dipraglurant in Parkinson’s disease

Phase 2a PD-LID data & broad potential for mGluR5 NAM

July 2012
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Addex Therapeutics

- Addex is located in Geneva, Switzerland
- ADXN is traded on the SIX Swiss Stock Exchange
- 55 people / founded in 2002
- Focus: pioneering oral small molecule allosteric modulation-based drug discovery and development
### Key Value Drivers

| Leading allosteric drug discovery | • Proprietary ~85,000 allostery-biased small molecule library  
|                               | • Proprietary HTS systems  
|                               | • Deep allosteric know-how & expertise |
| Validated emerging therapeutic class | • Proven mechanism, that has led to marketed products  
|                               | • Significant investment from all major pharma  
|                               | • Growing pipeline of allosteric modulators in the clinic |
| Robust pipeline | • 3 Phase II programs  
|                               | • 8 preclinical programs  
|                               | • Unmatched track record advancing allosteric modulators |
| Partnership with leading pharma | • Janssen Pharmaceuticals Inc. (JPI) for mGluR2 PAM in Phase II testing for schizophrenia & anxious depression |
| Dominant IP portfolio | • 13 issued patents  
|                              | • 45 pending patents |
| Strong balance sheet | • CHF36.1 (US$40 / €30) mil in cash as of Dec 31, 2011  
|                              | • No debt |
## Pipeline

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<td>ADX71149 mGluR2 PAM – schizophrenia</td>
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<td>Dipraglurant-ER (ADX48621) mGluR5 NAM – non-Parkinsonian dystonias</td>
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<td>GABA-BR PAM – overactive bladder</td>
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<td>mGluR4 PAM – Parkinson’s disease, anxiety, multiple sclerosis</td>
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<td>mGluR2 NAM – Alzheimer’s, depression</td>
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<td>TrkB PAM (RTK superfamily) – neurodegenerative and other diseases</td>
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<td>GLP1R PAM – type II diabetes</td>
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<td>TNFR1 NAM (TNF receptor superfamily) – RA; psoriasis; IBD; Alzheimer’s; MS</td>
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NAM = negative allosteric modulator (inhibitor)

PAM = positive allosteric modulator (activator)


# partially funded by a grant from the Michael J. Fox Foundation for Parkinson’s Research

[addex therapeutics logo]
dipraglurant in Parkinson’s disease
the opportunity
Parkinson’s disease and PD-LID

➤ There are currently over 4 million people suffering from Parkinson’s disease (PD) in the US, EU, China and India
  ➤ the patient universe is set to continue to grow due to improved awareness and diagnosis (particularly in China and India)

➤ 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
PD-LID epidemiology

- Dyskinesia results from long-term usage of levodopa and is considered by interviewed KOLs as the second most important unmet need (after disease modifying treatment).
- Dyskinesia makes further effective treatment difficult and has a high impact of patients’ quality of life.
- Levels of dyskinesia rise along with the rates of levodopa usage as Parkinson’s Disease progresses.
- By the late-stage of the Parkinson’s disease, nearly all patients will be on levodopa and up to 80% (depending on countries) will have resultant dyskinesia.

![Bar chart showing the percentage of patients receiving L-dopa treatment and suffering from dyskinesia, by PD stage for different countries.](chart.png)
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

Monotherapy
MAOB inhibitor or dopamine agonist or low dose levodopa

Monotherapy
Higher doses of levodopa

Combination therapies
levodopa plus DA agonists or MAOB inhibitors &/or other drugs

Deep brain stimulation
continued levodopa & other meds

mild
35% of PD patients

moderate to severe
43% of PD patients

severe PD
22% of PD patients

After five years of levodopa treatment, about 50% of PD patients suffer dyskinesia

dyskinesia incidence increases with levodopa use
## PD: Significant unmet needs

<table>
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<th>Unmet Need</th>
<th>Support</th>
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| Levodopa induced dyskinesia (LID) | - Most patients suffer from LID after five years on dopaminergic therapy  
- No treatment is indicated for LID  
- Off-label use of amantadine / other drugs is inadequate |
| Non-motor symptoms                | - Anxiety, depression, GI motility, compulsive behaviors, etc  
- Current anti-depressants are not effective  
- Benzodiazepine drugs cause sedation & other side effects |
| Motor symptoms                    | - KOLs & patients agree that the efficacy afforded by current drugs is suboptimal in mid- & late-stage disease  
- Levodopa-induced dyskinesia is cited as the key reason levodopa cannot be used in optimal fashion |
| Disease modification              | - No drug has been shown to slow, prevent or reverse disease progression  
- mGluR5 inhibitors have been shown in multiple preclinical studies to afford neuroprotection |
PD market may seem crowded but is largely dissatisfied: Better treatments are needed desperately

- Current treatments are suboptimal
  - Levodopa remains gold standard for PD treatment, however:
    - Concern of developing dyskinesia leads to suboptimal use of levodopa
    - Most “newer” drugs work via dopaminergic mechanisms
      - None slow progression of PD or address PD-LID
    - Most patients achieve only suboptimal efficacy &/or suffer from debilitating dyskinesia
    - Important comorbidities (e.g. anxiety/depression) are not satisfactorily controlled with existing drugs
- Significant opportunity
  - Adjunctive therapies that facilitate optimal efficacy
    - Facilitate the broader and more effective use of levodopa by preventing, delaying or treating dyskinesia (PD-LID)
    - Replace or Decrease dependence on Dopamine agonists, MAOB inhibitors, amantadine, etc
    - Decrease or avoid need for deep brain stimulation (DBS)
  - Disease modification
    - Neuroprotective agents that slow/reverse progression
dipraglurant has potential to manage multiple facets of Parkinson’s disease

- Levodopa-induced dyskinesia indication - most direct path to market
- Motor symptoms (preclinical validation)
- Non-motor symptoms (preclinical validation)
- Neurodegeneration and disease modification (preclinical data)

Dipraglurant has potential to change PD treatment paradigm.

Levodopa-induced dyskinesia indication - most direct path to market
dipraglurant has the potential to transform the PD market

**Competitive/Payer Pressures**
- Generics: DA agonists, MAOB Inhibitors, levodopa, etc.
- Increasing payer control
- A2A antagonists

**Unmet Need**
- Anxiety & depression insufficiently treated
- High co-morbidity
- Neuroprotection / disease modifying potential
- LID will remain a leading unmet need that renders other treatments impotent
- Complementary treatment for motor symptoms
- Delay / avoid deep brain stimulation

**Pharmacoeconomic Arguments**
- Reduce caregiver burden
- Reduced need for DA agonists, MAOB inhibitors, amantadine, anti-depressants, anxiolytics, etc.

**Pharmacoeconomic Arguments**
- Increasing payer control

**Generics**
- DA agonists
- MAOB Inhibitors
- Levodopa
- A2A antagonists
- Dipraglurant has the potential to transform the PD market
dipraglurant in Parkinson’s disease

the data
dipraglurant (ADX48621) overview

- Dipraglurant is a highly selective oral brain penetrant small molecule metabotropic glutamate receptor 5 (mGluR5) inhibitor (negative allosteric modulator - NAM) discovered at Addex.
- mGluR5 inhibition has validation in multiple indications.

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<th>Clinical validation for mGluR5 NAM</th>
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<td>Parkinson’s disease levodopa-induced dyskinesia (PD-LID)</td>
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<td>Generalized anxiety disorder (GAD)</td>
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<td>Fragile X Syndrome (i.e. autism)</td>
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<th>Preclinical validation for mGluR5 NAM</th>
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<td>Parkinson’s disease (PD) motor symptoms</td>
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<tr>
<td>Pain</td>
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- 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 Phase IIa trial in 76 PD-LID patients successful:
  - Top-line data showed statistically significant reduction in dyskinesia
    - Reduction in mAIMS (both at peak levodopa concentrations & area under the curve)
    - 50 min reduction in off-time in week 4
    - 2.3 hours more on-time without dyskinesia in week 4
  - Concordance of mAIMS with the diary and the PGIC and CGIC data
  - Michael J. Fox Foundation supported the trial with a $900,000 grant
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

- 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 were 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

- 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 dykinesias 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 ≥ 200mg
- Food reduced and delayed Cmax, 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 Cmax of approx 800 ng/ml and Tmax approx 1h
  - 100 mg dose a Cmax approx 1500 ng/ml and Tmax approx 1h
  - 50 & 100mg doses have been selected for the Phase 2A study in PD-LID
EU and US Phase 2A dipraglurant trial for PD-LID

- 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)

Positive top-line data reported 1Q12
study ADX48621-201 Phase IIa proof of concept study in patients with PD-LID:

All Key Objectives achieved

• The three objectives of the PD-LID study were achieved
• Primary Objective
  – Safety and tolerability in PD-LID patients
• Secondary objectives
  – Clinical effect
  – Effective dose identification
Phase 2A patient disposition

Patients screened
N = 83

Patients randomized
N = 76

Dipraglurant
Safety and FAS populations
N = 52

PP population
N = 47

Withdrawals
N = 2

Other major violations
N = 3

Placebo
Safety and FAS populations
N = 24

PP population
N = 24

Other major violations
N = 3
Ph 2A study primary objective achieved: dipraglurant 50 and 100 mg demonstrated good safety and tolerability in PD patients

- Safety monitoring comprised 12-lead ECG, heart rate, blood pressure sitting and standing, haematology, biochemistry and adverse events.
- There were no treatment effects seen on any of the safety monitoring variables.
- Adverse events common in both treatment groups
  - Typical mGluR5 type AEs seen in < 10% dipraglurant patients (vertigo, visual disturbance, feeling drunk)
    - none were severe or dose limiting
- The majority of patients completed the dose escalation regimen i.e. to 50mg t.i.d by start of Week 2 and 100mg t.i.d by start of Week 4
- Severity distribution is similar in the two treatment groups. Approx 80% of AEs were mild or moderate in severity
- Safety profile appears suitable for continued development in PD
- Good safety and tolerability confirmed by KOLs and DSMB
robust exploratory efficacy of dipraglurant

- Good concordance of mAIMS with the diary and the PGIC and CGIC data
Phase 2A data: mAIMS
(modified abnormal involuntary movement scale)
an objective observer, efficacy evaluation
dipraglurant reduces LID severity for the entire duration of the levodopa activity in PD-LID patients

- Dipraglurant reduced dyskinesia severity to a greater extent than placebo on treatment Days 1 (50mg), 14 (100mg) and 28 (100mg).
- The effect was significant on Day 14 ($p = 0.042$)
- Magnitude of effect is durable - maintained through Day 28
**dipraglurant reduces LID severity in PD-LID patients**

- Peak mAIMS was significantly lower on Days 1 and 14; percentage reduction in the dipraglurant group as follows:
  - Day 1: 19.9% vs 4.1% (placebo) p = 0.042
  - Day 14: 32.3% vs 12.6% (placebo) p = 0.034
  - Day 28: 31.4% vs 21.5% (placebo) p = ns

- Target reduction in levodopa-induced dyskinesia severity over the entire 3 hour post levodopa dose period, was achieved for the dipraglurant group at Day 14 (32.7%) and Day 28 (27.5%)

- The reduction in AIMS AUC$_{0-3}$ in the dipraglurant 100mg group was statistically significant at Day 14 (p = 0.042 ANCOVA)

- Deep Brain Stimulation patients were included in the covariate analysis and did not affect the outcome i.e. dipraglurant was as effective in these patients as in non DBS patients
dipraglurant has an effect on levodopa-induced dystonia as well as chorea in PD-LID patients

- The majority of patients in the study had only chorea as their type of dyskinesia.

- Pure dystonia patients; dipraglurant n = 4 and placebo n = 3
  - Data were limited, so statistical analyses were not performed.

- The magnitude of dystonia improvement with dipraglurant appears to be similar to that of chorea
  - mAIMS 3 hours time course
  - peak dose dystonia scores
Phase 2A data: patient diary data
good correlation of patient reported dyskinesia severity with mAIMS

- No increase in “off” time seen with dipraglurant use.
  - No detrimental effect on levodopa efficacy
- At Week 4 “off” time decreased by 50 minutes per day in the dipraglurant group (placebo no change)
  - Suggestion of beneficial effect on parkinsonian symptoms
- Greater increase in “on” time without dyskinesia in the dipraglurant group compared to placebo in all 4 Treatment Weeks
  - By week 4 patients in the dipraglurant group had an extra 2.3 hours per day “on” time without dyskinesia
- Apparent benefit of both the 50 and 100 mg dose levels
Phase 2A study: overall evaluation from KOL investigators

- The KOL investigators agreed the study was positive and dipraglurant should proceed to further investigation in PD
- The magnitude of reduction in mAIMS clinically meaningful
- Safety and tolerability were good in this population
  - The DSMB also concurred with this opinion
- The information from this study provides a sound base on which to design future studies
- A treatment arm of a lower dose than 50mg should be included in a future study
- Study was well designed and the data are very robust
- Good concordance of mAIMS with the diary and the PGIC and CGIC data adds to the robustness of the findings
- Week 4 reduction in “off” time is of interest and may possibly signal a benefit on parkinsonian symptoms
This first study in Parkinson’s patients met its primary objective in demonstrating good safety and tolerability.

Exploratory efficacy data showed anti-dyskinetic effect on both observer evaluated mAIMS and in patient reported diary data:
- 50 min reduction in off time (week 4)
- 2.3 hour increase in on time without dyskinesia (week 4)

Patients and clinicians favoured dipraglurant treatment for dyskinesia (PGIC and CGIC)

Both the 50 and 100mg doses of dipraglurant showed anti-dyskinetic effect.

Dipraglurant appears to be as effective in reducing the severity of levodopa induced dystonia as in chorea.

Suggestion of beneficial effect on parkinsonian motor symptom control from patient diaries, which warrants further investigation.
dipraglurant-IR has potential to change PD treatment paradigm

- **Monotherapy**
  - MAOB inhibitor or dopamine agonist or low dose levodopa
  - dipraglurant has potential to enable earlier use of levodopa instead of MAOB inhibitors or DA agonists
  - dipraglurant plus levodopa has potential to delay onset of dyskinesia & reduce need for MAOB inhibitors & DA agonists
- **Combination therapies**
  - levodopa plus DA agonists or MAOB inhibitors &/or other drugs
- **Dipraglurant**
  - has potential to replace or delay DBS &/or treat breakthrough dyskinesia after DBS
- **Deep brain stimulation**
  - continued levodopa & other meds

- **mild**
  - 35% of patients
- **moderate to severe**
  - 43% of patients
- **severe**
  - 22% of patients

After five years of levodopa treatment, about 50% of PD patients suffer dyskinesia.

Dyskinesia incidence increases with levodopa use.

**First indication being pursued for dipraglurant is PD-LID treatment**

Additional indications: non-motor symptoms (e.g. anxiety/depression and/or compulsive behaviors) & motor symptoms; mGluR5 NAM has validation for treating anxiety, addiction & motor symptoms.
dipraglurant beyond PD-LID
beyond PD-LID

- Potential for mood disorders (often co-morbid in PD)
  - Anxiety and depression
    - Dipraglurant has shown efficacy in animal models of anxiety and depression (see next slide)
    - Fenobam, an mGluR5 inhibitor, was effective in a Phase 2 trial in generalized anxiety disorder (GAD)
  - Impulse control disorders & addiction
    - mGluR5 NAM reduces cocaine self administration in rats
    - mGluR5 NAM effective in marble burying model (see next slide)
    - ICD neurocircuitry cortico-striatal pathway overlaps with that involved in dyskinesias and ICD often co-exists with LID in PD patients

- Adjunctive treatment of PD motor symptoms
  - Dipraglurant is effective in the haloperidol induced catalepsy (HIC) model (see slide below)
  - Reduced off-time was observed during Week 4 of the Phase IIa trial

- Non-parkinsonian 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 and in Phase 2A clinical study

- Dystonia therefore represents a significant additional market opportunity for dipraglurant

Source: Dystonia Medical Research Foundation http://bit.ly/tRa1hX
broad therapeutic potential for Dipraglurant

dipraglurant market access strategy starts with PD-LID, the most direct path to market

life cycle management - expand to additional indications

PD Indications
- PD-LID
- Earlier use with levodopa (i.e. LID prevention facilitates levodopa use)
- PD non-motor symptoms
  - Anxiety/depression
  - Impulse control disorders
- PD motor symptoms
- Disease modification

Non-Parkinson Dystonia  Anxiety / Depression

PD-LID
- movement disorders
  - dystonia
  - anxiety & depression
- co-morbid affective/movement disorders (e.g. dystonias with psychogenic involvement)
- co-morbid affective/movement disorders (e.g. anxiety in PD)
Modeling U.S. + 5EU sales of dipraglurant*

- Launch for acute treatment of troublesome LID in patients with moderate & severe PD
- Co-administration with levodopa to treat co-morbid anxiety / depression
- Dipra for PD & PD-LID + non PD dysonia
- Dipraglurant for dystonia + PD & PD-LID + non-PD related anxiety/depression

- $800m
- $1b
- $1.5b
- >>$1.5b

Asian markets are expected to add significantly to the above

*Datamonitor research 2012
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 NDA 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
expanding the realm of possible…

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