dipraglurant (mGlu5 NAM) and dystonia

- Dystonia - a high and growing unmet medical need
  - Potential for orphan drug designation
- Molecular basis for mGlu5 in dystonia
  - Experimental evidence
  - Dipraglurant in the treatment of dystonia
- Clinical development of dipraglurant in dystonia
- Market opportunity for dipraglurant in dystonia
Dystonia

- Dystonias are movement disorders characterized by involuntary muscle contractions that force the body into abnormal, sometimes painful, movements and positions (postures).
- Dystonia etiologies and symptoms are heterogeneous – can affect a single part of the body (focal), multiple areas (segmental) or the whole body (generalized). Further, dystonias are distinguished as either primary (idiopathic, genetic) or secondary (drugs, toxins or metabolic disorders).
- Several types of dystonia are classified by NIH as “rare” (e.g., cervical dystonia, DYT1 familial generalized dystonia and X-linked dystonia parkinsonism).
- An estimated 300,000 people in the United States have been diagnosed with some type of dystonia.
current therapeutic approaches to dystonia are largely inadequate or ineffective

- Drugs currently used to treat dystonia symptoms are prescribed off-label and have not undergone rigorous clinical trials specifically for dystonia indication(s)
- Current therapies include oral drugs such anticholinergic agents, dopamine receptor agonists/antagonists and baclofen
  - Efficacy of these drugs is marginal at best
  - Side effects further limit compliance and usage (e.g. dizziness, memory impairment observed with anticholinergics)
  - L-dopa used in a subset of dystonia conditions
- Injectable botulin toxins are used for treating patients with focal or segmental dystonia
- Deep brain stimulation (DBS) is used for both focal and generalized refractory dystonias
- Clearly, a significant unmet need exists for an oral, safe and effective treatment for combating dystonia

1Jankovic, Lancet Neurol. 5, 2006, 864
mGlu5 inhibition - a novel mechanism for the treatment of dystonia

- Dystonias share common mechanisms of pathogenesis on discrete neuroanatomical regions and neurotransmitter systems (Thompson et al., Expert Opin Ther Targets. 2011, 15, 1387)

- Dysfunctions in basal ganglia synaptic signaling and plasticity are considered central to the development of dystonic symptoms
  - Basal ganglia receive excitatory input from glutamatergic neurons from the cortex and thalamus and mGlu5 receptors are abundant in the striatum where they are closely associated to NMDA receptors (Breakefield et al., Nat. Rev. Neurosci. 2008, 9, 222)
  - Dystonia may be generally linked to the disruption of synaptic homeostasis in the basal ganglia favoring a facilitation of excitatory transmission and synaptic potentiation together with loss of synaptic inhibitory processes (Quartone and Pisani, Neurobiol. Dis. 2011, 42, 162)
  - At the neurotransmitter levels, glutamate receptors also appears to play a key role in dystonia (Fan et al., J. Pharm. Exp. Ther. 2012, 340, 733)
  - Potential involvement of cerebellum over-activity suggested by neuroimaging studies (Niethammer et al., Neurobiol. Dis., 2011, 42, 202)

- Antagonists of mGlu5 receptors reduce over-activity of NMDA-mediated glutamatergic neurotransmission thereby potentially decreasing the over-excitability - the basis of dystonic symptoms
dipraglurant (ADX48621) overview

- Dipraglurant is a highly selective oral brain penetrant small molecule metabotropic glutamate receptor 5 (mGlu5) inhibitor (negative allosteric modulator-NAM) discovered at Addex
- mGlu5 inhibition has been validated in multiple indications

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preclinical and clinical validation of dipraglurant efficacy in dystonia

- DYT-1 mouse model (genetic dystonia)\(^1\)
- Tottering mouse model (paroxysmal dystonia)\(^1\)
- PD-LID MPTP monkey (drug induced dyskinesia with features of dystonia)
- Phase 2a studies in PD-LID Patients

\(^1\)Confidential and not included in presentation
The LID study was conducted by Motac Neuroscience

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 and 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 severity of both dystonia and chorea in the macaque PD-LID model

- Dipraglurant dose-dependently reduced the severity of dyskinesia during the 4 hour "on" period following levodopa
- The effective Cmax was ≥ 1000 ng/ml and reduced both, chorea and dystonia to an equal extent
- No adverse effect on levodopa efficacy; levodopa was fully effective in all dose groups
EU and U.S. Phase 2A dipraglurant clinical 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 results reported 1Q 2012
dipraglurant efficacy in the dystonia component of L-dopa induced dyskinesia in PD-LID patients

- Majority of patients presented with chorea however, there were 4 dystonia patients in the dipraglurant arm and 3 dystonia patients in the placebo arm.
  - Data were limited so statistical analysis was not performed.
- For both the mAIMS 3 hours time course and peak dystonia scores, the data suggests that the magnitude of dystonia improvement with dipraglurant is similar to that of chorea.

![Graph showing peak mAIMS dystonia score (90 min) at baseline (Day 0) and on Treatment Days 1, 14 and 28 (FAS).]
dipraglurant development activities
2013 dipraglurant development activities

• Development activities are intended to:
  – Further characterize dose response to dipraglurant
  – Inform and de-risk the Phase 2b trial design for PD-LID
  – Increase the likelihood of regulatory and market success for dipraglurant in additional high-value indications such as dystonia and Huntington’s disease
  – Advance necessary CMC/toxicology activities for clinical development

• Proposed activities:
  – PET mGlu5 receptor occupancy study in humans*
  – PET mGlu5 receptor occupancy study in primates*
  – Clinical pharmacology studies*
  – P2a study in certain forms of dystonia
  – CMC and long-term toxicology studies and activities

* Michael J. Fox Foundation for Parkinson’s disease supporting the trial with a $1,000,000 grant
dipraglurant dystonia-specific activities

- Pilot phase 2a study in rare form of dystonia (e.g., cervical dystonia)
  - Expect to initiate in 2H 2013
- Phase 2b extension in DYT1 generalised dystonia
  - Expect to initiate in 1H 2014
- KOL/patient foundation consultations on-going
- Potential for grants to fund the studies
- Dystonia animal model work on-going to continue to build non-clinical supportive data
- Expect Orphan drug designation in US and EU in 2013
- Accelerated approval possible
dipraglurant and dystonia market opportunity
Dipraglurant was viewed positively and was expected to become a key addition to treatment algorithm

**KEY FINDINGS – DYSTONIA**

- The overall perception of dipraglurant was generally positive, with an average score of 5 out of 10
- Low level of current treatment satisfaction for dystonia
- Efficacy stands out as the primary unmet need for all types of dystonia. Efficacy and side effects are the 2 key barriers to treatment
- The overall impression of dipraglurant is mixed, partly due to lack of data (as mentioned by several respondents)
- Overall, most KOLs believe that dipraglurant would be of interest for both focal and general types of dystonia, due to the low satisfaction with existing treatment options
Dystonia is generally classified in large subgroups

- Dystonia is commonly divided by muscles involved: general (multiple muscles) and focal (a particular muscle)
- General dystonia is typically managed with oral medications such as anticholinergics (most common), benzodiazepine, Baclofen, tetrabenazine or other muscle relaxant-type drugs
- Focal dystonia is typically primarily managed with Botox injections, but DBS can also be used

“There are five, or eight different classifications but … the most widely used classification, you go by the involved muscles.”
“…diagnose it just like the text books say, number one is by location, so it’s segmental, generalised, or focal and it’s divided into aetiology, so dominant, that is primary, so dominant, or secondary and then you go ahead and you take a secondary dystonia.”

Q1. a. How is dystonia generally treated? Q1b. How do you differentiate dystonia patients? Do they differ by dystonia type? If so how? (focal dystonia, dystonia affecting several parts of the body, secondary dystonia?)
Efficacy stands out as the primary unmet need for the various types of dystonia

- General unmet need for general dystonia:
  - Most respondents commented on the general lack of effectiveness as the key unmet need
  - Many respondents commented on the need for treatments with improved side effect profile

- General unmet need for focal dystonia:
  - Most respondents commented on the relative short duration of effectiveness and limited use because Botox cannot be used on all muscles
  - One respondent comment on the need for an oral, well tolerated treatment which negates the need to have botulinum toxin treatments.

- The vast majority of respondents considered unmet needs to be higher in general dystonia because of the progression of the disease and the general satisfaction of Botox for focal in terms of efficacy, with the exception of neck dystonia where the effect of Botox is not great at the beginning of treatment

Q4: What are the key unmet needs in the treatment of dystonia, starting with the most important, and explain your reasons for each? If relevant, please differentiate between specific dystonia types. Q5: For which dystonia types do you consider that the level of unmet need is highest? Please explain your reasons.
Overall, most KOLs believe that Product X would be of interest for both focal and general types of dystonia

- 66% of respondents who answered felt that Product X would be of interest in both types of dystonia patients, however, two respondents need to know more information before estimating what line of treatment it would be used in.
- Of the respondents that believed Product X would be suitable for both types of dystonia, three believed it would be 1st line, 2nd line and 3rd line respectively.
- Of the three respondents that felt Product X would only be of interest to general dystonia patients, two thought it would be 1st line or 2nd line respectively while one respondent felt Product X would be 1st line.
- One respondent could not answer without having more information.

“I would use it for any dystonia patient and I would say, 'Okay, I'll give you three months with this medication and we'll make adjustment of doses afterwards and we'll see.”

Q13a. Would this product be of interest for all types of dystonia patients or would it be best suited to specific types instead? If so, which ones? Q13b. How would it be used for each type (e.g. first-line, second-line, etc.) Please explain your reasons
Dipraglurant for dystonia is forecast to reach sales of over $520m by 2025 in the US and EU5 markets.
Summary
dipraglurant for the treatment of dystonia – a compelling opportunity

- Dystonias are a set of heterogeneous diseases with a huge unmet medical need and no viable treatment alternatives
- Dipraglurant, a highly selective, oral mGlu5 NAM, has been shown to be safe and effective in human clinical testing
- Dipraglurant has shown positive anti-dystonia effect in multiple animal models of dystonia as well as positive anti-dystonia effect in Parkinson’s patients
- Dipraglurant could be a first-in-class dystonia therapeutic with the potential to significantly change the treatment paradigm for a variety of dystonias
- Dipraglurant could establish a dominant position in the $500 MM+ dystonia market
- Dipraglurant orphan drug designation in dystonia is expected by end of 2013
- Data from human clinical testing of dipraglurant in dystonia is expected by end of 2013
expanding the realm of possible

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