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IPX066: a new intermediate-and extended-release carbidopa–levodopa formulation

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SUMMARY

Carbidopa–levodopa (CD–LD) is the mainstay of treatment for Parkinson’s disease (PD), yet most patients with advanced PD develop motor fluctuations with time when treated with CD–LD. Development of longer-acting CD–LD formulations is a major goal for reducing motor fluctuations in advanced PD. IPX066 is a new formulation of CD–LD that contains both an immediate-release and a sustained-release levodopa component, which is currently under review by the US FDA. Recent clinical trials have demonstrated improved effectiveness of IPX066 compared with other CD–LD formulations in advanced PD, with a reduction in ‘off’ time of approximately 37%. While it has also been shown to be effective in early PD compared with placebo, its role in early PD compared with other available medications for PD is unclear at this time.

Parkinson’s disease (PD) is the second most common neurodegenerative disorder, and its prevalence is expected to double in the next 20 years [1]. Classically, PD has been viewed predominantly as causing motor dysfunction, with resting tremor, bradykinesia, rigidity and gait impairment, due to loss of dopaminergic neurons in the substantia nigra. However, this disorder affects many other areas of the nervous system beside the nigrostriatal pathway. Nonmotor features of the disorder include autonomic dysfunction, cognitive impairment and psychiatric disorders.

Currently, there is no treatment that has been shown to unequivocally slow or reverse the neurodegenerative process in PD. Current pharmacologic management of the disease is based on treating the symptoms of the disorder, in particular the motor symptoms. The mainstay of treatment is based on augmentation of dopamine, which is reduced in the nigrostriatal pathway and is responsible for the motor symptoms of the disorder. Dopamine neurotransmission can be augmented by several methods: presynaptically by providing the dopamine precursor levodopa (LD), postsynaptically by using agonists to the dopamine receptors, or by using inhibitors to the enzymes that metabolize dopamine, including catechol-*O*-methyltransferase (COMT) and monoamine oxidase (MAO).

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While in use for decades, LD is still the gold standard of PD therapy. LD is converted into dopamine by the enzyme aromatic acid decarboxylase (AADC), which is present peripherally as well as in the CNS. LD is given with carbidopa (CD) or benserazide to reduce peripheral conversion by AADC in order to minimize side effects and maximize the amount of drug crossing the blood–brain barrier (BBB). Many years of clinical use and clinical trials have shown that LD is very effective at reducing motor symptoms of PD, including resting tremor, bradykinesia and rigidity [2,3]. It is less effective at treating the gait impairment associated with the disorder. It also fails to treat the non-motor symptoms increasingly recognized to cause disability in patients. There has been concern that LD could promote neurotoxicity through oxidative stress mechanisms, yet clinical studies in patients have not supported this concern [3–6].

Despite the expectation that LD could eventually become ineffective in patients due to the continued loss of dopaminergic neurons that convert LD to dopamine, patients with PD continue to respond to LD for years [7,8]. Other cell types may convert LD into dopamine [7,9]. The main limitation of LD is the development of motor complications with chronic LD use. These include dyskinesia and motor fluctuations, such as wearing off, delayed ‘on’ and dose failures. It is estimated that 50% of patients treated with LD for >5 years will develop these motor complications [10–12], and younger patients have a higher risk of developing these complications [12,13].

Development of wearing off and other motor fluctuations is a phenomenon of disease progression. Early in the disease, motor benefit in response to one dose of CD–LD lasts much longer than the plasma half-life of CD–LD, which is approximately 60–90 min, most likely due to the storage of LD in remaining dopaminergic neurons [14,15]. With the continued loss of dopaminergic neurons as the disease progresses, the plasma half-life of LD becomes more critical with regard to clinical effect, and motor benefit starts to follow the plasma half-life of LD. Therefore, each dose tends to last for a shorter interval. While mechanisms of dyskinesia development are not fully understood, wide fluctuations in plasma LD levels causing pulsatile stimulation of dopaminergic receptors in the striatum have been implicated [16]. Therefore, methods to extend CD–LD have been pursued to try to eliminate or reduce these motor complications related to the short half-life of immediate-release CD–LD (CD–LD IR).

One method to prolong LD levels and minimize wearing off is continuous infusion of LD. Enteral LD infusions are currently used for the management of advanced PD in Europe, and such delivery is under clinical trials in the USA. Continuous LD infusion is associated with reduced ‘off’ time and dyskinesias [17]. Another approach is coadministration of CD–LD with drugs that inhibit enzymes that metabolize LD, including COMT and MAO. Tolcapone was the first COMT inhibitor used and can inhibit both peripheral and central COMT, but its use has been limited due to liver toxicity. Entacapone is most commonly used in combination with CD–LD IR and does increase the half-life and bioavailability of LD by inhibiting the conversion of LD to *O*-methyldopa (3-OMD) peripherally [18,19]. Clinical studies have demonstrated that entacapone increases on time and reduces off time [20,21]. Co-administration with MAO inhibitors, particularly rasagiline, has also been shown to reduce off times in combination with CD–LD [22,23].

Another approach is to develop longer-acting formulations of CD–LD. Development of sustained-release formulations has been limited due to the absorption of LD that is most effectively absorbed in the region of the duodenum, which contains the amino acid transporters that are able to uptake LD [15]. A continued release (CR) formulation of CD–LD has been available for a number of years, but its use has been limited by a delayed time of onset compared with CD–LD IR [24,25].

IPX066 (Impax Pharmaceuticals, CA, USA) is a newly developed formulation of CD–LD that combines an immediate-release formulation with a sustained-release formulation. Several clinical trials currently published in abstract form have suggested that it is a promising new agent to be used in the management of PD (see below).

Indications & usage

IPX066 is not currently approved for any clinical indications. A new drug application was submitted to the US FDA in December 2011 by the manufacturer Impax Pharmaceuticals for potential approval to treat idiopathic PD. The FDA has recently issued a complete response letter, which indicates an end to the review cycle but that the drug application is not ready for approval at this time. Based on information from a press release from Impax Pharmaceuticals, drug application approval is upheld at least until the company fulfills a reinspection of one of its facilities.

Dosage & administration

IPX066 is available as a combined immediate-and sustained-release CD–LD capsule with a one-to-four ratio of CD to LD. In the APEX-PD trial in early PD, subjects were given three fixed doses of 145, 245 or 390 mg orally three-times a day [26,27]. Because of the lower bioavailability of IPX066, these doses are comparable with 300-, 500- and 800-mg LD daily. In two randomized trials in advanced PD (ADVANCE-PD and ASCEND-PD), dosing was individually titrated to clinical benefit [28–30]. The dosing interval was fixed at three-times a day in the APEX-PD trial [26,27]. Mean dosing intervals were 3.6 doses in ADVANCE-PD or 3.5 doses in ASCEND-PD [28–30].

Clinical pharmacology

IPX066 is a new formulation of the natural compound LD along with the AADC inhibitor CD, at a one-to-four ratio of CD to LD. This CD–LD formulation contains an immediate- and sustained-release CD–LD. LD is a precursor for dopamine neurotransmitter synthesis. LD is absorbed primarily in the proximal small intestine via the large neutral amino acid transporter and then crosses the BBB via the large neutral amino acid transporter. In the brain, it is converted by AADC into dopamine, presumably in remaining dopaminergic neurons. Dopamine packaged into synaptic vesicles is then released into the synapse to activate postsynaptic dopamine receptors. Due to the continued effectiveness of LD in advanced PD, despite the loss of most dopaminergic neurons, it has been hypothesized that other cells also convert LD to dopamine [7,9]. Activation of the dopamine nigrostriatal system is associated with improved motor function in PD patients, including reduction of tremor, bradykinesia and rigidity. The active metabolite dopamine is metabolized by reuptake of dopamine into the presynaptic terminal or by the enzymes MAO and COMT found in the synaptic cleft. MAO converts dopamine to 3,4-dihydroxyphenylacetic acid, which is then converted to homovanillic acid by COMT. Alternatively, COMT converts dopamine to 3-methoxytyramine, which is then converted to homovanillic acid by MAO.

Peripherally, LD can be converted to dopamine by peripheral AADC, which can cause side effects such as hypotension and nausea. LD can also be converted to 3-OMD by peripheral COMT. This peripheral conversion of LD to dopamine or 3-OMD results in reduced levels of LD getting into the brain. While 3-OMD can cross the BBB, it does not activate dopamine receptors and dopamine cannot cross the BBB. The use of CD with LD minimizes this peripheral conversion to dopamine to maximize transfer of LD across the BBB and to minimize side effects. Similarly, COMT inhibitors reduce the peripheral conversion to 3-OMD to maximize LD crossing the BBB. Dopamine metabolites are excreted in urine.

Pharmacokinetics of IPX066 were compared with CD-LD IR in a recent, open-label study in which 27 subjects were randomized to either IPX066 followed by CD-LD IR or vice versa [31]. Single-dose data showed a mean maximum LD plasma concentration of 3000 ng/ml 2 h following IPX066 dose; it should be noted that subjects were treated with different doses of IPX066. Time to reach 50% of maximal plasma concentration was 0.78 h for IPX066, comparable with that of CD-LD IR (0.76 h). Duration of plasma LD concentration above 50% of maximal plasma concentration was 4 h, compared with 1.4 h for CD-LD IR ($p < 0.0001$). Relative bioavailability of IPX066 was 74.5% of CD-LD IR. With multiple-dose administration, IPX066 showed reduced plasma LD variability, with a fluctuation index ([mean maximum LD plasma concentration - mean minimum LD plasma concentration]/average LD plasma concentration) of 1.5 compared with 3.2 for IR ($p < 0.0001$).

Clinical evidence

Evidence for regular LD in the treatment of PD is well established and will not be reviewed here. The extended-release IPX066 formulation has been evaluated in three double-blinded trials [32]. The APEX-PD trial evaluated the use of IPX066 in early PD, while the ADVANCE-PD and ASCEND-PD trials focused on IPX066 in advanced PD. Results of these three trials have been presented at the American Academy of Neurology and Movement Disorders Society annual meetings [26–30], but these results have not yet been published in peer-reviewed journals. These trials are summarized in Table 1.

The ADVANCE-PD trial was a randomized, double-blinded study comparing CD-LD IR with IPX066 in subjects with advanced PD who had motor fluctuations on CD-LD IR [28,32]. Four hundred and seventy one patients were enrolled and first underwent a two-stage, open-label period in which subjects underwent a 3-week dose optimization period for CD-LD IR followed by a 6-week dose conversion period to IPX066. Three hundred and ninety three subjects were then randomized to either CD-LD IR or IPX066 given at the finalized dose for 13 weeks. A double-dummy design was used with subjects taking both active medication for one drug and placebo for the other drug. The primary outcome was off time as a percentage of waking hours as determined by 24-h subject diaries. Percent off time was reduced by 37% in subjects taking IPX066, compared with a reduction of 17% in subjects on CD-LD IR ($p < 0.0001$). Mean off time was reduced by 2.2 h in subjects on IPX066, an additional 1.2-h reduction compared with those randomized to CD-LD IR ($p < 0.0001$). Conversely, on time without troublesome dyskinesia increased by 1.1 h in the IPX066 treatment group compared with the CD-LD IR group ($p < 0.001$). Subjects on IPX066 also showed a greater reduction in Unified Parkinson's Disease Rating Scale (UPDRS) scores and significant improvement in the Patient and Clinical Global Impression (PGI, CGI) scales and the Parkinson Disease Questionnaire-39 Quality of Life (PDQ-39) scale compared with subjects on CD-LD IR. IPX066 was administered at a mean of 3.6-times a day, compared with CD-LD IR, which was given at a mean of 5.1-times per day.

The ASCEND-PD trial examined the use of IPX066 in advanced PD [29,30]. The ASCEND-PD trial was a randomized, double-blinded crossover study designed to compare IPX066 with CD-LD given with the COMT inhibitor entacapone (CD-LD-E). During the first, open-label phase, 110 subjects on stable CD-LD-E were initially dose converted to IPX066. During the second phase, 91 subjects were randomized to either IPX066 for 2 weeks followed by CD-LD-E for 2 weeks or vice versa (CD-LD-E for 2 weeks followed by IPX066 for 2 weeks). The primary outcome measure was percent off time during waking hours based on subject diaries. Percent off time was significantly lower for subjects when on IPX066 (24%) compared with CD-LD-E (32%; $p < 0.0001$). Mean off time was 3.82 h for IPX066 and 5.22 h for CD-LD-E ($p < 0.0001$), while on time without troublesome

dyskinesia increased by 1.52 h with IPX066 and 0.14 h with CD-LD-E ($p < 0.0001$). IPX066 was given at a mean of 3.5-times a day, compared with CD-LD-E, which was given at a mean 5.0-times per day.

The APEX-PD study was a randomized, fixed-dose, placebo-controlled study to evaluate the safety and efficacy of IPX066 in patients with early PD [26,27]. Three hundred and eighty one subjects who had never had LD were randomized to one of four treatments for 30 weeks: placebo; IPX066 145 mg three-times daily (equivalent to 300-mg LD daily); IPX066 245 mg three-times daily (equivalent to 500-mg LD daily); or IPX066 390 mg three-times daily (equivalent to 800-mg LD daily). The primary outcome measure was change from baseline in UPDRS parts II plus III score at week 30, and secondary measures included change from baseline in total UPDRS, PGI and CGI scales, and PDQ-39 scale. Mean change in UPDRS II and III score were statistically different in all three IPX066 arms compared with placebo. Mean change in combined UPDRS part II and III score from baseline was -0.6 for placebo, -11.7 for the 145-mg dose, -12.9 for the 245-mg dose and -14.9 for the 390-mg dose (all $p < 0.0001$ compared with control). Secondary measures, including PGI and CGI scales and PDQ-39 scale scores, were also statistically different in the three drug arms compared with placebo.

Based on these trials, Impax Pharmaceuticals has filed a new drug application for IPX066 in the treatment of idiopathic PD.

Adverse reactions

The adverse reactions for IPX066 are comparable with those for immediate-release CD-LD. The most common adverse events documented in the APEX-PD trial, in which IPX066 was compared with placebo, included nausea, headache, dizziness and insomnia, but no serious drug-related adverse events were reported [26,27]. The percentage of subjects reporting adverse events was similar for the two higher doses of IPX066 and placebo and lower for the lowest IPX066 dose. In the ADVANCE-PD trial, the percentage of subjects reporting adverse events were similar for IPX066 (43%) compared with CD-LD IR (40%) [28]. The most common adverse events during the double-blind phase were dizziness, nausea, insomnia, falls and dyskinesia. No serious adverse events related to IPX066 were noted in ADVANCE-PD. During the double-blind phase of the ASCENDPD trial, 20% of subjects treated with IPX066 experienced adverse reactions compared with 14% of subjects treated with CD-LD-E [29,30]. The most common adverse reactions during the double-blind phase were dyskinesia, confusion and insomnia. Six serious adverse events were recorded, including atrial fibrillation, constipation, gastroenteritis, dehydration, hyperkalemia and sciatica during IPX066 treatment.

Drug interactions

No data have been specifically published on IPX066 with regard to drug interactions. Drug interactions for IPX066 are expected to be the same as for LD. Potential drugs that interact with LD are discussed elsewhere [15].

Use in specific populations

No data have been specifically published on IPX066 with regard to any differences in pharmacokinetics or clinical benefit based on race, gender or other specific populations. Differences in LD pharmacokinetics and development of adverse reactions have been described with regard to gender and age. Women have higher peak plasma concentration and greater LD bioavailability [33–36], and have been shown to require lower LD doses compared with men [37]. Body weight differences may play a role in this gender difference

[35,36,38], although other studies suggest that body weight is not a factor [33,34]. Dyskinesia and motor fluctuations are more prevalent with younger age of LD onset [12,13]. Ethnic differences have been described in erythrocyte COMT activity [39–41], and patients with COMT haplotypes associated with increased activity have been shown to require higher LD doses [42].

Clinical issues

While LD is still the most effective medication available for PD, the main drawback of this medication is the development of motor complications. Patients eventually develop motor fluctuations, particularly wearing off, such that a given dose does not last as long as it does earlier in the disease course. With disease progression there are fewer dopaminergic neurons to store LD, and improvement in motor symptoms starts to follow the plasma half-life of LD, which is only 90 min when combined with CD [14,15]. Wide fluctuations in plasma LD levels are thought to promote the development of dyskinesia [16]. Therefore, the development of extended CD–LD formulations has been pursued to try to eliminate or reduce these motor complications related to the short half-life of CD–LD IR.

CD–LD CR has been available for many years and does show a slower decline in plasma LD levels compared with CD–LD IR [25]. However, absorption of CD–LD CR is much slower than IR, resulting in a delayed clinical benefit [24,25]. Peak plasma levels and bioavailability is reduced compared with CD–LD IR [24,25]. Controlled studies comparing CD–LD CR to IR show mixed results with regard to improvement of motor fluctuations [24,43,44], and initial treatment with CD–LD CR did not show a lower rate of developing motor complications compared with CD–LD IR [45,46].

The use of COMT inhibitors, such as entacapone, in conjunction with CD–LD also prolongs the plasma half-life of LD [18,19]. Clinical trials have confirmed that off time is reduced in patients treated with COMT inhibitors [20,21,47]. Wide fluctuations in LD concentration still occur in the presence of entacapone [48–50], and entacapone increases the rate at which dyskinesias develop on CD–LD when started early in disease [51]. MAO-B inhibitors, particularly rasagiline, also reduce off time when combined with LD [22,23]. Another strategy to reduce off time is the addition of the longer-acting dopamine agonists as adjunct therapy in patients with motor fluctuations [15,52,53]. This benefit of dopamine agonists is thought to be secondary to their longer half-lives compared with LD.

The longer duration of plasma LD levels with IPX066 would theoretically be useful in patients with advanced PD who have motor fluctuations. Time for clinical benefit is faster than the other longer-acting formulations, with a similar time to reach 50% of the maximum concentration as CD–LD IR, and it lasts longer than CD–LD IR [31]. Two blinded studies show that IPX066 is superior to CD–LD IR and CD–LD–E in advanced PD. The ADVANCE-PD trial showed a reduction in off time and increase in on time without troublesome dyskinesia in subjects treated with IPX066 compared with CD–LD IR [28]. Similarly, the ASCEND-PD trial showed a reduction in off time and a gain in on time without troublesome dyskinesia with IPX066 treatment compared with CD–LD–E treatment [29,30]. Dosing frequency to obtain good motor benefit is reduced with IPX066 compared with both CD–LD IR and CD–LD–E; in the ADVANCE-PD trial, mean dosing frequency was 3.6-times daily for IPX066 compared with 5.1-times daily for CD–LD IR [28], and in the ASCEND-PD trials subjects on IPX066 required on average 3.5 doses daily compared with five doses daily with CD–LD–E [29,30]. The potential limitation of these two studies is that patients could have been unblinded to treatment because of the initial open-label phase in which treatment dosing was optimized [32]. In ADVANCE-PD, patients were first dose-adjusted for CD–LD IR over 3 weeks and then converted to IPX066 for another 6-week

period. Similarly, the ASCEND-PD trial involved a 6-week, open-label period for dose conversion to IPX066. If subjects became aware of differences in medications during this open-label phase, it is possible that they could surmise which medication they were randomized to during the blinded phase, thereby effectively becoming unblinded. Additionally, IPX066 doses in these studies were given at higher daily LD doses than the comparative treatment, which could have affected the results despite the lower bioavailability for IPX066 [32].

One difficulty is the question of dose equivalence of CD-LD IR and IPX066. IPX066 has reduced bioavailability compared with the IR formulation [31], but practical substitution of CD-LD IR by IPX066 is complicated as has been demonstrated by both the ASCENDPD and ADVANCE-PD trials. In both trials, the conversion from CD-LD IR to IPX066 occurred over 6 weeks – highlighting this issue of dose equivalence. When estimating the equivalent IPX066 dose when switching from CD-LD IR, patients may be started on a relatively higher dose of IPX066 and this could lead to increased risk of side effects, including dyskinesia in patients with advanced PD. Indeed, the IPX066 doses in the clinical trials did represent a higher daily LD dose than the comparative treatment, although no differences in side effects were noted. This issue of dose equivalence makes the design of the ideal clinical trial comparing different CD-LD formulations difficult.

The role of IPX066 in early PD is less clear at this time. The APEX-PD trial did show that IPX066 reduced motor disability at all three doses compared with placebo [26,27]. However, with the lack of clinical studies comparing IPX066 to other commonly used PD medications used early in disease, it is currently unknown if IPX066 is equivalent, better or worse than CD-LD IR or dopamine agonists in early PD. One theoretical benefit of IPX066 is that it may be less likely to cause the development of dyskinesia due to its pharmacological profile of lower plasma LD fluctuations. One main hypothesis for the development of dyskinesia in PD is that the pulsatile, nonphysiologic administration of CD-LD IR leads to dopamine receptor supersensitivity [16]. Therefore, the reduced fluctuations in LD levels seen with IPX066 would be theorized to reduce the development of dyskinesias compared with CD-LD IR. On a cautionary note, subjects treated early with CD-LD-E were recently shown to have an increased predilection for developing dyskinesia compared with subjects treated with CD-LD IR [51], although CD-LD-E induces wide fluctuations in LD plasma levels, which may account for this unexpected increase in dyskinesia development in the presence of entacapone [48,50]. Future studies need to assess whether early use of IPX066 alters the development of motor complications compared with other commonly used PD medications.

Conclusion & future perspective

If approved, the new CD-LD formulation IPX066 will provide neurologists with a new and effective tool in the management of PD. The ADVANCE-PD and ASCEND-PD trials clearly demonstrate that IPX066 is more effective at reducing off time in advanced PD compared with CD-LD IR and to CD-LD-E. Future studies are required in order to determine how IPX066 compares with other means of managing wearing off, including MAO-B inhibitors, dopamine agonists and continuous LD infusion. Interestingly, the combination of IPX066 with other modes of managing wearing off may lead to even more effective means of prolonging on time. These include combining IPX066 with COMT inhibitors, MAO-B inhibitors and/or dopamine agonists. A potential issue with such combination therapies will be any potentiation of dyskinesias, particularly with co-administration with COMT inhibitors.

The jury is still out on the use of IPX066 in early PD, and this needs to be the focus of future clinical trials. Compared with placebo, IPX066 is effective at treating motor symptoms of PD. How it compares with dopamine agonists or CD-LD IR is unknown. Because of its lower plasma fluctuation index, it is anticipated that it would be less likely to promote dyskinesia compared with other CD-LD formulations, and therefore may be an effective therapy particularly for young-onset PD patients. Its favorable plasma fluctuation index may also allow for a lower LD dose to be effective in treating motor symptoms, which may also reduce the development of dyskinesia. However, IPX066 is not free of the risk of dyskinesia; the APEX-PD trial showed that up to 5% of patients treated with IPX066 did develop dyskinesia. A trial to compare IPX066 to CD-LD IR and to dopamine agonists in early PD is required to answer these questions.

Ultimately, the use of the drug will be dictated to some extent by the cost of the medication. With the availability of many generic PD medications, a new drug such as IPX066 may be prohibitively costly for many patients. However, if IPX066 is shown to be superior to other PD medications used in early PD, particularly with regard to the development of motor complications, then its potential higher cost relative to other medications may be cost effective in the long run.

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Practice Points

- IPX066 is a newly developed carbidopa–levodopa formulation with both immediate- and sustained-release levodopa.
- IPX066 has been shown to reduce ‘off’ time in advanced Parkinson’s disease (PD) in two recent clinical trials.
- IPX066 reduces motor symptoms in early PD compared with placebo, but how it compares with other PD medications in early PD is not known at this time.
- The most common adverse events for IPX066 are similar to those for immediate-release carbidopa–levodopa.
- IPX066 is currently not approved by the US FDA, but a new drug application has been submitted.

Table 1
Key clinical trials investigating the clinical effect of IPX066[†] in patients with Parkinson's disease.

Clinical trial	Patient population	Comparator treatment	Study design	Findings	Ref.
ADVANCE-PD	Advanced PD	IPX066 vs CD-LD IR	Randomized, double-blinded, double-dummy design	Primary outcome: % 'off' time reduced by 37 (IPX066) vs 17% (CD-LD IR) Mean off time: reduced by an additional 1.2 h on IPX066 vs CD-LD IR Mean 'on' time: increased by 1.9 (IPX066) vs 0.8 h (CD-LD IR) from baseline Decreased UPDRS II + III score on IPX066 compared with CD-LR IR Improved PGI, CGI and PDQ-39 scores on IPX066 compared with CD-LR IR	[28]
ASCEND-PD	Advanced PD	IPX066 vs CD-LD-E	Randomized, double-blinded, crossover design	Primary outcome: % off time 24 (IPX066) vs 32% (CD-LD-E) Mean off time: 3.82 (IPX066) vs 5.22 h (CD-LD-E) Mean on time: increased by 1.52 (IPX066) vs 0.14 h (CD-LD-E) Decreased UPDRS II + III score on IPX066 compared with CD-LD-E	[29,30]
APEX-PD	Early PD	IPX066 vs placebo	Randomized, fixed-dose design	Primary outcome: decreased UPDRS II + III scores on all three doses (-11.7 for 145-mg dose, -12.9 for 245-mg dose, -14.9 for 390-mg dose) vs placebo (-0.6 mg) Improved CGI, PGI and PDQ-39 scales on IPX066 vs placebo	[26,27]

[†]Impax Pharmaceuticals, CA, USA.

CD: Carbidopa; CD-LD-E: Carbidopa-levodopa-entacapone; CGI: Clinical Global Impression Scale; IR: Immediate release; LD: Levodopa; PD: Parkinson's disease; PDQ-39: Parkinson Disease Questionnaire-39 Quality of Life; PGI: Patient Global Impression Scale; UPDRS: Unified Parkinson's Disease Rating Scale.