Ibudilast is a small molecular weight, orally administered compound that was originally developed and approved in Japan over 20 years ago for bronchial asthma and poststroke complication (subsequently defined as poststroke dizziness in 2002). Over the last 10 years, there has been substantial progress in better understanding ibudilast’s molecular and cellular actions including macrophage migration inhibitory factor inhibition, phosphodiesterase inhibition and attenuation of activated glia. Moreover, its potential safety and efficacy in new neurological indications has been explored via animal models and Phase I and II clinical studies. Phase II clinical trials have now initiated in methamphetamine and other drug addictions, progressive multiple sclerosis and pain. A current model of ibudilast target action and a review of its translational progress and prospects as a new medication in these disorders is described.

Keywords: addiction • anti-inflammatory • glial cell attenuation • MN-166 • MIF • MIF inhibitor • neuroprotection • neurotrophic • PDE inhibitor

Ibudilast & its target action

Ibudilast is an anti-inflammatory/neuroprotective agent that has been in use for over 20 years in Japan and some other Asian countries for the treatment of asthma and poststroke dizziness with 20–30 mg/day dosage based on attenuating airway hypersensitivity and improving cerebral blood flow, respectively [1,2]. Ibudilast, in delayed-release capsule format, is marketed as Ketas® (via innovator, Kyorin Pharmaceuticals, Tokyo, Japan) or Pinatos® (a generic by Teva/Taisho Pharmaceuticals). While ibudilast has not yet been approved for any conditions outside of Asia, clinical development for neurological conditions, including certain drug addictions, multiple sclerosis (MS) and pain has been undertaken by MediciNova (as MN-166; previously AV411 with the subsidiary Avigen Inc.) [3–5]. In its current development for the new neurological conditions, clinical target doses range between 60 and 100 mg/day based on guiding preclinical and/or initial clinical study outcomes as described in greater detail below.

In understanding the ongoing clinical development paths for ibudilast, a review of its known mechanisms of action is warranted. Ibudilast is a 230 MW small molecule that is orally administered as an extended release capsule and partitions well into the brain and peripheral tissues [6,7]. Its structure is shown in Figure 1. Mechanistic investigations suggest that there are two primary molecular targets and a specific cellular response that may account for the pharmacological actions relevant for ibudilast’s potential benefit in certain drug addictions as well as progressive MS and neuropathic pain. At safe and well-tolerated doses and respective plasma concentrations that have demonstrated reproducible efficacy in animal models, or preliminary efficacy in human trials in these conditions, known molecular
targets include MIF and PDE-4 and -10 (and, less so, PDE-3 and -11) [4,8,9]. Ibudilast may interact with NCS-1 at clinically relevant concentrations and such activity may be pertinent to neuroprotection in chemotherapy-induced neuropathy [10] but has unknown relevance in other therapeutic settings.

A sensitive cellular response to ibudilast exposure, and presumably but not definitively linked to MIF inhibition and/or cAMP/cGMP elevation, is the attenuation of activated glial cells in vitro and in vivo [3,11,12]. Researchers have identified activation of glial cells (astrocytes, microglia and oligodendrocytes) as an important component of the pathogenesis and/or maintenance of neuropathic pain or progression of MS [3,13–16]. Glial activation and glial attenuator utility has additionally been linked to reward and relapse (i.e., resumption of drug use after a period of abstinence) phenomena associated with methamphetamine, opioid, alcohol and other drugs of abuse in animals and humans [4,12,17–20].

A model of ibudilast molecular and cellular action is depicted in Figure 2. Note that at high enough doses or concentrations, it is feasible through MIF and/or cAMP regulation that ibudilast could attenuate the activation of other inflammatory or immunocompetent cells besides glia [21]. Interestingly, the documented spectrum of action of ibudilast in model systems includes both the attenuation of proinflammatory processes and the enhancement of potentially neurotrophic processes [22]. An additional outcome of its molecular and cellular actions is regulation of certain neurotransmitters such as glutamate and dopamine in certain regions of the brain – including the nucleus accumbens or ‘reward center’ that likely contributes to ibudilast’s efficacy in certain models of drug abuse [12,18,19,23]. It is this unique repertoire or balance of actions that may enable the utility of ibudilast in multiple neurological disorders described herein.

Enabling preclinical data

■ Drug withdrawal & relapse

As noted above, the dependence associated with certain drugs of abuse including methamphetamine, opioids, alcohol and cocaine may involve glial cell activation. Given some initial outcomes of opioid dependence studies in rodents (discussed further below), ibudilast was incorporated into the National Institute on Drug Abuse (NIDA) Pharmacotherapy division’s assessment of new drug candidates for methamphetamine dependence in collaboration with preclinical experts. NIDA-sponsored and subsequent independent studies were completed:

■ In a methamphetamine reinstatement model [24], rats were trained to self-administer methamphetamine by pressing a lever (active-lever) to receive intravenous (iv.) drug infusions. Following subsequent extinction of the drug-reinforced behavior, a single re-exposure to methamphetamine (1 mg/kg intraperitoneal injection [ip.]) was able to reinstate drug-seeking behavior, as indicated by a significant increase in active-lever presses. Systemic administration of 7.5 mg/kg ibudilast attenuated this prime-induced lever-pressing behavior. In a separate study, ibudilast treatment at 2.5 and 7.5 mg/kg significantly decreased stress (footshock)-induced methamphetamine reinstatement;

■ Ibudilast was evaluated in adult male Long-Evans hooded rats for potential modulation of methamphetamine self-administration efficacy [25]. Ibudilast, an analog (AV1013) with reduced PDE-inhibitory action but retained glial regulation and MIF inhibition, and the antibiotic and glial-attenuator, minocycline, all significantly (p < 0.05) reduced responding maintained by infusions of methamphetamine.

Prior to the preclinical studies with methamphetamine, ibudilast was profiled in a number of rodent opioid dependence and tolerance studies. Outcomes indicated that ibudilast could:

■ Ameliorate precipitated or spontaneous opioid withdrawal, reduce nucleus accumbens dopamine levels (an indication of reducing ‘reward’), and attenuate morphine-induced microglia activation in the brain [3,4,12];

■ Attenuate morphine-induced reward involved rat conditioned place preference (CPP) testing. Morphine administration induced a strong CPP, which was reduced by ip. ibudilast [26];

■ Enable more rapid extinction of drug-seeking behavior and reduced relapse of morphine- or stress-induced reinstatement – a model for human relapse – for weeks after ibudilast treatment [27].

Most recently, studies sponsored by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) in collaboration with alcohol dependence experts indicated that ibudilast treatment could reduce alcohol drinking and relapse in alcohol-preferring (P) rats, in high-alcohol drinking (HADI) rats, and in mice made alcohol dependent through cycles of alcohol vapor exposure [28]. It is this broad preclinical package in models of methamphetamine, opioid and alcohol dependence, along with glia-related clinical investigations in certain forms of dependence that has supported the rationale and dosing guidance for completed and ongoing clinical trials with these drugs of abuse [17–19,29].
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Pain
Based principally on its glial-regulating action, ibudilast was originally studied in various models of pain [3,6]. More recently, attenuation of glial activation and potential ibudilast utility has been recognized as a viable approach to address the progressive neurodegeneration in progressive MS [16,30]. The efficacy of ibudilast has been demonstrated in multiple well-established rat models of peripheral or central neuropathic pain including sciatic nerve chronic constriction injury, spinal nerve ligation, spinal cord avulsion and chemotherapy-induced neuropathy. End points included the attenuation of mechanical allodynia and hyperalgesia in peripheral or central chronic pain models when administered systemically via ip. or subcutaneous injection or oral gavage [3,4,6,31]. More recently, the target rationale for ibudilast utility in pain was substantiated by the beneficial outcome of MIF knockout in rodent inflammatory and chronic pain models [32,33].

Neurodegeneration & progressive MS
Ibudilast utility in MS originated from drug efficacy in experimental autoimmune encephalomyelitis (EAE) with Dark August rats that received ibudilast orally at 10 mg/kg/day starting on the day of immunization with bovine myelin basic protein and adjuvants [34]. Fewer signs of neurologic disability per standard EAE clinical scoring were observed throughout a subsequent 16-day course of ibudilast treatment relative to vehicle-treated animals. Ibudilast-treated animals showed significantly reduced histopathology (inflammatory cell infiltration) in lumbar spinal cord. Oral administration of ibudilast from day 0 to 16 reduced the disease indicators in a dose-related manner.

Figure 2. Ibudilast molecular and cellular action.
Ibudilast has also been studied in models of neurodegeneration. Notably, substantial efficacy of postnatal ibudilast treatment was demonstrated in a rodent genetic model of Krabbe’s neurodegeneration (Twitcher mouse). Dosing at 10 mg/kg ip. once daily at days 30–45 postnatal, reduced body weight loss, demyelination on histology, microglial inflammatory mediator expression, and the development of tremor, ataxia and paralysis in Twitcher mice [35]. Additional means by which ibudilast may impart neuroprotective action include enhanced release of cell growth factors (NGF, GDNF, NT-4) in glial-neuronal cocultures [22], and inhibition of MIF, which has been linked to neurodegeneration in EAE and other models [36–38].

Clinical development overview

Whereas ibudilast (as Ketas or Pinatos) is most typically dosed in Japan at total doses of 20–30 mg/day for asthma or poststroke dizziness, the dose—efficacy and pharmacokinetic (PK)—efficacy indicators to date in drug addiction, progressive MS, or chronic pain warrant optimal dosing regimens of ≥60 mg/day and preferably 80–100 mg/day. These regimens, via a twice daily (b.i.d.) schedule, correlates with peak plasma ibudilast levels under steady-state dosing conditions ranging approximately from 60 to 120 ng/ml [4,39]. Clinical trials in healthy volunteers or patients have therefore focused upon safety, tolerability, and PK characterization at these elevated doses. A summary of completed MediciNova (and Avigen) and collaborative Investigator-initiated trials is depicted in Table 1 and ongoing trials are discussed later.

These studies established the safety and tolerability of ibudilast (at least as the delayed-release Pinatos formulation) in healthy volunteer and patient populations at dose levels up to 100 mg. Indeed, the maximum tolerated dose has not yet been formally established and, hence, is at least 100 mg/day. While safety and efficacy outcomes are additionally described in sections below, some key PK outcomes from these completed studies included:

- Validation of linear and dose-proportional repeat-dose oral PK, which is also comparable between healthy volunteers or certain neurological patients;
- Lack of drug accumulation or a clear food effect;
- Identification that a primary plasma metabolite, 6,7-dihydrodiol ibudilast, is present at concentrations ranging from 20 to 55% of the parent;
- An elimination half-life at steady-state of a multi-day 50 mg b.i.d. regimen of about 21–28 h, such that b.i.d. dosing provides a plasma ibudilast concentration profile with limited trough and peak variations [4,7,39].

Phase I & II trials in drug addiction

Methamphetamine

Given the devastating social and medical consequences of methamphetamine addiction, and as there is no approved pharmacotherapy for methamphetamine dependence, development in this neurological condition has proceeded rapidly. Indeed, the FDA has recently granted MediciNova’s ibudilast fast-track status in recognition of the unmet need. From a clinical perspective, a Phase Ib investigator-initiated trial (UCLA-Meth) has completed enrollment and partial data analysis with additional efficacy end point analyses in progress. The objectives of this trial were to assess the safety and tolerability of ibudilast when combined with methamphetamine and to investigate potential effects of ibudilast on the subjective and reinforcing effects of methamphetamine. A total of 11 patients completed the trial with multiple cross-over arms and there were no serious or unexpected adverse events. Cardiovascular end points were not adversely affected with oral ibudilast administration during methamphetamine infusions and subjective measures are still under analysis. Given that chronic methamphetamine use is associated with numerous cognitive difficulties including attention deficits [40], a number of neuropsychological assessments were performed including the Conner’s continuous performance test-II (CPT-II), a measure of sustained attention. Of participants randomized and completing an ibudilast course (100 mg/d; n = 5) versus placebo course (n = 6) and 48 h after exposure to 30 mg iv. methamphetamine, the ibudilast group showed reduced variability in response times (U = 0.00; p = 0.006; r = 83) and less perseverative responses (U = 2.00; p = 0.01; r = 75) in comparison with the placebo group [41]. While this outcome in a relatively small Phase I trial may be encouraging, additional study outcomes must be analyzed and placed in context.

Importantly, a Phase IIb proof-of-concept trial led by the same investigators has been initiated. Treatment-seeking volunteers will be randomly assigned to ibudilast or placebo (n = 70 each) and the primary study outcome is evaluation of safety and efficacy. In each treatment set, half of the patients will also have a HIV co-diagnosis. This is based on the near-epidemic co-occurrence of methamphetamine abuse and HIV infection especially in men having sex with men. The outpatient treatment period is 12 weeks and patients will participate in clinic visits two- to three-times per week for health checkups, counseling, urine drug screens and monitoring of medication adherence. The trial is powered for a statistically significant effect of ibudilast over placebo on improving methamphetamine abstinence during the last 2 weeks of treatment. This is an end point preferred by regulatory authorities for addiction.
<table>
<thead>
<tr>
<th>Phase</th>
<th>Study identifier</th>
<th>Study objectives</th>
<th>Study design and type of control</th>
<th>Regimen (all oral administration)</th>
<th>Subjects (n)</th>
<th>HV or diagnosis of patients</th>
<th>Duration of treatment</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>AV411–009</td>
<td>To assess safety, tolerability and PK</td>
<td>R (3:1), DB, PC</td>
<td>On day 1 subjects received a single dose of ibudilast 30 mg, or Pbo. Day 2 was a drug holiday and on day 3 subjects were dosed with ibudilast 30 mg or Pbo b.i.d. for 14 days</td>
<td>18 (14 active, 4 Pbo)</td>
<td>HV 18–70 years old</td>
<td>2 weeks</td>
<td>[9]</td>
</tr>
<tr>
<td>I</td>
<td>AV411–016</td>
<td>To assess safety, tolerability and PK</td>
<td>R (3:1), DB, PC, single escalating dose</td>
<td>30, 50, 70, 80, and 100 mg or Pbo</td>
<td>60 (45 active, 15 Pbo)</td>
<td>HV 18–55 years old</td>
<td>Single dose except 80 mg group who were dosed in both fed and fasted state</td>
<td>[4]</td>
</tr>
<tr>
<td>Ib</td>
<td>AV411–026</td>
<td>To assess safety, tolerability and PK</td>
<td>R (3:1), DB, PC, multiple dose</td>
<td>On days 1–6, subjects received ibudilast (or matching Pbo) as follows: 20 mg b.i.d. × 2 days, then 30 mg b.i.d. × 2 days, and then 40 mg b.i.d. × 2 days. On days 7–14, subjects received 50 mg b.i.d. or matching Pbo</td>
<td>24 (18 active, 6 Pbo; 12 HV, 12 DM)</td>
<td>HV and DM patients (Type 1 and 2), 18–75 years old</td>
<td>2 weeks</td>
<td>[4]</td>
</tr>
<tr>
<td>Ib/Ia</td>
<td>AV411–010</td>
<td>To assess safety, tolerability, PK and preliminary efficacy</td>
<td>R, DB, PC, 7 day single-blind run-in phase (Pbo and active dose) followed by 14-day treatment phase</td>
<td>Treatment phase: Cohort 1: randomized 1:1 to 40 or 60 mg or Pbo. Cohort 2: randomized 2:1 (active: Pbo) to 60 or 80 mg or Pbo</td>
<td>34 (24 active, 10 Pbo)</td>
<td>Diabetic peripheral neuropathic pain patients, 18–75 years old</td>
<td>Single and multiple dosing 2 weeks</td>
<td>[4]</td>
</tr>
<tr>
<td>Ib/Ia</td>
<td>AV411-OWA</td>
<td>To assess safety, tolerability and preliminary efficacy in opioid withdrawal and enhanced opioid analgesia</td>
<td>R (11:1), DB, PC</td>
<td>20 mg b.i.d. × 14 days, 40 mg b.i.d. × 14 days, Pbo</td>
<td>44 (22 active, 22 Pbo)</td>
<td>Heroin addicts, 21–45 years old</td>
<td>Multiple dose 2 weeks</td>
<td>[42,43]</td>
</tr>
<tr>
<td>II</td>
<td>MN166-CL-001</td>
<td>To assess safety, tolerability and efficacy in RRMS</td>
<td>R, DB, PC followed by an OLE</td>
<td>10 mg t.i.d., 20 mg t.i.d., Pbo for 12 months, then ibudilast for 12 months</td>
<td>297 (194 active, 103 Pbo in year 1)</td>
<td>MS patients, 18–55 years old</td>
<td>12 month core + 12 month extension</td>
<td>[5]</td>
</tr>
<tr>
<td>IIb</td>
<td>UCLA-Meth</td>
<td>To assess safety, tolerability, PK and MA interaction</td>
<td>R, DB, PC, within-subject CO</td>
<td>20 mg b.i.d., 50 mg b.i.d. × 7 days, Pbo</td>
<td>15</td>
<td>MA addicts, 18–55 years old</td>
<td>2 weeks</td>
<td>[41]</td>
</tr>
</tbody>
</table>

b.i.d.: Twice daily; CO: Cross-over; DB: Double-blind; DM: Diabetes mellitus; HV: Healthy volunteers; MA: Methamphetamine; MS: Multiple sclerosis; OLE: Open-label extension; Pbo: Placebo; PC: Placebo-controlled; PK: Pharmacokinetics; R: Randomized; RRMS: Relapsing-remitting multiple sclerosis; t.i.d.: Three times a day.
medication assessment. Ibudilast’s effects on methamphetamine use and neurocognitive ability, as well as impact on factors related to HIV infection including T-cell counts and sexual behavior will also be analyzed.

### Opioids

Preclinical studies indicated ibudilast could reduce opioid withdrawal in rats, improve opioid acute analgesic efficacy and potentially lessen tolerance. All these options were explored in the AV411-OWA study: patients addicted to heroin were randomized into treatment groups of placebo or ibudilast at 40 or 80 mg/day. Major outcomes analyzed were safety and tolerability and preliminary efficacy. In this study, dose-related efficacy by ibudilast was observed. There was a significant reduction in symptoms of physical withdrawal by ibudilast treatment via the subjective opioid withdrawal scale. Additionally oxycodone-mediated analgesia (McGill pain questionnaire) was increased (p ≤ 0.05) by 80 mg/day ibudilast in comparison with placebo. Finally, pupil constriction from opioid treatment was more substantial (p < 0.05) in the 80 mg/day (but not 40 mg/day) ibudilast versus the placebo recipients and this outcome was considered indicative of less development of tolerance. The were no serious adverse events in the study nor discontinuations related to treatment. Importantly, ibudilast also did not adversely impact potential opioid-related respiratory changes [42,43].

### Alcohol

In the second half of 2013, a NIAAA-funded Phase IIa study led by an alcohol dependence expert at University of California, Los Angeles (CA, UA) was initiated. The trial will enroll nontreatment seeking individuals (n = 24) that are alcohol abusers or alcohol dependent and who will be assigned randomly to a 7-day treatment period with ibudilast or placebo administered orally each day, with ibudilast reaching a dose of 100 mg/day. Some of the procedures during the treatment phase include iv. alcohol challenge, laboratory tests of alcohol craving, certain mood surveys and common measures of safety. After a 5–10 day wash-out period, patients will re-enroll for another 7-day period with cross-over to the alternative treatment. Safety, tolerability and preliminary efficacy are primary outcomes of the trial and would, hence, inform the feasibility of a regulatory-path Phase IIb outpatient study of alcohol dependence.

### Phase I & II trials in progressive MS & chronic pain

#### Progressive MS

Ibudilast’s preclinical and clinical anti-inflammatory and potential immunoregulatory profile led to its initial consideration for utility in MS in Japan. Two small pilot studies with MS patients were conducted in Japan. A 60 mg dose of delayed-release ibudilast was administered orally in three divided doses daily for 12–20 months. The investigators noted reductions in relapse rates and improved EDSS scores when comparing pretreatment versus post-treatment values, but these study results were never openly published. A second pilot trial was conducted to investigate the immunoregulatory effects of ibudilast in patients with MS. In this trial, 12 patients with relapsing–remitting MS (RRMS) were administered 60 mg of ibudilast orally in three divided doses daily for 4 weeks. Serum T helper type 1 and T helper type 2 cytokine levels were measured before and after 4 weeks of treatment. After 4 weeks of treatment with ibudilast, TNF-α mRNA decreased in all but one patient and this change was statistically significant. After treatment with ibudilast, there was a trend for T helper type 1 cytokine mRNAs including IFN-γ and TNF-α to be downregulated and for mRNA of T helper type 2 cytokines such as IL-4 and IL-10 to be elevated. The reductions in IFN-γ and TNF-α were statistically significant. This study showed that ibudilast induced a shift in the cytokine profile from T helper type 1 towards type 2 and increased the natural killer T cell subset in MS patients [44].

MediciNova then chose to investigate ibudilast in a powered MS trial. In a Phase II trial (MN-166-CI-001) conducted in Central and Eastern European RRMS patients, subjects were treated with either placebo or ibudilast, 30 or 60 mg/day for up to 2 years, as described in Table 2.

Study retention and safety/tolerability were encouraging. For example, 2-year completion of the 60 mg/day ibudilast treatment group was 86% and there were 21 SAEs reported during the entire 2-year MS study – none of which were clearly attributed to ibudilast [5]. While the primary outcome of cumulative active MRI lesions over 12 months of treatment did not clearly decrease with ibudilast treatment, there were indications of a neuroprotective action by ibudilast treatment (Figure 3). The brain atrophy rate was significantly reduced in the 60 mg/day group. Moreover, post hoc analysis showed that conversion of new lesions to permanent black holes was reduced by ibudilast treatment suggesting that ibudilast protected neurons from persistent damage following acute inflammation – perhaps via attenuation of the ‘smoldering’ glial activation involved in progressive disease.

The safety and potential neuroprotective outcome results of this trial [5] were instrumental in consideration of ibudilast utility in progressive MS – particularly at doses ≥60 mg/day.

In collaboration with Robert Fox at the Cleveland Clinic, a NIH-based grant for a Phase IIb trial of ibudilast in patients has been funded by, and will be implemented with, the NeuroNEXT clinical trial network.
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within the National Institute of Neurological Disorders and Stroke at the NIH. The Phase II study involves nearly 25 enrolling clinical sites across the USA and is designed to evaluate the safety, tolerability and efficacy of ibudilast administered twice daily to patients with primary or secondary progressive MS (PPMS or SPMS, respectively). In total, 250 qualifying patients will be randomly assigned 1:1 to inactive control (placebo) or ibudilast administered at 100 mg/day (i.e., 50 mg b.i.d.). The progressive MS patients may be either untreated with long-term disease-modifying therapy or may continue either glatiramer acetate (GA) or interferon beta (IFNβ-1a or IFNβ-1b) treatment. Hence, randomization will be controlled (stratified) by three factors: clinical site, pre-existing therapy status (IFN/GA vs no disease-modifying therapy), and disease status (PPMS vs SPMS). The primary objectives of the study are, first, to evaluate the safety and tolerability of ibudilast (100 mg/day) versus placebo administered orally in patients with primary or secondary progressive MS and, second, to evaluate the efficacy of ibudilast versus placebo at 96 weeks as measured by quantitative MRI analysis for whole-brain atrophy using brain parenchymal fraction.

A similar trial to the MN-166-NeuroNext study described above is pending initiation in the UK. It is denoted MS-SMART and it will test the efficacy and mechanism of action of ibudilast and two other repurposed drugs (riluzole and amiloride). The study is a multicenter, multi-arm, double-blind, placebo-controlled Phase Ib randomized controlled trial with a total of 440 patients and a 2-year treatment and analysis period. What is particularly unique in comparison with the NeuroNext trial design is that only SPMS patients will be enrolled (vs SPMS and PPMS in the US trial) and patients will not be taking any concomitant MS drugs (vs the option of GA or IFNβ in the US trial).

Table 2. A 2-year study of ibudilast in multiple sclerosis patients.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Enrolled patients (n)</th>
<th>Core period (12 months): year 1</th>
<th>Extension period (12 months): year 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Pbo to 30 mg/day</td>
<td>Pbo to 60 mg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>49</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pbo to 30 mg/day</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td></td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Figure 3. Indicators of neuroprotection in MN 166-treated RRMS patients. (A) Time to first relapse. (B) EDSS progression. (C) Brain volume loss. (D) Progression to PBH.

*p < 0.05 versus placebo.

EDSS: Expanded Disability Status Scale; PBH: Permanent black holes.
Chronic Pain
The first Phase Ib/IIa clinical trial in any patients with dose escalations >60 mg/day was a study in primary diabetic peripheral neuropath patients denoted AV411–010. It was a randomized, placebo-controlled trial to assess its safety, tolerability, PKs and preliminary efficacy in the treatment of neuropathic pain [4]. The study consisted of a screening phase, a 7-day single-blind run-in phase followed by a 14-day double-blind treatment phase. A total of 34 patients were enrolled and the highest dose arm was 80 mg/day (40 mg b.i.d.). Analysis for efficacy included pain assessment by visual analog scale (VAS) and post hoc analyses of a potential PK–pharmacodynamic relationship for pain response, opioid usage by placebo versus active treatment, and proinflammatory cytokine changes in peripheral blood. The VAS outcome proved inconclusive – partly due to a relatively high placebo response. Analysis for correlation of individual pain response (≥1 point VAS reduction at end vs baseline) with PK parameters yielded a roughly bimodal population response with a clear trend for differential responsiveness across all three PK parameters. Furthermore, the mean or median daily amount (mg morphine equivalent) at end of treatment versus first week average decreased in the ibudilast groups but the daily amount increased in the placebo group. These results support more rigorous investigation in a formal proof-of-concept trial and infer that doses ≥80 mg/day should be considered.

Investigators in Australia and Denmark have embarked upon the evaluation of ibudilast safety and efficacy in certain forms of chronic headache pain. It has been recognized that repeated opioid exposure can facilitate pain by activating glia and such action may be linked to opioid-induced hyperalgesia [45]. It has been established that excessive intake of medications used to treat primary headaches, particularly those containing opioids, can induce a form of secondary headache, known as medication-overuse headache. Even chronic migraine has been linked to glial dysregulation [46]. Accordingly, investigator-sponsored trials involving 8-week dosing of ibudilast up to 80 mg/day have initiated. In the medication-overuse headache study at the University of Adelaide (Adelaide, Australia), patients with a primary diagnosis of headache pain following regular use, for at least 3 months, of opioid-containing analgesics wherein the headache developed or markedly worsened during medication use are enrolled. The primary end points are safety and headache index during treatment (weeks 2, 4 and 8) and post-treatment (week 24). Secondary end points include analgesic medication use, migraine frequency, and allodynia measurements. The chronic migraine trial is a collaboration between University of Adelaide and Aalborg University (Aalborg, Denmark) researchers and involves the recruitment of adults with migraine with or without aura and an onset of migraine before 50 years of age that is considered ‘chronic’ based on headache for 15 or more days per month and migraines on 8 or more days per month. Both studies are randomized and double-blind with approximately 20 patients randomized to each of placebo versus 80 mg/day (40 mg b.i.d.) treatment groups. The primary efficacy end point in the migraine trial is the number of headache days per month with moderate or severe intensity and secondary end points include migraine frequency, medication use, cutaneous allodynia and serum biomarker analyses.

Overview of clinical safety
In the completed Phase I and II clinical studies described above, over 450 subjects have been treated with ibudilast and safety and tolerability outcomes to date have been supportive of continued development [4,5,39]. Adverse events that appear to be drug-related based on the available data are headache, nausea, vomiting, dyspepsia and hyperhidrosis. In the largest and longest study in MS, there was a weak dose-dependent increase in percentage of subjects with headache and gastrointestinal adverse events. The incidence of nausea demonstrated a dose-related increase with the greatest incidence in the 60 mg/day group compared with the 30 mg/day and placebo groups although the number of subjects experiencing nausea was small. Similarly, the incidence of vomiting followed the same pattern. ibudilast also appeared to occasionally cause transient changes in laboratory chemistry values particularly AST, ALT and GGT, which, in most cases, resolved over time. These adverse events appear to be consistent with the more commonly reported adverse drug reactions reported in the Ketas package insert. Across all the trials, including studies with multiple daily dosing at 100 mg/day, ibudilast does not appear to cause significant changes in blood pressure, heart rate or ECGs when administered alone or in combination with other approved drugs or drugs of abuse, including methamphetamine or opioids. Moreover, no new adverse events appear to present with long-term exposure at the doses and durations studied to date.

Overview of efficacy
It is still premature to firmly assess the translational record of ibudilast in its newer clinical indications, including drug addiction, progressive MS and pain. There are probably three reasons, typical in drug development, for inconclusiveness regarding ibudilast:

- Identification of the most appropriate patient setting and end point (e.g., perhaps progressive MS and brain atrophy versus RRMS and gadolinium contrast);
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■ Dose optimization;
■ Powering.

In the clinical trials wherein efficacy outcomes have been assessed, the translational merit for ibudilast in drug addiction and other neurological conditions has, nonetheless, been generally positive. Some such outcomes are summarized in Table 3.

More conclusive efficacy determinations will be enabled in the next few years due to the escalation of dosing to the 60–100 mg/day range and with the readout of powered Phase Ib clinical trials. Several indications are being explored in parallel at this time via corporate-, individual investigator-, and government-supported Phase II trials (Table 4). Accordingly, the most favorable development path – from both clinical efficacy and safety perspectives – will be much more apparent in the near future.

New development paths in neurological conditions for ibudilast, founded upon at least target rationale, if not preclinical study results as well, include delirium [47] and traumatic brain injury. The potential utility in traumatic brain injury is founded upon studies from the University of Colorado (Boulder, CO, USA), wherein investigators have shown that both peri-injury and delayed administration of ibudilast prevented reactive gliosis and anxiety-like behavior in a rat lateral fluid percussion injury model for a period of up to several months [48,49]. An additional neuro-oncology path may involve chemotherapy-induced neuropathy. Recent studies by Yale University (CT, USA) researchers have demonstrated that ibudilast treatment could inhibit the development of paclitaxel-induced peripheral neuropathy in mice by disrupting the interaction between paclitaxel, NCS-1 and the InsP3R [10,50].

Financial & competing interests disclosure

Y Iwaki and K Matsuda are full-time MediciNova employees and K Johnson is a consultant. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. No writing assistance was utilized in the production of this manuscript.

Table 3. Dose versus efficacy in drug addiction and multiple sclerosis.

<table>
<thead>
<tr>
<th>Study</th>
<th>Indication</th>
<th>End point</th>
<th>Dose (mg/day)</th>
<th>Significance (p &lt; 0.05)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>UCLA-Meth</td>
<td>Methamphetamine dependence</td>
<td>Primarily safety, but secondarily cognitive and subjective effects</td>
<td>40</td>
<td>-</td>
<td>[41]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>100</td>
<td>+ (Connor’s Performance test)</td>
<td></td>
</tr>
<tr>
<td>AV411-OWA</td>
<td>Opioid analgesia, dependence</td>
<td>McGill pain survey, subjective opioid withdrawal scale</td>
<td>40</td>
<td>-</td>
<td>[42,43]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>80</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>MN-166-CL-001</td>
<td>RRMS (small subset of SPMS)</td>
<td>Reduced brain atrophy</td>
<td>30</td>
<td>-</td>
<td>[5]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>60</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>MN-166-CL-001</td>
<td>RRMS (small subset of SPMS)</td>
<td>Reduced PBH formation</td>
<td>30</td>
<td>-</td>
<td>[5]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>60</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>MN-166-CL-001</td>
<td>RRMS (small subset of SPMS)</td>
<td>Time to first relapse&lt;sup&gt;†&lt;/sup&gt;</td>
<td>30</td>
<td>-</td>
<td>[5]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>60</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

<sup>†</sup>Appearance or reappearance of one or more neurological abnormalities persisting for at least 48 h and immediately proceeded by a relatively stable neurological state of at least 30 days.


Table 4. Ongoing ibudilast trials in neurological conditions.

<table>
<thead>
<tr>
<th>Study</th>
<th>Clinical trials</th>
<th>Indication</th>
<th>Phase</th>
<th>Anticipated outcome (year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MN-166-Meth</td>
<td>NCT01860807</td>
<td>Methamphetamine dependence</td>
<td>IIIb</td>
<td>2015</td>
</tr>
<tr>
<td>MN-166-SA</td>
<td>NCT01740414</td>
<td>Opioid dependence</td>
<td>IIa</td>
<td>2014</td>
</tr>
<tr>
<td>MN-166-Alcohol</td>
<td>NCT02025998</td>
<td>Alcohol dependence</td>
<td>IIb/IIa</td>
<td>2014</td>
</tr>
<tr>
<td>MN-166-NeuroNext</td>
<td>NCT01982942</td>
<td>Progressive MS</td>
<td>IIIb</td>
<td>2016</td>
</tr>
<tr>
<td>MS-SMART</td>
<td>NCT01910259</td>
<td>Progressive MS</td>
<td>IIb</td>
<td>2016</td>
</tr>
<tr>
<td>Ibu 02-MOH</td>
<td>NCT01317992</td>
<td>Chronic headache pain</td>
<td>IIa</td>
<td>2014</td>
</tr>
<tr>
<td>Ibu 03-Migraine</td>
<td>NCT01389193</td>
<td>Chronic headache pain</td>
<td>IIa</td>
<td>2014</td>
</tr>
</tbody>
</table>

†Appearance or reappearance of one or more neurological abnormalities persisting for at least 48 h and immediately proceeded by a relatively stable neurological state of at least 30 days. PBH: Permanent black holes; RRMS: Relapsing–remitting multiple sclerosis; SPMS: Secondary progressive multiple sclerosis.
References


Ibudilast for the treatment of drug addiction & other neurological conditions


