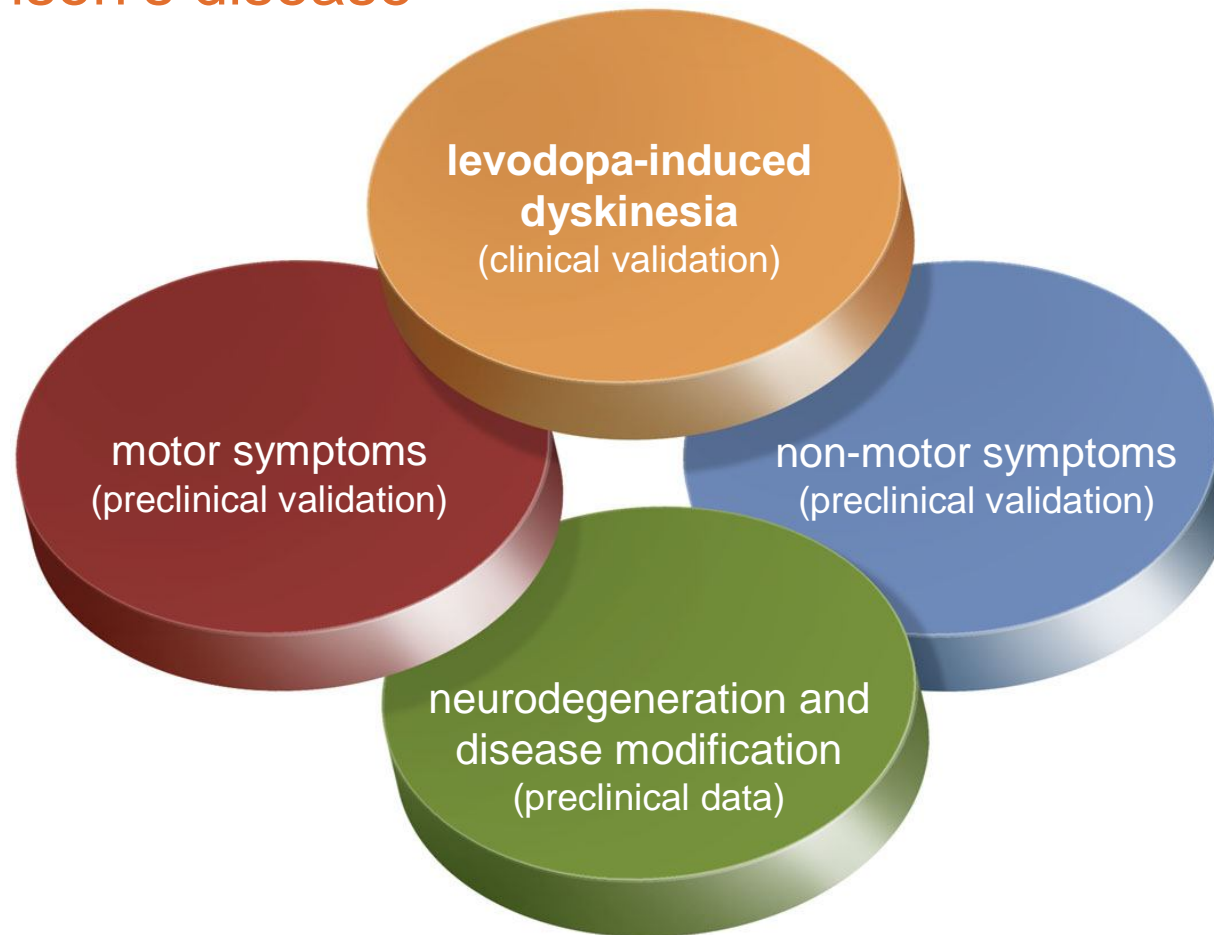
- Dipraglurant is an oral small molecule metabotropic glutamate receptor 5 (mGluR5) inhibitor (negative allosteric modulator - NAM) discovered at Addex
- mGluR5 inhibition has validation in multiple indications

Clinical validation for mGluR5 NAM	
PD levodopa-induced dyskinesia (PD-LID)	Acute migraine pain
Generalized anxiety disorder (GAD)	Gastroesophageal reflux disease (GERD)
Preclinical validation for mGluR5 NAM	
Parkinson's disease (PD) motor symptoms	Depression
Pain	Addiction

- Initial Phase I program of dipraglurant successful
 - Three studies: single & multiple ascending doses, gender/food effects
 - 132 subjects studied to date, including 30 older subjects
 - Dipraglurant – IR formulation developed and tested
 - Pharmacokinetics ideal for acute treatment of PD-LID
 - Safety & tolerability support further clinical study
- Dipraglurant-IR is being studied in a Phase IIa trial in 72 PD-LID patients
 - Top-line data end of 1Q12
 - Michael J. Fox Foundation awarded Addex \$900,000 for trial
- Dipraglurant-ER formulation development is complete
 - Preclinical testing indicate it has potential to be twice- or once-daily
 - ER form has potential for non-Parkinsonian dystonias and validated indications above
 - Phase I testing will be initiated in 2012



dipraglurant has potential to manage multiple facets of Parkinson's disease



dipraglurant has potential to change PD treatment paradigm
levodopa-induced dyskinesia indication - most direct path to market



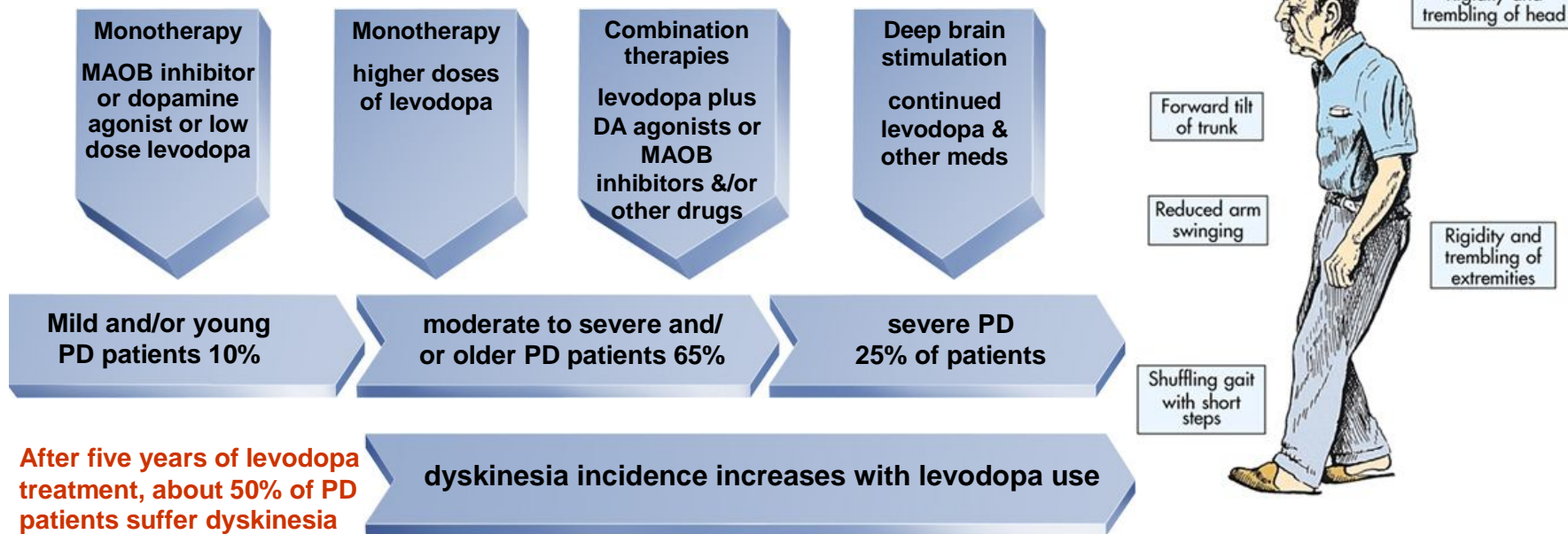
Parkinson's disease and PD-LID

- Parkinson's disease (PD) is characterized by the death of dopamine producing neurons in the substantia nigra
 - Clinical symptoms include tremor, bradykinesia and rigidity
 - Later in the disease, cognitive impairment, behavioral problems, autonomic dysfunction and dementia occur
 - Anxiety & depression are common co-morbidities
- Levodopa-Induced Dyskinesia (LID)
 - Abnormal involuntary movement following levodopa dosing. Two main types:
 - **chorea** - rapid uncontrolled movements
 - **dystonia** - slow writhing movements
 - Dyskinesia occurs at different times
 - *peak dose* - most common, occurring at 60-90 minutes after levodopa dosing
 - *biphasic* - at onset and offset of "on" time
 - *off dystonia* - after levodopa wears off
 - The neurodegenerative process (loss of substantia nigra cells) reduces the threshold for dyskinesia caused by dopamine replacement therapy
 - Both levodopa and dopamine agonists have been shown to cause dyskinesia
 - More frequent lower doses or extended release formulations of levodopa are used to attempt to reduce dyskinesias **but** may be at the expense of optimal motor function

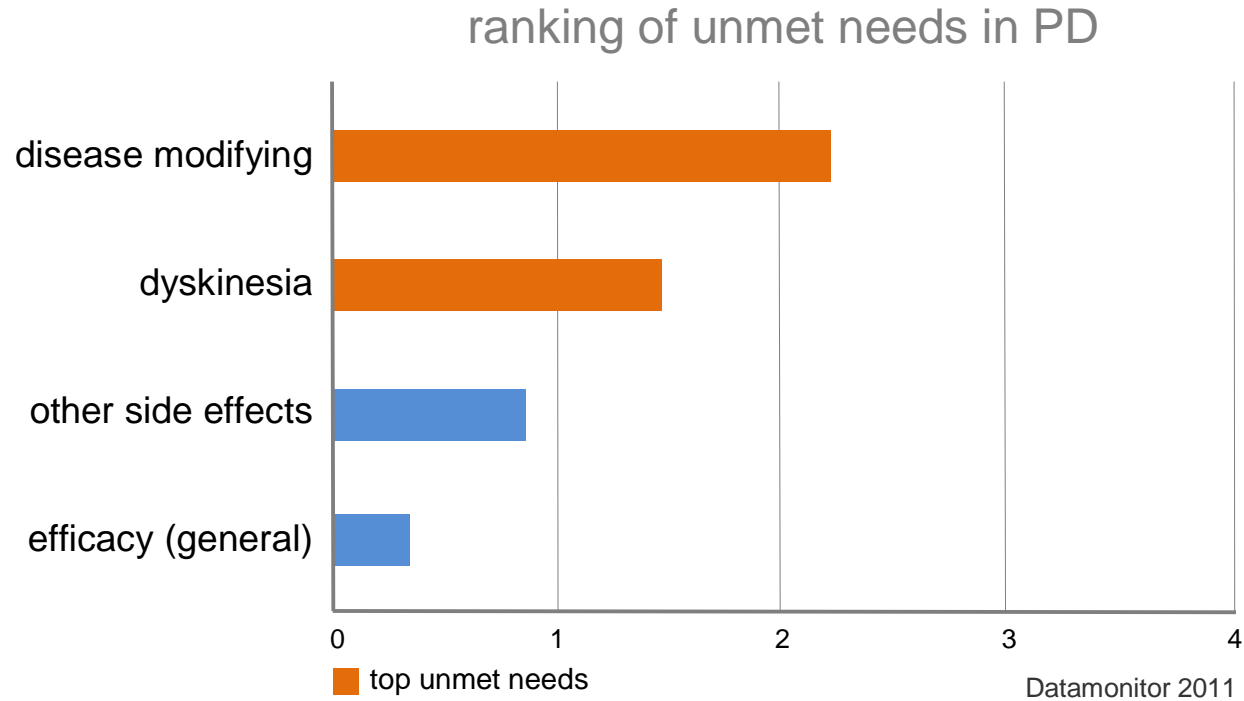


current PD treatment strategies

- Levodopa is the most effective treatment **but** its use is delayed as long as possible due to concerns about levodopa induced dyskinesia (LID)
 - As a result, first line PD treatments are primarily dopamine agonists & MAOB inhibitors
 - There is no approved drug for LID and a substantial unmet need for LID treatments exists



dyskinesia is an underappreciated opportunity



- LID is the most important unmet medical need in PD after disease modification*
- LID is as disabling as PD symptoms
 - 40% of PD patients experience LID 4–6 years after starting levodopa**
 - Up to 90% of patients have LID 9–15 years into treatment**



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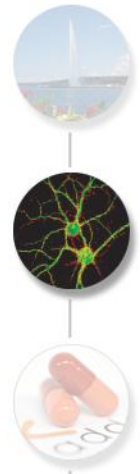


* Addex funded market research with KOLs in U.S., EU and Asia by Datamonitor

** Ahlskog JE and Muentner MD, *Mov Disord* 2001; 16: 448-458

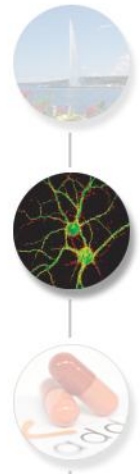
rationale for mGluR5 inhibition in Parkinson's disease levodopa induced dyskinesia (PD-LID)

- During the neurodegenerative process of PD, loss of striatal dopaminergic modulation results in an increase in glutamatergic output from the substantia nigra
 - mGluR5 are abundant in the striatum and implicated in the excess glutamate activity in PD
 - mGluR5 is the only mGlu receptor type involved in substantia nigra neuronal depolarisation
- Blockade of mGluR5 e.g. with MPEP has been shown to have anti-PD and antidyskinetic effects in a variety of animal models
- mGluR5 inhibition is clinically validated for LID in PD patients*



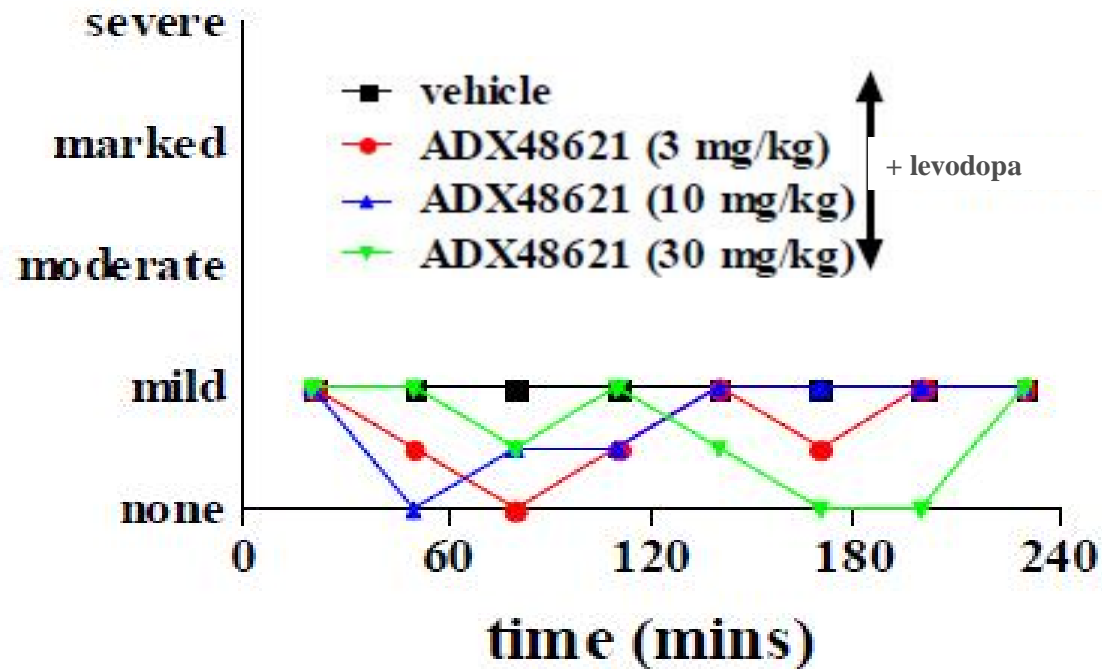
preclinical validation of dipraglurant using the MPTP macaque LID model

- The LID study was conducted by Motac Neuroscience
 - Motac has extensive experience in movement disorders
 - Motac tested many of the compounds in development for PD / PD-LID
- The severity of LID induced in this model is comparable to human PD-LID
 - A score of 10 corresponds to severe disability in patients
 - Both types of dyskinesia – chorea & dystonia – can be seen
- The study was a 4-way crossover with 8 animals receiving all treatments
- Dipraglurant–IR (3, 10 and 30 mg/kg in 1% water) or vehicle was administered 30 min prior to levodopa dose
 - Behavioral assessment began upon levodopa administration
 - Trained observers performed video review
 - Dyskinesia & PD scoring (10 min every 30 min for 4hrs)

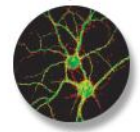


dipraglurant reduced dyskinesia severity in macaques without affecting levodopa efficacy

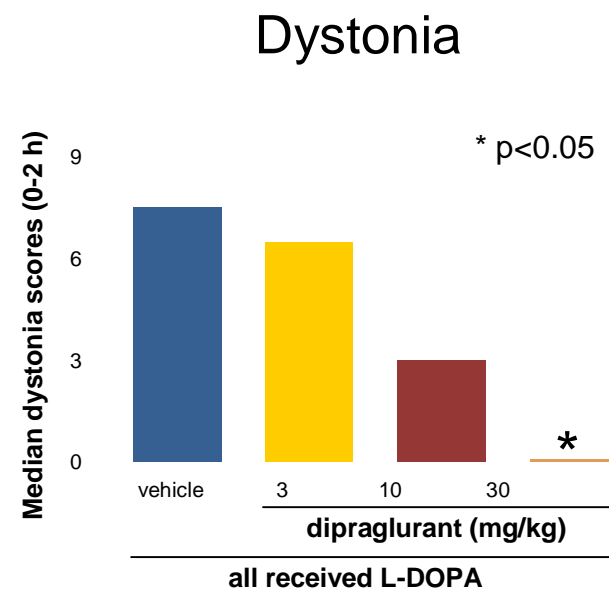
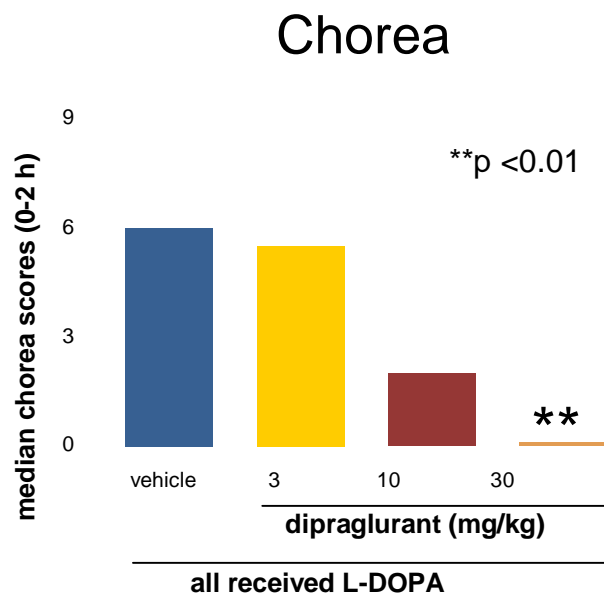
Parkinsonian Disability (Levodopa efficacy)



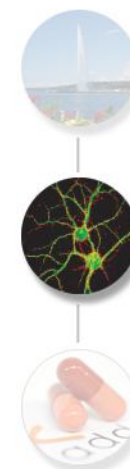
- Dipraglurant dose-dependently reduced the severity of dyskinesia during the 4 hour “on” period following levodopa
- The effective Cmax was ≥ 1000 ng/ml and this Cmax has been targeted for the Phase 2 clinical trial (see slide 11).



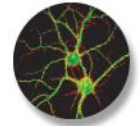
dipraglurant is the first compound reported to reduce dystonia as well as chorea in the macaque PD-LID model



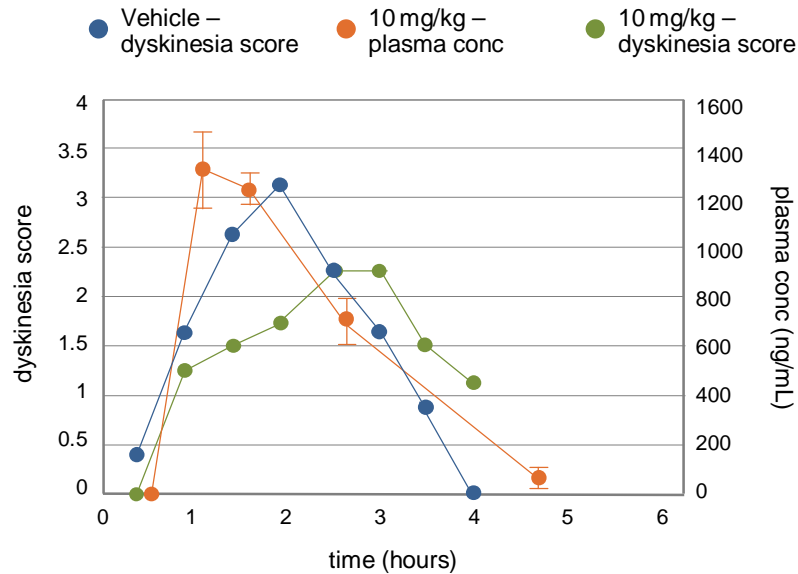
- Dipraglurant reduced both, chorea and dystonia to an equal extent
- Effects was seen at 10 mg/kg and the 30 mg/kg dose was statistically significant
- No other compound has been reported to have an anti-dystonia effect in this model



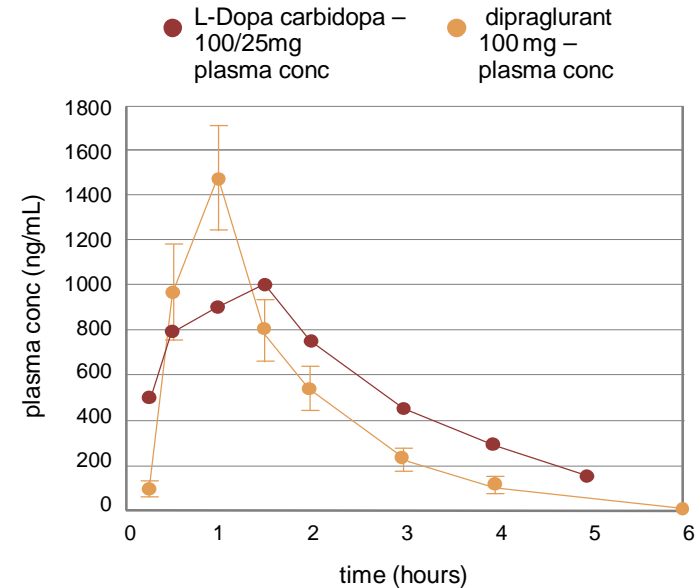
dipraglurant-IR PK/PD profile is ideal for PD-LID



PK/PD non-human primates



PK in humans

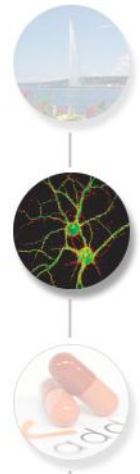


- Primate data show PK/PD correlation predictive of human efficacy in LID with an effective plasma concentration of approx 1000 ng/ml
- LID occurs most commonly at peak levodopa plasma concentration. Hence effective anti-dyskinetic drug concentration is needed at peak levodopa concentrations
- PK of dipraglurant-IR used in the clinic mirrors that of levodopa in humans
- The 100 mg dose of dipraglurant-IR delivers a mean Cmax of approx 1500 ng/ml

why dipraglurant-IR is ideal for treating LID

The immediate release (IR) formulation is ideally suited for acute treatment of PD-LID because:

- Its pharmacokinetic profile is similar to levodopa so dipraglurant is delivered precisely when needed
- Its rapid onset of action is ideal for dyskinesias which can occur within 30 minutes of dosing
- The rapid clearance reduces unnecessary drug exposure, between levodopa doses and should reduce side effects as a result
- The PK characteristics of dipraglurant-IR have potential to give flexibility of use, which is common practice and desirable in PD treatment.



dipraglurant Phase 1 trials summary

- Three Phase 1 studies completed in 132 healthy male and female subjects (ADX48621 n = 114) aged 18 to 70 years.
- Study 101: Single ascending dose and food effect of API-filled capsule
 - Part 1 (n = 48): single ascending dose trial placebo, 20 mg, 50 mg, 100 mg, 250 mg, 400 mg and 500 mg
 - Part 2: food effect 100mg (N = 16),
- Study 102: Single and multiple dose kinetics of dipraglurant-IR (Gelucire capsule)
 - Part 1: 100mg single dose, dipraglurant –IR Gelucire capsule vs API-filled capsule;
 - Part 2: multiple ascending dose with dipraglurant-IR (Gelucire) capsule: 50, 100 and 200 mg b.d. for 7 days
- Study 103: Gender and food effect of dipraglurant-IR in healthy, male (N = 15) and female (N =15) subjects aged 50 to 70 years
- No adverse effects on safety monitoring in any study
- Well tolerated by all subjects
 - mild to moderate CNS type AEs apparent at doses \geq 200mg
- Food reduced and delayed C_{max}, but AUC maintained
- Fasting administration gives a similar PK profile to levodopa
- Dose titration schedule for Phase 2A trial based upon results of fasting PK data
 - 50 mg dose gives C_{max} of approx 800 ng/ml and T_{max} approx 1h
 - 100 mg dose a C_{max} approx 1500 ng/ml and T_{max} approx 1h
 - 50 & 100mg doses have been selected for the Phase 2A study in PD-L1D



EU and US Phase 2A dipraglurant trial for PD-LID



72 patients

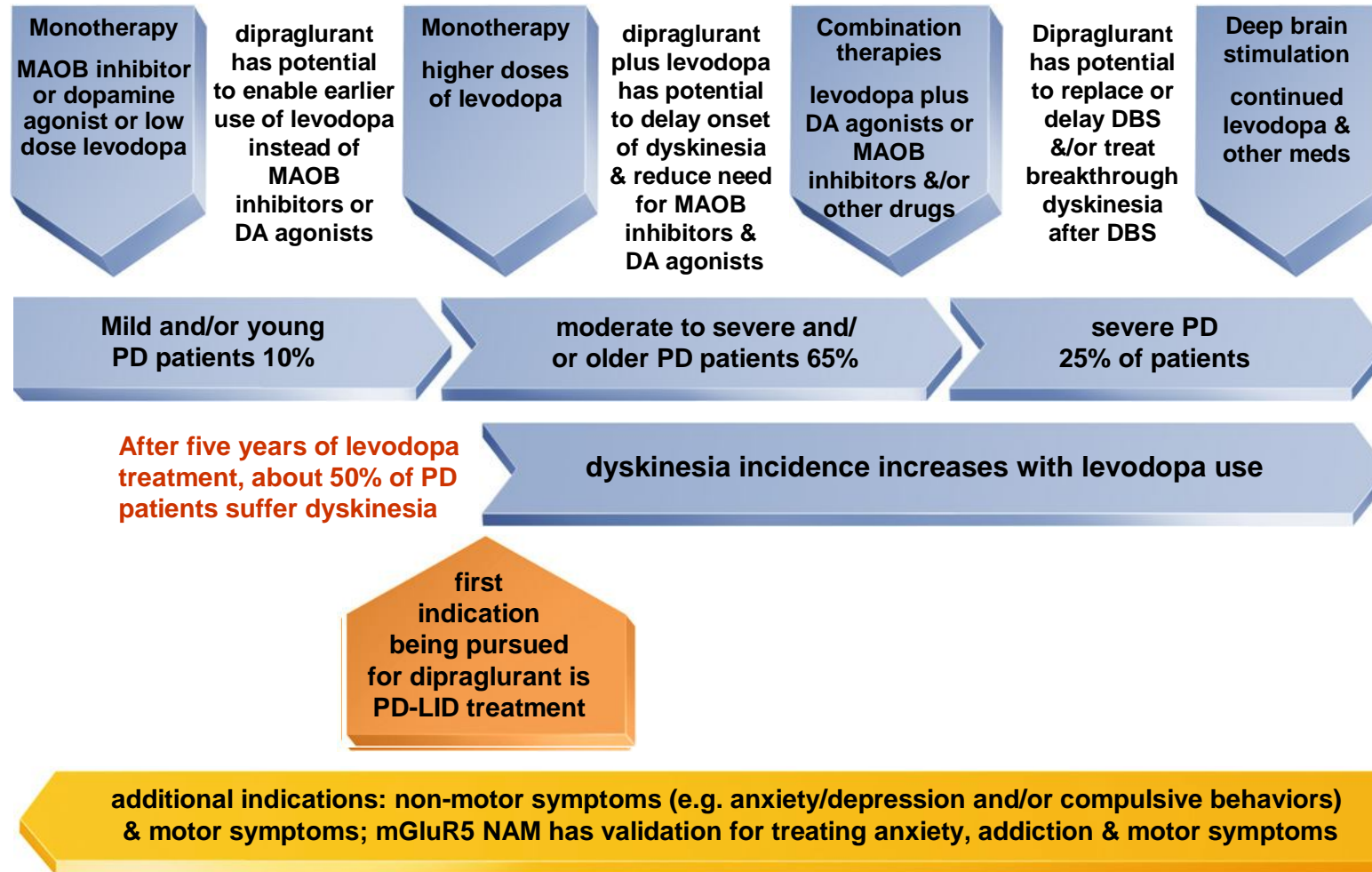
- Randomized, double-blind, placebo-controlled, multi-center trial
- Moderate to severe LID patients

- Dipraglurant taken with levodopa
- Dipraglurant titration from 50mg q.d. to 100mg t.i.d over 4 weeks
- Individual levodopa regimens remain constant for duration of study (300 -1500mg/day)

- **Primary objective:** safety & tolerability
- **Secondary objective:** exploratory efficacy
- **Objective evaluation in the clinic on day 1 and 14 & 28**
 - Trained observer scores LID severity using **mAIMS** – modified Abnormal Involuntary Movement Scale
- **Patient diaries of on & off time**
- **Unified Parkinson's Disease Rating Scale (UPDRS)**
- **Patient and clinician global impression of change (PGIC & CGIC)**
- **Evaluation of mood using Hospital Anxiety & Depression Scale (HADS)**

top-line data end of 1Q12

dipraglurant-IR has potential to change PD treatment paradigm

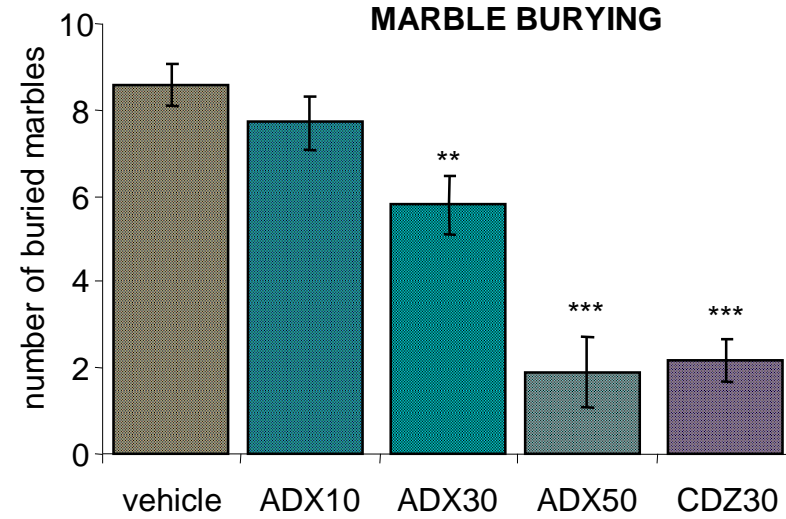
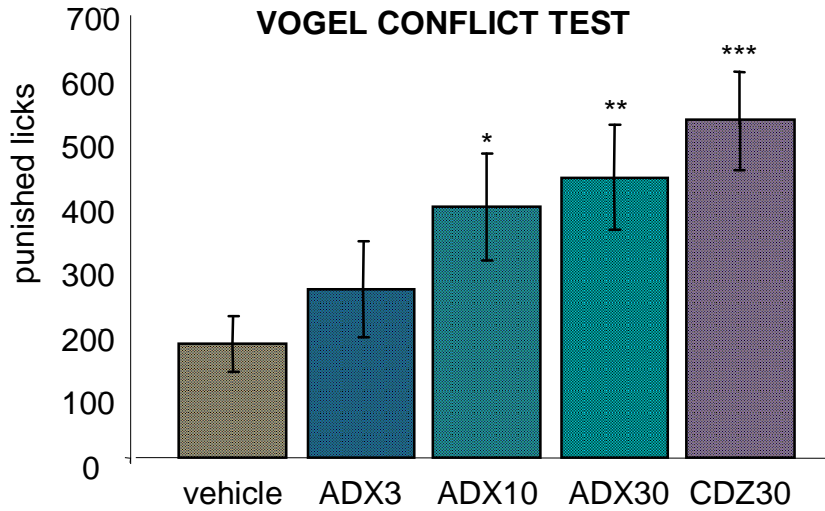


beyond PD & PD-LID

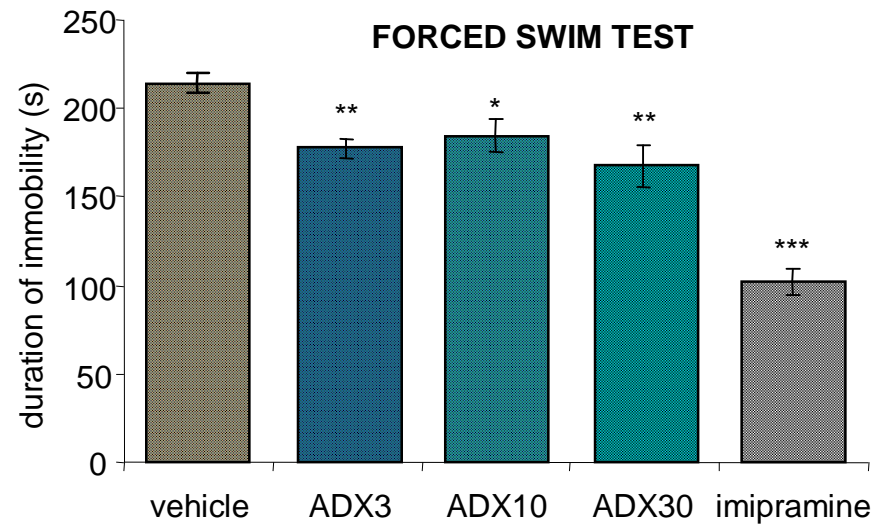
- Treatment of non-motor symptoms in PD
 - Anxiety and depression
 - Dipraglurant has shown efficacy in animal models of anxiety and depression (see slide 17)
 - Fenobam, an mGluR5 inhibitor, was effective in a Phase 2 trial in generalized anxiety disorder (GAD)
 - Impulse control disorders
 - mGluR5 NAM reduces cocaine self administration in rats
 - ICD neurocircuitry cortico-striatal pathway overlaps with that involved in dyskinesias and ICD often co-exists with LID in PD patients
- Adjunctive treatment of motor symptoms
 - Dipraglurant is effective in the haloperidol induced catalepsy (HIC) model (see slide 18)
- Dystonias
 - mGluR5 inhibition with MPEP and MTEP can normalize dysregulation of long term potentiation in dystonia models



dipraglurant is effective in rodent models of anxiety and depression

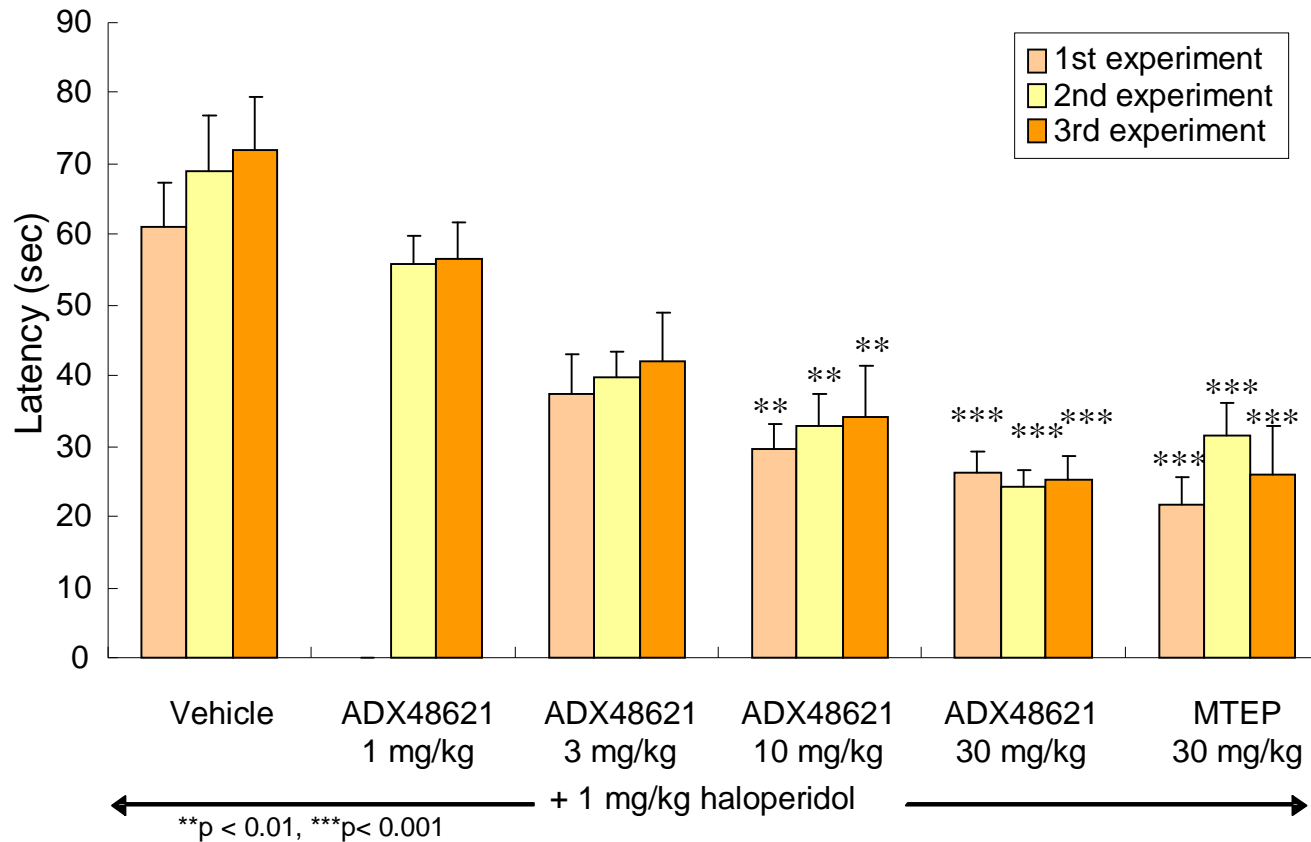


Effective plasma concentrations are similar to those that were effective in PD-LID and PD symptom models *i.e.* 500 to 1000ng/ml



*p < 0.05, **p < 0.01, ***p < 0.001 statistical significance vs. vehicle group.

dipraglurant has potential for PD motor symptom control – rat haloperidol-induced catalepsy model



- Dipraglurant dose-dependently reversed haloperidol-induced catalepsy in 3 separate experiments
- Full effect reached in animals showing plasma conc. above 800-1000 ng/ml which is consistent with the other PK/PD models, including non-human primates
- Supports Phase 2A study dose selection



non-Parkinsonian dystonia and mGluR5

- Sixteen types of dystonia have been identified
 - Dystonia may affect a single body area or be generalized throughout multiple muscle groups
 - Dystonia causes varying degrees of disability and pain, from mild to severe
 - Dystonia affects men, women, and children of all ages and backgrounds
 - Estimates suggest that no less than 300,000 people in North America are affected
 - Dystonia is a chronic disorder, but the vast majority of dystonias do not impact cognition, intelligence, or shorten a person's life span
 - It is not a neurodegenerative disorder
- mGluR5 are involved in dysregulation of long term potentiation in dystonia models which can be rectified with MPEP and MTEP
- Dipraglurant is the only compound reported to have reduced dystonia in the MPTP non-human primate model of PD-LID
- **Dystonia therefore represents a significant additional market opportunity for dipraglurant**



lifecycle management: multiple potential label extensions

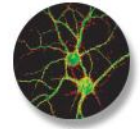
- After Phase 2A, we foresee a seamless phase 2B/3 program
 - Initial registration target is: “acute treatment of moderate to severe levodopa induced dyskinesia”
 - NDA/MAA filing end 2015
- Follow-up indications – first wave to start during IND review, with a view to extend product license by end 2019
 - Early use with levodopa
 - Acute treatment of impulse control disorders
 - Treatment of co-morbid anxiety/depression
 - Treatment of non-Parkinsonian dystonia
- Second wave, with a view to further extending the product license by 2022
 - Long-term treatment of non motor symptoms
 - PD motor symptom control adjunctive therapy
- Dipraglurant-ER formulation expands opportunities in non-Parkinsonian indications, including dystonia
 - Preclinical & CMC development completed (potential for once-daily dosing)
 - Phase I study to start in 2012



summary

- Dipraglurant is a novel and highly differentiated drug within the Parkinson's disease market
 - LID is a direct path to market and recognized as an unmet need by regulatory authorities, KOLs & patient advocacy groups
- The therapeutic and market potential of dipraglurant is vast
 - Datamonitor estimates peak sales over \$1 billion/yr in PD alone
 - Dystonia market could more than double the opportunity
- There is great potential for a strong lifecycle management for dipraglurant
- Seeking a partner with the vision, expertise and capability to fully exploit dipraglurant's broad commercial potential





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