

Dipraglurant Immediate Release (IR) Formulation for the Treatment of Parkinson's disease Levodopa Induced Dyskinesia (PD-LID)

Importance of the IR Formulation and the potential to change the treatment paradigm for Parkinson's disease

Executive Summary

Dipraglurant is a novel metabotropic glutamate receptor 5 inhibiting, small molecule with potential to be used as a stand alone treatment, or in combination with levodopa or dopamine agonists, for treatment of:

- levodopa-induced dyskinesia (PD-LID)
- non-motor symptoms of PD *e.g.* anxiety, depression, impulse control disorders.
- motor symptoms of PD
- non-parkinsonian dystonias

The combined peak U.S. annual sales potential (excluding disease modification) for the PD indications alone is estimated to be in the range of \$1.8bn to \$2.7bn , (source Michael J Fox Foundation 2011). Datamonitor market research with PD specialists in the U.S., EU, China and India show that dipraglurant has an attractive product profile and can capture over \$1 billion in annual revenues if fully exploited in PD indications. Additional labelling for indications in non-parkinsonian movement disorders such as dystonias, offers similar peak sales potential.

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

- Its pharmacokinetic profile is similar to levodopa so drug is delivered precisely when needed.
- Its rapid onset of action is ideal for dyskinesia 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

An extended release (ER) formulation has completed preclinical evaluation and will start Phase 1 clinical testing in 2012. The ER formulation offers the possibility of important product line extensions and comprehensive life-cycle management, especially outside of the PD indication.

Introduction

Dipraglurant is a potent, selective metabotropic glutamate 5 receptor, negative allosteric modulator (mGluR5 NAM). It is an orally available, small molecule drug.

Inhibition of mGluR5 is clinically validated in acute treatment of PD-LID but also has clinical and non-clinical validation in other indications both within and outside of PD.

Dipraglurant IR has shown effect in non-clinical pharmacology models of anxiety, depression, parkinsonian motor symptom control and also levodopa-induced dyskinesia in parkinsonian macaques. In this last model, oral dipraglurant IR reduced the severity of both chorea and dystonia, to an equal extent, during the 4 hour post levodopa dosing period. This effect on dystonia has not been reported with other anti-dyskinetic drugs tested in this model.

The glutamate mechanism is a highly sought-after target for new PD medicines.

Dipraglurant IR is currently being studied in the US and EU in a 72 patient, Phase 2A clinical trial for acute treatment of levodopa induced dyskinesia (PD-LID). Top-line data are expected in 1H12.

Parkinson's disease Levodopa-induced Dyskinesia (PD-LID)

Oral levodopa remains the most effective treatment available for motor symptoms of Parkinson's disease. However, long-term levodopa use is invariably associated with the development dyskinesias which may become as disabling as the parkinsonian symptoms themselves. Levodopa-induced dyskinesias (LID) are experienced by over 40% of patients with Parkinson's disease 4–6 years after starting levodopa, and up to 90% of patients by 9–15 years of treatment (Ahlskog JE and Muentner MD, *Mov Disord* 2001)

Dyskinesias are not solely related to levodopa use. They are also seen following use of DA agonists, although most research has been based upon observation of levodopa induced dyskinesias.

Dyskinesia results from the neurodegenerative process (loss of substantia nigra cells) and is not solely linked to the duration of dopamine replacement therapy, *e.g.* in severe advanced stage PD patients, dyskinesia can be provoked after a first high dose of levodopa. Chronic and pulsatile dopamine replacement treatments do not lead to dyskinesia *per se*, but may lower the threshold for dyskinesia to occur following dosing, as neurodegeneration progresses.

Efforts to reduce pulsatile dosing (high C_{max}) of levodopa and/or DA agonists, by using more frequent lower doses, or extended release formulations, can improve dyskinesias, but may be at the expense of optimal motor function, so that in the later stages of Parkinson's disease, the patient and physician have to juggle good motor symptom control, against the occurrence of levodopa-induced dyskinesia.

Although levodopa provides the most effective motor symptom control, due to the inevitability of dyskinesia, physicians leave using levodopa for as long as possible, and use dopamine agonists and/or monoamine oxidase B inhibitors in the early stages of the disease. These compounds become less effective as the disease progresses and are also associated with dose limiting side effects. Increasingly recognized as being of particular concern with dopamine agonists, are Impulse Control Disorders (ICD), such as pathological gambling, food, shopping or sex addiction, which can occur in up to 15% of patients taking these compounds (Antonini A et al. *Lancet Neurol* 2009)

Doctors would like to use levodopa earlier in the disease if dyskinesia could be effectively treated or better still, delay or eliminate its occurrence completely. Thus there is a major need for effective anti-dyskinetic agents in the management of PD, acknowledged by physicians and regulatory authorities. If dipraglurant IR proves to be an effective anti-dyskinetic compound, it has potential to change the treatment paradigm of Parkinson's disease, enabling earlier and more effective use of levodopa

Why dipraglurant immediate release (IR) is ideal for PD-LID

Parkinsonian dyskinesia falls into three types. The most common are peak dose dyskinesias which occur at maximum levodopa plasma concentration, 60-90 mins post-dose. Biphasic dyskinesia, occurs at the beginning and end of "On" time around 30 mins and 120 to 150 mins post levodopa dose and the third, less common, type is "Off" dystonia, which occurs once levodopa has worn off.

The immediate release formulation of dipraglurant is ideal for the acute treatment of levodopa-induced dyskinesia, because the plasma concentration, time profile closely parallels that of levodopa, with peak plasma concentration occurring around the same time as that of levodopa and the duration of plasma concentration covers that of the "On" period.

Figure 1 shows human plasma concentration time profiles (non-contemporaneous data) for 100 mg of dipraglurant IR (from Addex' Phase 1 clinical studies) and levodopa (levodopa-carbidopa 100/25mg formulation). It can be seen how the plasma concentration time profile of dipraglurant follows that of levodopa.

Figure 1

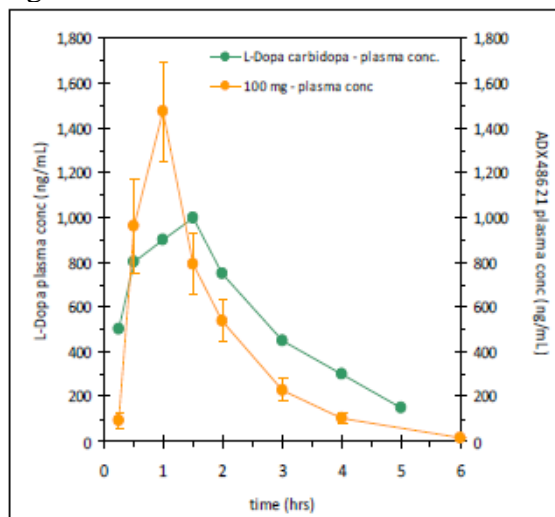


Figure 2 A shows the time course of dyskinesia following dosing with levodopa in the MPTP macaque model (n = 8) and the effect of different doses of dipraglurant on LID. It can be seen that dyskinesia peaks at 60 to 120 minutes after levodopa dosing and that dipraglurant IR dose-dependently reduced the severity of peak dose dyskinesia during the 4 hour “On” period following levodopa. Figure 2B shows the plasma concentration time profiles and pharmacodynamic effect of the 10mg/kg dose from 4 animals in this experiment. The peak plasma concentration required for good pharmacological effect was approximately 1000 ng/ml, which can be achieved in patients with a dose in the range of 50 to 100 mg (see Figure 1).

Figure 2A

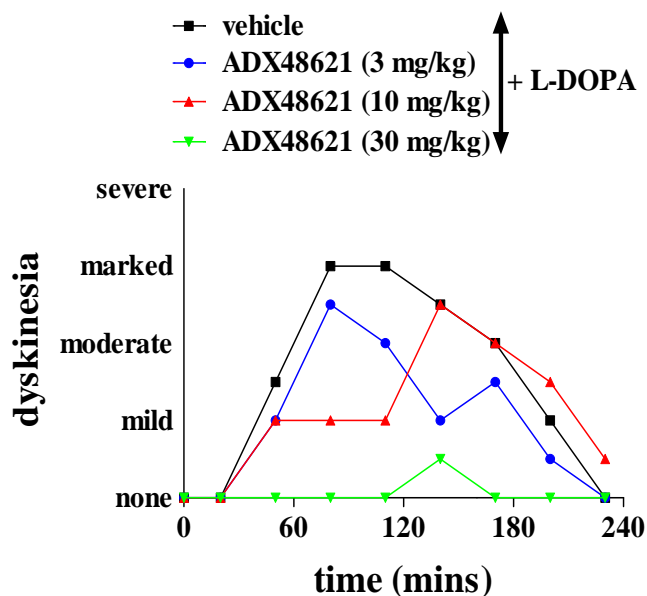
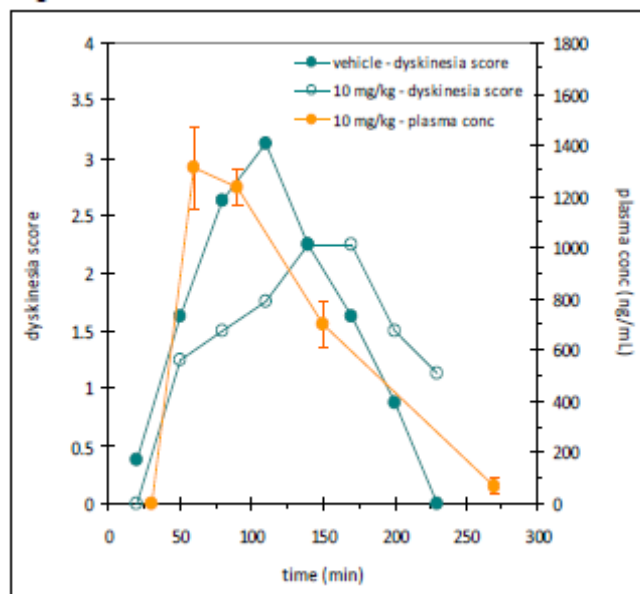


Figure 2B



These pharmacology and pharmacokinetic data have formed the basis of the design of the Phase 2A study in PD-LID patients, where the aim is to study the safety and efficacy of acute treatment of LID with dipraglurant-IR, co-administered with levodopa.

The rapid absorption of dipraglurant-IR means effective plasma concentrations should be achieved when most needed, *i.e.* at peak levodopa levels. In addition, the short half-life has the advantage that the patient washes out between doses, avoiding, drug accumulation, rebound effects and also side effects resulting from high, constant drug levels, which are not needed to control LID.

The Phase 2A trial

The double-blind, placebo-controlled, 72-patient U.S. and EU clinical trial has a four-week treatment duration. At the screening visit, patients select 3 of their daily levodopa doses, with which they will also take dipraglurant-IR or placebo. These are levodopa doses that generally cause troublesome dyskinesia. The study has a dose titration schedule where patients start with a single 50 mg or placebo capsule at the beginning of Week 1 and escalate to 2 capsules (100 mg or placebo) three times daily at the start of Week 4. The doses have been chosen so the the C_{max} will bracket the target C_{max} for efficacy *i.e.* 1000 ng/ml. Average C_{max} for 50 mg is approximately 800 ng/ml and that for 100 mg approximately 1500 ng/ml. Efficacy is evaluated firstly by in-clinic observation of dyskinesia severity for 3 hours, following the “middle of the day” levodopa dose, using the Abnormal Involuntary Movement Score, performed by a trained observer. Secondly, the patients complete a diary for 48 hours in the pretreatment week and each of the 4 treatment weeks. In the diary, every 30 minutes, they note whether they are asleep, are in “Off” or in “On” and if so, whether they

have troublesome dyskinesia. In this way all the doses of dipraglurant can be evaluated.

Compliance is not a problem with dipraglurant IR

Conventional wisdom dictates that patient compliance is better with once or, at most, twice daily treatment. For the most part that is true, especially in generally asymptomatic conditions, like hypertension. However, Parkinson's disease patients typically take an intricate treatment regimen, tailored specifically to their needs, to optimize "On" time and avoid motor fluctuations, and this regimen often changes regularly as patients tend to tune their treatment to their changing needs. Patients typically take medication at least three times a day and, in some cases, as frequently as eight times per day. In this case a drug that is taken concomitantly with levodopa to avoid side effects associated with levodopa and improve the quality of their "On" time, is not expected to pose a problem for compliance.

Other uses of the IR formulation

Apart from LID in moderate to severe PD patients, the dipraglurant-IR formulation could be used whenever an acute LID treatment with rapid onset of action and short-term, high plasma concentrations are desired.

Early use of levodopa in PD

An effective anti-dyskinetic drug would enable use of levodopa earlier in the course of Parkinson's disease and might delay the onset and/or reduce the severity of dyskinesia.

Levodopa dose optimization

An effective antidyskinetic drug could allow levodopa doses to be increased, thereby reducing "Off" time.

For the above two uses, there may be a possibility also to develop a levodopa plus dipraglurant-IR combination product in a single capsule or tablet.

Acute/emergency treatment of Impulse Control Disorders

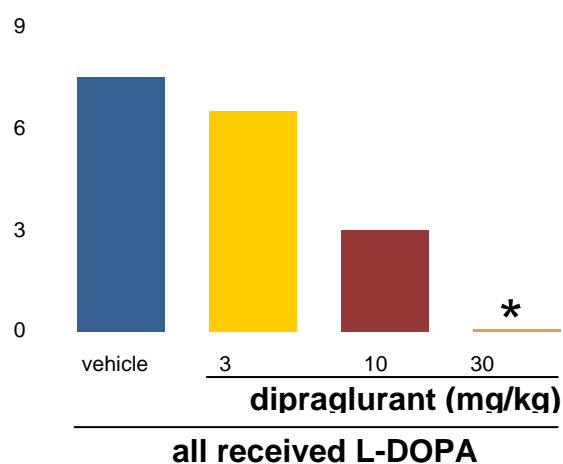
Levodopa-induced dyskinesia and Impulse Control Disorders may result from similar mechanisms involving excessive glutamate activity and sensitization of NMDA receptors resulting from a lack of dopaminergic control. Impulse Control Disorders occur in approximately 15% of PD patients taking dopamine agonists (Antonin A et al. *Lancet Neurology* 2009) and commonly co-exist with dyskinesia. Inhibition of mGluR5 has been shown to reduce cocaine self administration in rats Kumaresan V, et al. *Behav Brain Res.* 2009) and the mechanism is generally considered to be anti-addictive. In PD patients the antiglutamatergic, NMDA antagonist amantadine, has been shown to reduce the severity of pathological gambling (Thomas et al *Annals of Neurology* 2010). Acute rapid onset treatment could be of use for patients admitted to hospital with severe ICD, alongside stopping or reducing their DA agonist therapy. In addition, dipraglurant could be studied in combination with DA agonist as it may have complementary efficacy and reduce the incidence of ICD.

Acute intermittent forms of dystonia (parkinsonian and non parkinsonian)

In the MPTP macaque model of levodopa-induced dyskinesia, dipraglurant was able to control both dystonia and chorea, reducing the severity of each, by a similar magnitude. mGluR5 are involved in dysregulation of long term potentiation in dystonia models which can be rectified with MPEP and MTEP (Pisani et al personal communication at Dystonia congress, Rome, May 2011). Dystonia typically does not occur when patients are asleep. Acute intermittent dystonias (eg blepharospasm, writers cramp or “Off” dystonias in PD patients) may be more appropriately treated with a high plasma concentration of short duration provided by the IR formulation.

Figure 3

**MPTP macaque
Median dystonia scores (0-2 h)**



Product line extension and life cycle management opportunities using the dipraglurant extended release (ER) formulation

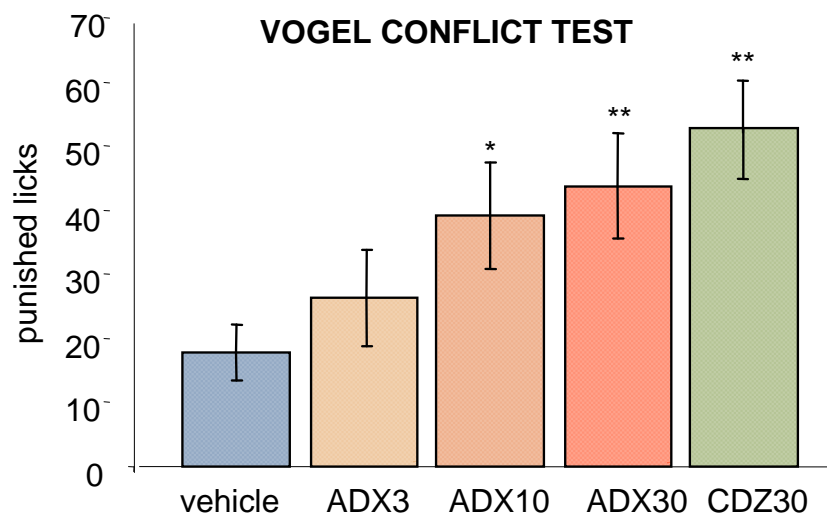
An extended release formulation of dipraglurant is in development. The choice of two formulations offers the flexibility to tailor treatment to patients and their particular problems. It also offers the possibility of an extensive product range and comprehensive life-cycle management.

Compared to the IR formulation, the ER formulation prototype has a longer T_{max} , approximately 4 hours, and sustained exposure for approximately 6 hours thereafter, a profile consistent with once or twice daily dosing. For IR and ER formulations with the same bioavailability, the maximal plasma concentration C_{max} for dipraglurant ER is targeted to be lower than that achieved with the IR formulation but the overall exposure measured by AUC_{0-t} is targeted to be the same as for the IR form. Hence the ER form can be considered for indications that require longer term, lower, steady state plasma exposure to provide therapeutic effect, such as non-motor and motor symptom control of PD as well as more persistent forms of dystonia.

Treatment of non-motor symptoms of PD

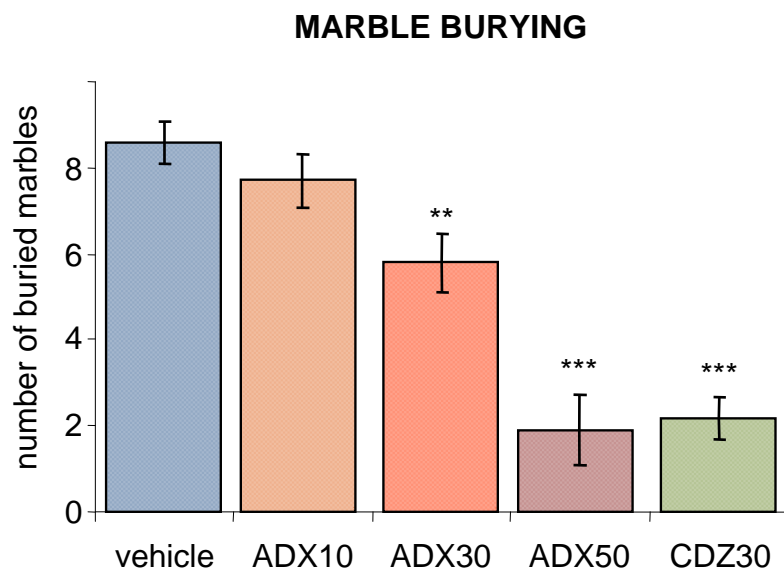
dipraglurant has demonstrated significant effects after oral administration in animal models of anxiety and depression (Figures 4A, B and C). Effective therapeutic plasma concentrations were in the range of 500 to 1000 ng/ml.

Figure 4A



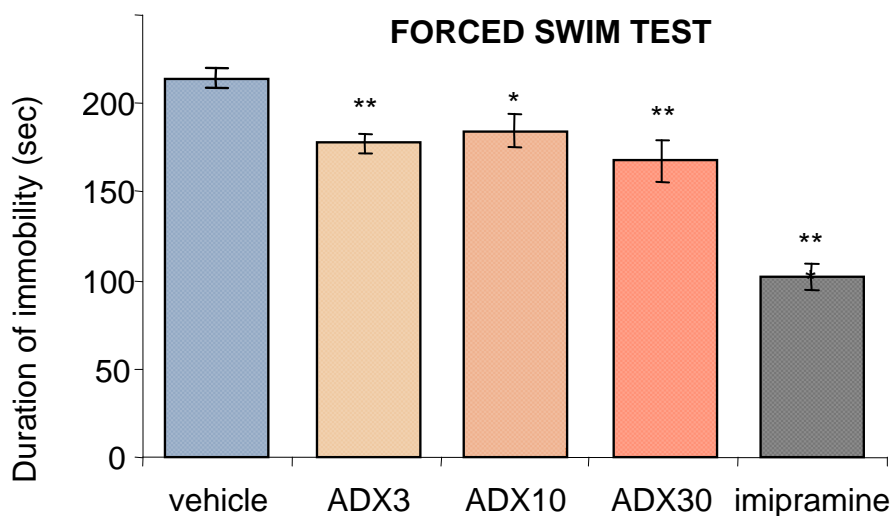
*p < 0.05, **p < 0.01, ***p < 0.001 statistical significance vs. vehicle group.

Figure 4B



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

Figure 4C

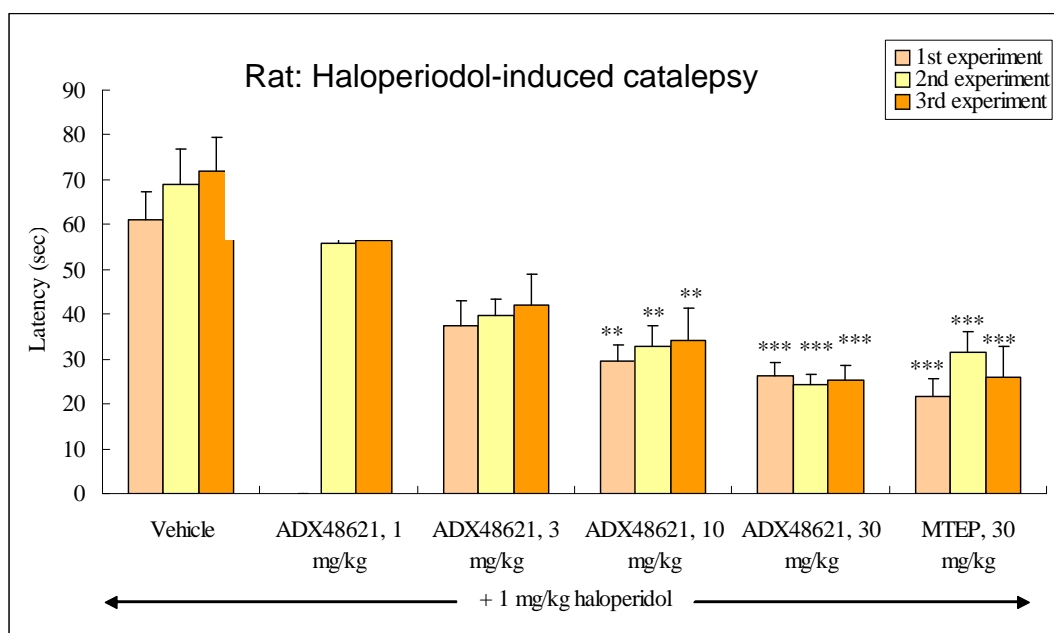


*p <0.05, **p < 0.01, ***p < 0.001 statistical significance vs. vehicle group.

Parkinson’s disease motor symptom control

Dipraglurant showed effects in the rat Haloperidol Induced Catalepsy model (Figure 5) which suggests the possibility of using the drug for parkinsonian motor symptom control. In this case it could be considered as adjunctive therapy with DA agonists, MAOB inhibitors and levodopa and possibly also A2A antagonists and mGluR4 agonists/PAMs in the future. Dipraglurant has the possibility to enhance motor symptom control and have additive and/or synergistic effects with these other therapies.

Figure 5



Dystonias (parkinsonian and non parkinsonian)

Given in conjunction with dopaminergic therapies in PD patients, dipraglurant ER might improve “off” dystonias, or improve/reduce wearing off effects.

Dipragurant ER may have benefit in non parkinsonian dystonias *e.g.* limb, segmental or widespread dystonias, as monotherapy or as adjunct to botulinum toxins. The anxiolytic properties of an mGluR5 inhibitor may also be of benefit in dystonia, where anxiety can be an important aggravating factor.

Conclusions

The IR formulation is clearly the compound of choice for treatment of PD-LID and also has potential applications in other indications. An important product line extension can be achieved if the ER formulation is added for the treatment of dystonias and adjunctive treatment for parkinsonian motor symptom control.

The multiple potential uses for the dipraglurant IR and ER formulations would need to be explored thoroughly in adequate, well-controlled clinical trials, to determine the optimal product positioning. Nevertheless, if dipraglurant’s therapeutic potential in PD alone is exploited fully, the annual peak sales are estimated to be > \$1bn (Datamonitor analysis). The potential of dipraglurant as medicinal product represents an extraordinary opportunity for patients and potential partners.