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MN166 (ibudilast, AV411)
A Phase 2 Novel Therapeutic Approach for Treating Pain, Multiple Sclerosis, or Drug Addiction

An Asset Strengthened by a Strategic Merger around Ibudilast (MediciNova's MN-166 and Avigen's AV-411)

- **MediciNova**
  - San Diego based development company; founded in 2000; traded on Nasdaq & Osaka Securities Exchange - Hercules
  - Strong ties to Japanese innovators and financial community
  - New Approaches for the treatment of serious illness including MS (ibudilast/MN-166) & exacerbations of asthma (MN-221)
  - Deep pipeline with six clinical stage programs

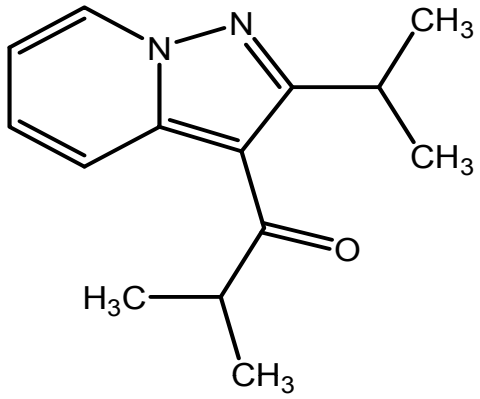
- **Avigen**
  - Clinical development of ibudilast (AV411) for neuropathic pain or opioid addiction
  - Recently issued patents, higher dose clinical experience, INDs.

- **Merger Completed December 2009**
  - Combined entity led by MediciNova (MNOV) in San Diego
  - Pipeline focus: Asthma & COPD (MN-221) and MN-166

Integrated MN-166/AV-411 Program

- Extensive preclinical pharmacology, DMPK, and Tox package.
- Proprietary GMP API, a prototype delayed-release product and acquired generic product to support Phase 2 trials.
- U.S. IND(s)
- Phase 2 Clinical proof-of-concept for safety, tolerability, and neuroregulatory (MS) efficacy. Neuropathic Pain POC-ready.
- Ongoing Ph 1b/2a opioid withdrawal trial.
- Analog program featuring an advanced lead.
- Issued patents, applications pending.

Ibudilast: New, proprietary indications for a well-established drug



Approved drug in Japan for ~20 yr

- bronchial asthma/cerebrovascular disorder
- good safety record
- apparent anti-neuroinflammatory and neuroprotective action in humans

a non-selective PDE inhibitor - *a glial cell attenuator*

New chemical entity in the United States and Europe; Composition of matter patent expired.

- issued U.S. patents for uses in Multiple Sclerosis and Chronic Neuropathic Pain; pending for Drug Addiction

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MN-166: Mechanism of Action

Specific Molecular Targets:

- Non-selective PDE Inh. – primarily 3, 4, 10, 11
  - IC50 ~1-10 μM
- Inhibition of Macrophage Migration Inhibitory Factor (MIF)
  - IC50 ~0.5 μM

Attenuates Proinflammatory Processes:

- NO and reactive oxygen species production
- Cytokine (TNFa, IL-1b) and Chemokine (MCP-1) release
- Neuroprotective? Stimulates neurotrophic and anti-infllammatory factor release (NGF,GDNF, NT-4, IL-10)
- Inhibition of TLR-4 signaling (IC50 ~3 μM)
- Reduces Leukotriene release

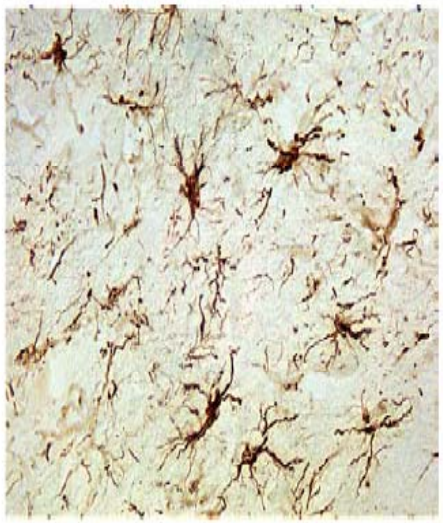
MN-166 Represents a Novel Approach

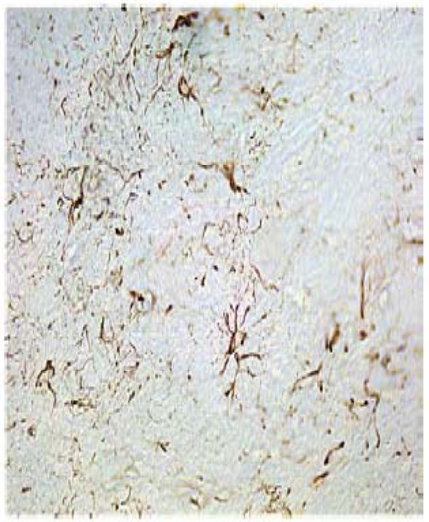
Attributes of a well-tolerated PDE inhibitory spectrum combined with demostrated Glial Attenuating Action.

Glial cells become “activated” and are thought to contribute to debilitating aspects in MS, Pain, and Drug Addiction.

Activated glial cells release pro-inflammatory mediators.

MN166 attenuates glial cells *in vivo* and may impart neuroprotective action.





control CCI + Ibudilast

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Enabled and Ongoing Clinical Development

- Neuropathic Pain
- Multiple Sclerosis
- Opioid Withdrawal & Addiction

Ibudilast Efficacy in Animal Models:

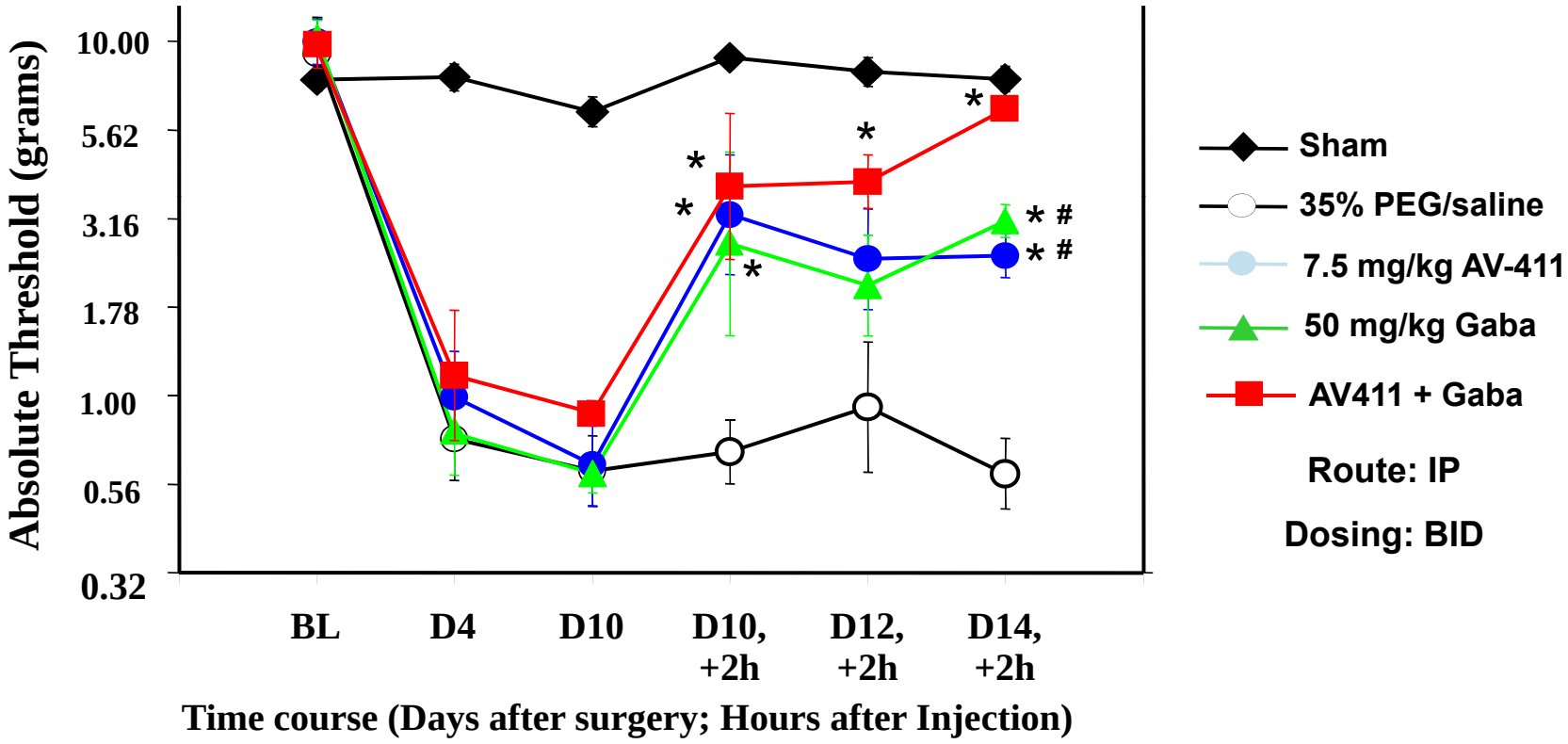
Neuropathic Pain Models:
- CCI, Chung & L5 transection
- Spinal cord injury
- Taxol-induced neuropathy

MS Models:
- EAE
- Demyelination (*twitcher* mouse)
- Cerebral aneurysms

Drug Addiction Models:
- Opioid withdrawal & conditioned place preference & neurochemical indicators of reward
- Methamphetamine relapse

Common Pharmacological Characteristics:
- Therapeutic (i.e. doesn't require prophylactic treatment)
- Duration of efficacy (PD) exceeds plasma exposure (PK)
- Animal PK/PD predicts human doses > Japanese approved regimen
- Stand-alone *or* adjunctive utility
- Competitive with reference standard drugs

CCI Animal Model: AV411, Gabapentin, Combo



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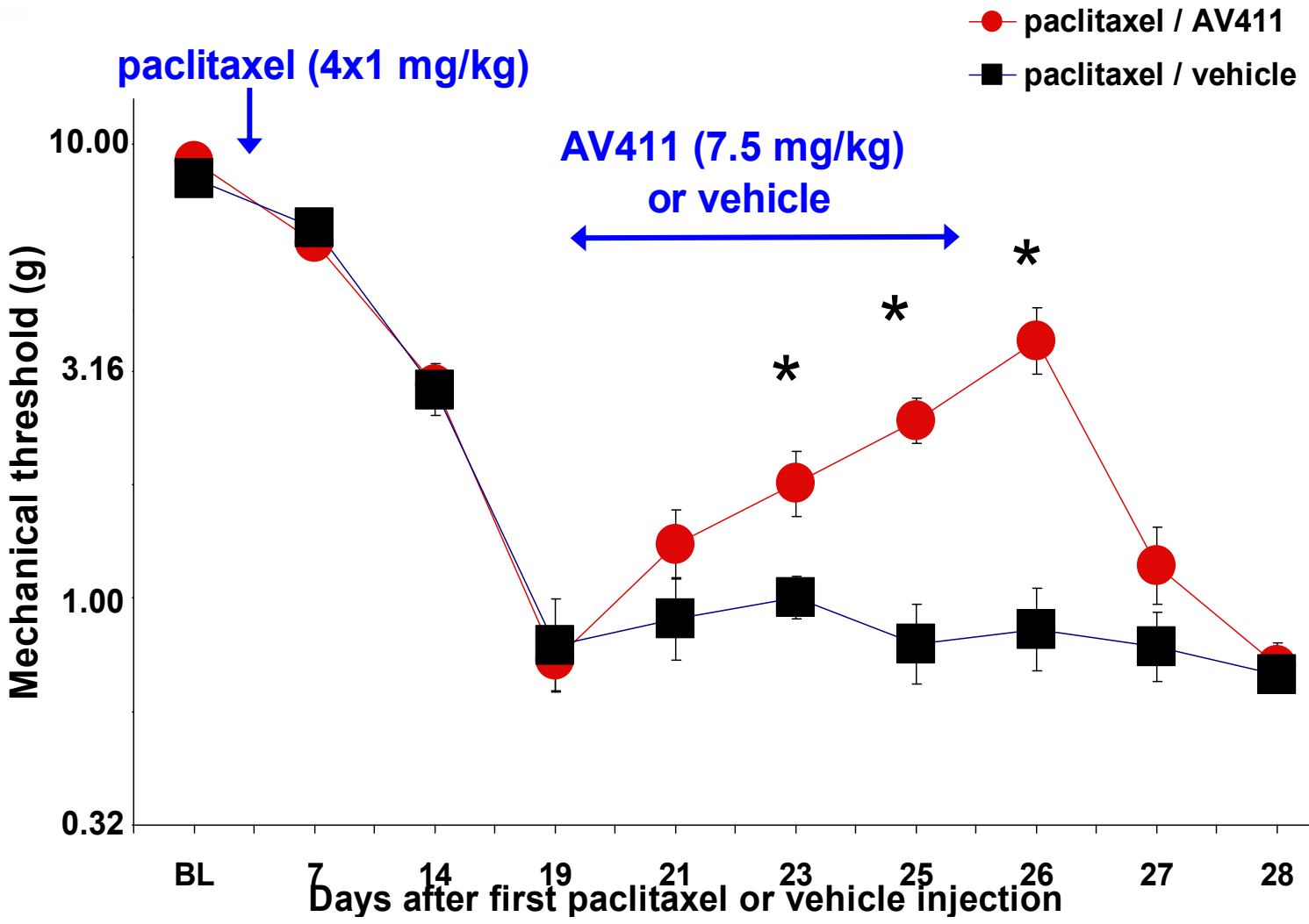
MN-166 (AV411) Reverses Taxol-induced Allodynia



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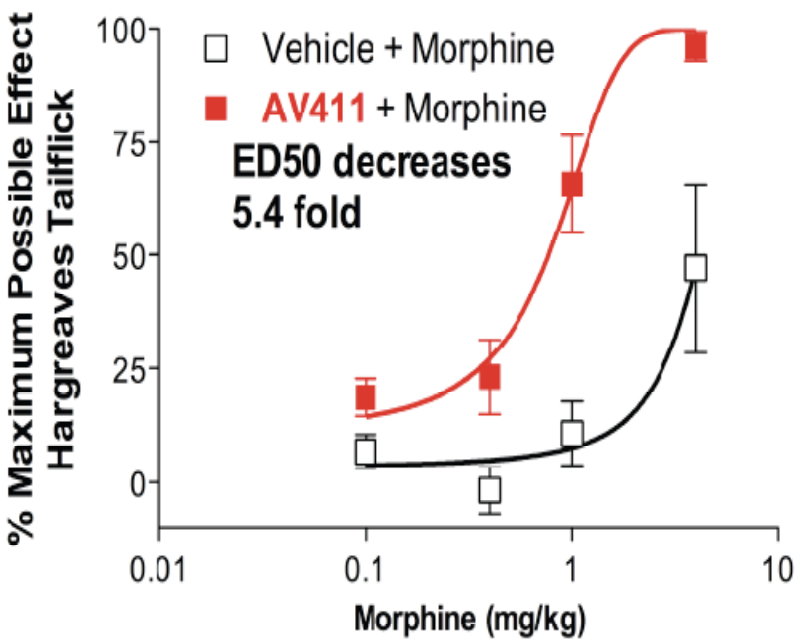
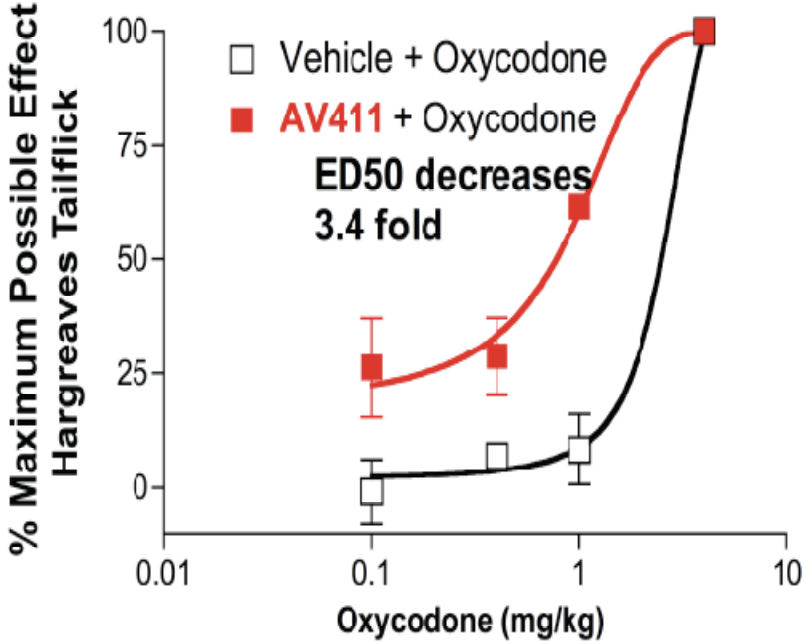
AV411 potentiation of Opioid-induced Acute Analgesia in Rats

Morphine



Oxycodone



PD-related, not linked to altered opioid PK

Hutchinson, Johnson, Watkins 2008

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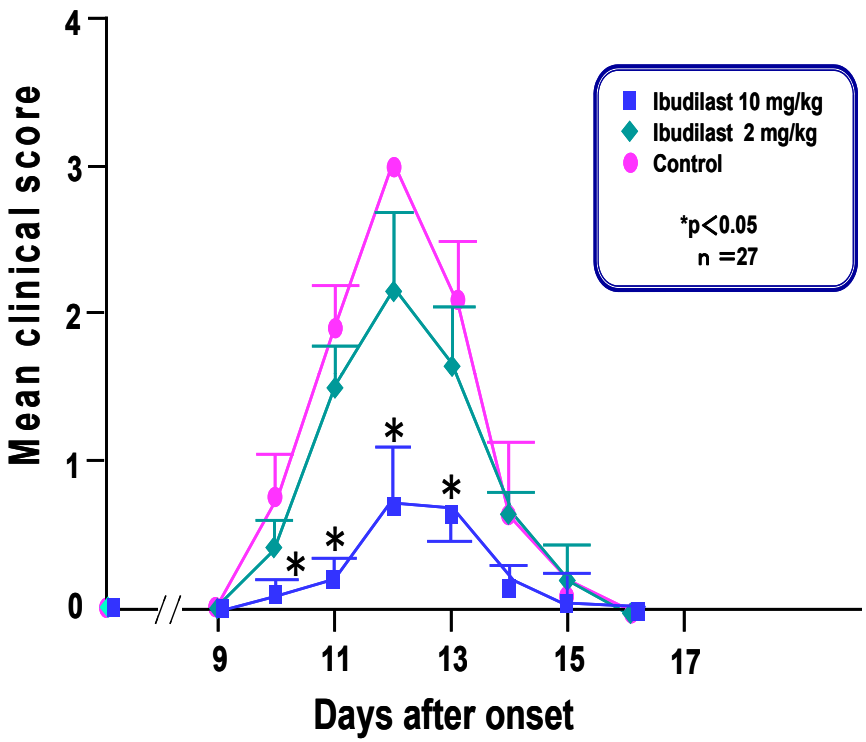
Preclinical Data: Experimental Allergic Encephalomyelitis (EAE) in Rats



Amelioration of MBP-induced EAE by MN-166

Twenty-seven rats were immunized by administering 100 µg MBP in CFA into both hind footpads and were equally divided into three groups. Beginning on the day of immunization, rats in the high dose MN-166 group (■) were given 10 mg/kg MN-166 orally in the volume of 5 ml/kg body weight; rats in the low dose MN-166 group (♦) were given 2 mg/kg MN-166 orally in 5 ml/kg body weight and control animals (○) were given the same volume of PBS orally. Vertical bars indicate SEM (*p<0.05 vs. control)

Fujimoto et al., J Neuroinflam 95:35-42, 1999

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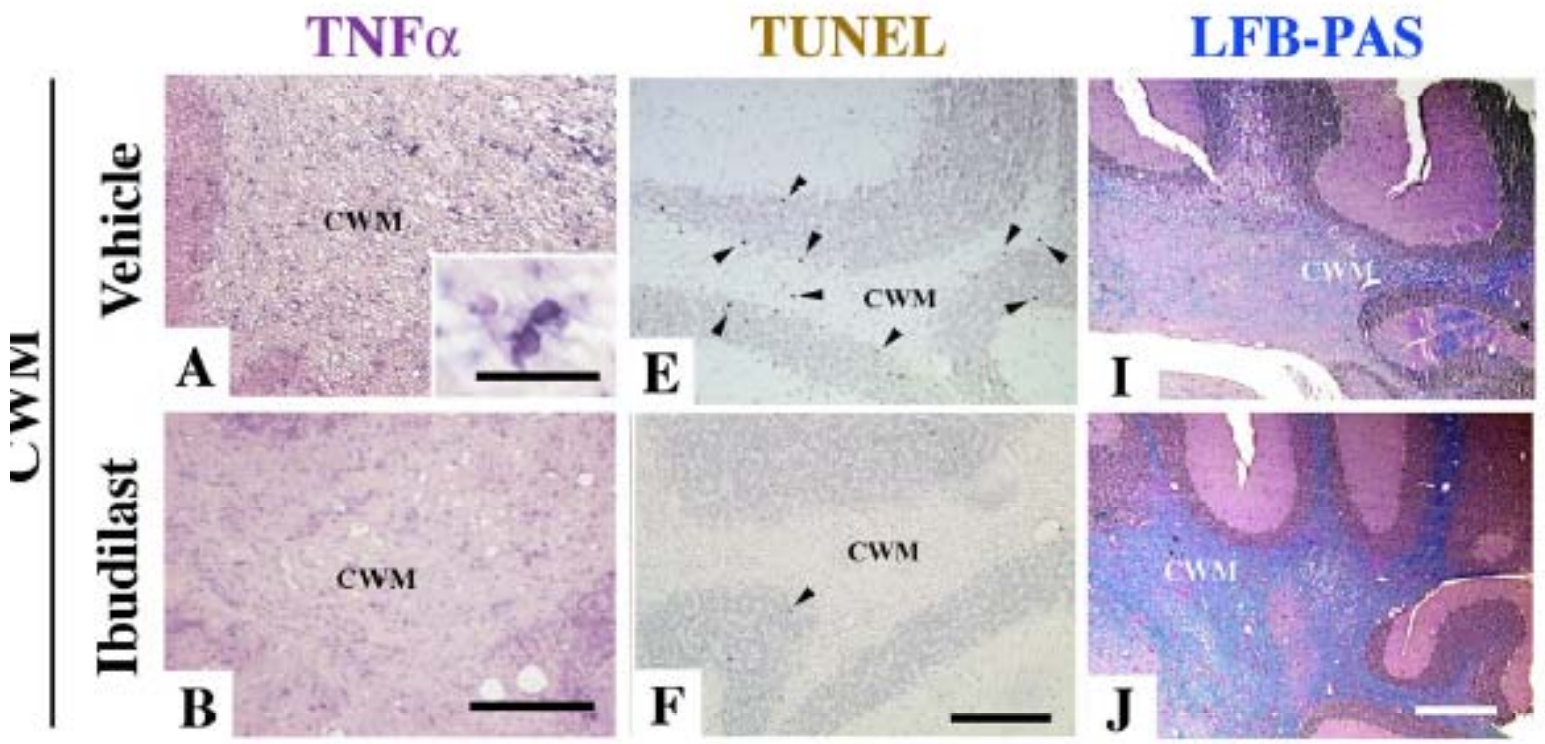
Preclinical Data: MN166 reduces apoptosis and demyelination in Twitcher mice



Ibudilast (10 mg/kg, ip) on PND45 reduces TNF-α RNA (A,B), apoptosis indicated by TUNEL-positive cells (E, F), and less demyelination shown by LFB-PAS (I, J) in Cerebellar White Matter (CWM) of Twitcher (twi, twi) mice

Kagitani-Shimono et al., J Neuroinflam 2:10-22, 2005

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Preclinical Safety Summary:

- A multi-species, GLP package involving both oral and subcutaneous routes of administration.
- Dose limiting toxicity tends to be GI-related and hypoactivity.
- Oral acute toxicity in rats, minipigs, dogs & monkeys
- Subchronic oral & s.c. tox in rats, rabbits, dogs, monkeys.
- Chronic Tox completed in rats and cyno monkeys (report finalizing).
- Clear Safety Pharm and Genotox
- Little DDI risk
- Repro Tox partly completed; published Carcinogenicity study
- Safety Margin: NOAELs generally > clinical exposures for confident efficacy.

Clinical Development

Phase 1's

- Single, ascending dose, placebo controlled, double-blind
- to 100 mg single doses (>3x Japanese daily dose)

- 2wk, placebo-controlled, double-blind
- 30-50 mg BID dosing for 2 wk
- Healthy volunteers & Diabetics (on conmeds)

➢ *No SAE's, generally well-tolerated, Plasma Cmax & AUC achieve predicted efficacious levels*

Phase 1b/2a in Painful DPN

- 2 wk, double-blind, placebo controlled
- with concomitant medications (including analgesics)
- 40-80 mg/day

Phase 2 in Multiple Sclerosis

- 1-2 year, double-blind, placebo controlled, primarily RRMS
- 30 and 60 mg/day
- *proof-of-concept neuroregulation*

Ongoing Ph 1b/2a Opioid Withdrawal Trial (Columbia/NIDA)

Clinical Trial Summary for MN166/AV411

Phase	Trial No.	Location	Dose Level	Duration	Subjects	# Active	# Placebo	SAEs
1	AV411-016	U.S.	30 mg - 100 mg	Single admin.	Healthy Volunteers	53	18	0
1	AV411-009	Australia	30 mg BID (60 mg/d total)	2 wk	Healthy Volunteers	14	4	0
1	AV411-026	U.S.	20 mg increased to 50 mg BID (100 mg/d total)	2 wk	Healthy Volunteers & Diabetics	18	6	0
1b/2a	AV411-010	Australia	20 mg BID, 20 mg TID, 40 mg BID (80 mg/d)	2 wk (subset ≥3mos)	Diab. Periph. Neuropath. Pain	20	10	0
1b/2a	AV411-OWA (ongoing)	U.S.	20 mg BID and 40 mg BID	2 wk	Heroin addicts	~12	~6	0
2	MN166-001	Eastern Europe	10 mg TID, 20 mg TID (60 mg/d)	1 - 2 yr	Multiple Sclerosis	192 (+100)	100	12 serious (unlikely MN166-related)
					Total	309 (409)	144	

AE's were mild to moderate; Primarily GI-related and generally transient and ≤2x placebo

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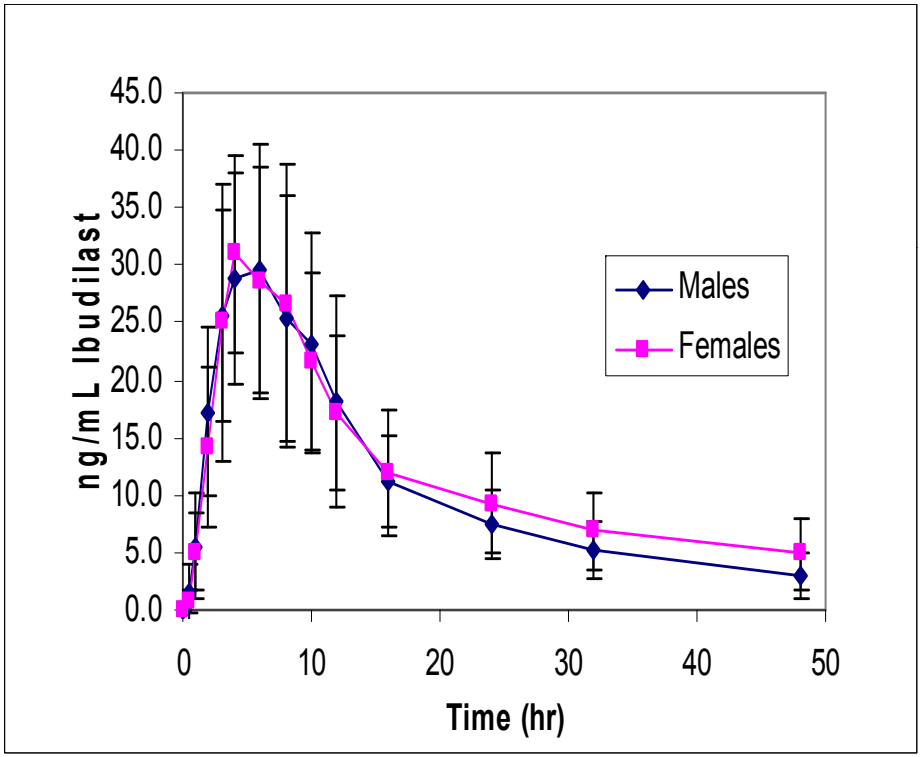
MN166 Human PK



- Median T_{max} = ~5 hr
  - similar after single dose and multiple dosing (Days 4 & 14)
- $t_{1/2}$: ~18 hr
- No gender difference
- No sig. food effect
- Dose-proporitonal PK
- 6,7-DHD is **primary metabolite**, ~40% of parent

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Completed Phase 2 MS Clinical Trial: MN166-CL-001

- Phase 2 placebo-controlled, randomized, double-blind study
  Year 1 - Placebo, 10 mg tid (30 mg/d), 20 mg tid (60 mg/d)
  Year 2 - 10 mg tid, 20 mg tid (placebo's rolled over to active)

- n = 297 MS patients randomized 1:1:1 at 25 sites in E. Europe

- Key Inclusion Criteria:
  - Males or females aged 18 to 55 years, with relapsing remitting (RR) and/or secondary progressive (SP) Multiple Sclerosis with continued relapses; *(final enrollment primarily RRMS)*
  - A definite diagnosis of relapsing MS using the new International Committee recommendations (MacDonald Criteria);
  - One MRI scan taken two weeks prior to treatment start using a standardized MRI protocol with at least one Gd-enhancing lesion;
  - An EDSS score of 5.5 or less at the screening and baseline visits

MN-166-CL-001:
Summarized Efficacy Outcomes

Dose-related changes:

Relapse: increased time to first exacerbation and increased relapse-free patients at 60 mg/d (p-value: 0.04)

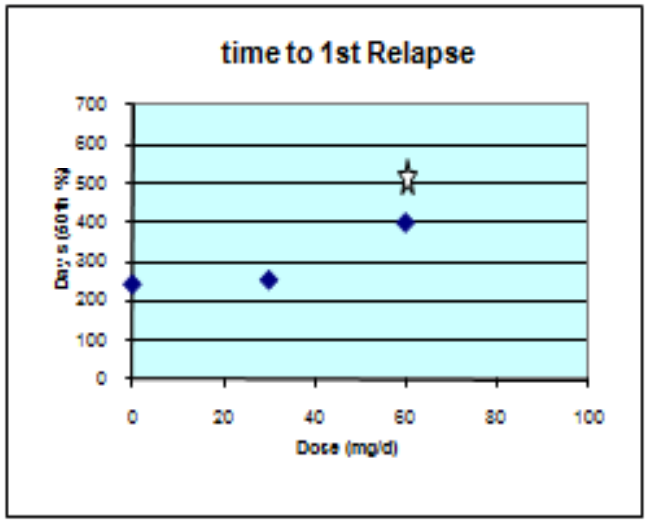
Contrast-enhanced lesions: trend for reduction

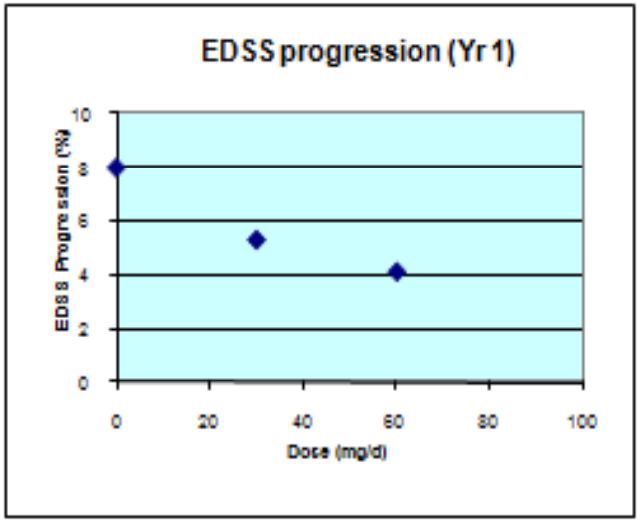
Disability progression: reduced in first year at 60 mg/d, post-hoc significant reduction for all MN-166 treated patients vs Placebo (p-value: 0.03)

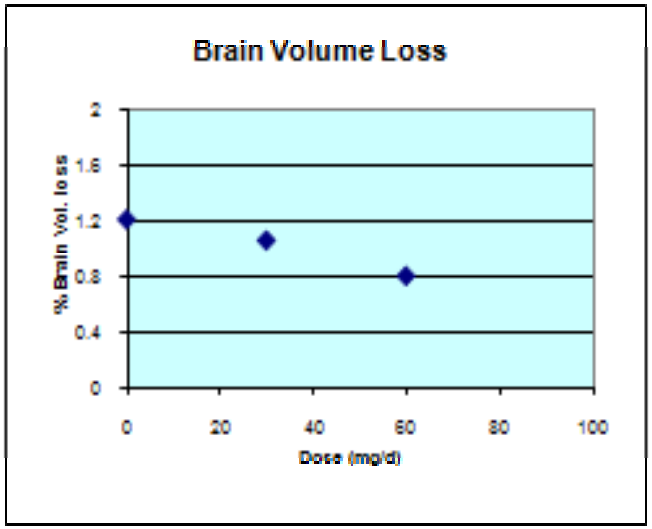
Significantly reduced brain volume loss: 60 mg/d (p-value: 0.03)

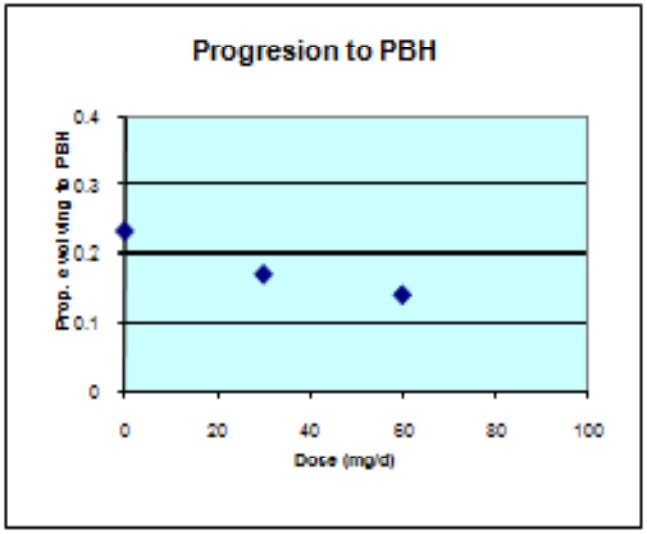
Persistent Black Hole evolution: significant reduction at 60 mg/d (p-value: 0.01)

MN-166-CL-001 Efficacy Outcome Examples









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MN-166-CL-001: Conclusions & Next Step

MN-166 was efficacious in MS by certain measures. Higher doses, now enabled, may yield broader and greater efficacy.

- Potential dual anti-inflammatory and neuroprotective action

MN-166 was safe and well tolerated;

- 89% of subjects completed the first 12 months (core) of the study
- Side effects were generally mild and self-limiting: no laboratory or ECG findings, limited GI AEs, SAEs unlikely related to treatment, no deaths

Next Step:

Powered Phase 2 MN-166 + βIFN *or* Glatiramer. For example…

- 30 and 50 mg BID MN-166
- 9-12 months with relapse endpoint as primary and/or 2nd year with EDSS progression as primary.

Hence, the MN-166 Safety/Tolerability/Efficacy profile supports a tentative product profile as a novel, viable, and differentiated stand-alone or combination therapy.

Reference Human Target Validation - Glial Activation in Chronic Pain & Glial-/PDE-Inhibitor impact on Pain

CRPS patient, post-mortem:

Lumbar (L3-L5) Dorsal Horn

derived from Del Valle et al., BBI 09

Glia	Side	Controls (mean of 4)	CRPS Pt
Microglia (CD-68)	L	1	75
	R	<1	42
Astrocytes (GFAP)	L	17	163
	R	17	160

i.v. infusion of pentoxifylline (MeXanthine glial regulator, PDE-1,3,4,5 Inh) **30 min prior to cancer surgery reduces morphine use** (amount & time between)

(Lu et al., Anesth Analg 99:1465 2004)

AV411-010: 2-wk Ph 1b/2a in DPN Patients

Design: 2-center (Australian), randomized, double-blind, placebo-controlled, parallel-group

Subjects:
Patients, aged 18 to 75 years, with painful diabetic peripheral neuropathy (DPN) or complex regional pain syndrome (CRPS) of ≥6 months duration and screening VAS score ≥4 cm on a 10 cm scale
29 subjects: 19 active, 10 placebo

Dosing:
single doses of 10, 20, 30, or 40 mg followed by 2-wks at 20 mg BID (n=4), 20 mg TID (n=4), or 30/40 mg BID (n=11)
AV411 *added* to patients' standard medication regimen for DM and *pain*

Study objectives:
Establish safety/tolerability & PK in intended patient population
Explore potential efficacy endpoints

Study 010 Outcomes

Safety:

- Well tolerated.

  No AV411-related SAEs, No withdrawals due to treatment

Efficacy:

- ~2 pt reduction in VASPI (end – start) in AV411 *and* Placebo groups
- Indicators of efficacy:
  - VASPI "Responder" correlate with ibudilast plasma C_{max} & C_{min} & AUC
  - Reduced Opioid useage in AV411 treatment groups vs Placebo
  - Biomarker: reduced plasma MCP-1 levels in AV411 grp vs Placebo

One indicator of efficacy in study 010: Greater % of "Responders" above ibudilast plasma thresholds

Plasma Ibudilast Parameter		VAS 'Responder' %
$AUC_{0\text{-}24h}$	> 1000 ng*hr/mL	60%
	< 1000 ng*hr/mL	25%
C_{max}	> 60 ng/mL	64%
	< 60 ng/mL	14%
C_{min}	> 27 ng/mL	55%
	< 27 ng/mL	29%

Recently-validated high doses assure levels above thresholds

Next Step, Neuropathic Pain Development

Proof-of-Concept, Placebo-controlled, powered Phase 2 trial designed and enabled

- DPN (vs PHN, TIN, SCI)

- Low and High dose levels

- 4-week duration (3 mos feasible)

Sufficient delayed-release clinical product available and projected stable

(GMP API available for proprietary product development)

Scientific Rationale – MN166 and Opioid Addiction

- Opioids (and Methamphetamine) activate Glia (microglia & astrocytes)
  - partly via TLR4 activation?

- Activated Glia may contribute to drug-seeking behavior, withdrawal, and relapse in animals (and preliminarily in humans).

- Pharmacological attenuation (ibudilast, others) of activated glia reduces reward and withdrawal in animals. Correlates with CNS glia immunohistochemical changes.

- PDE Inhibition may attenuate morphine withdrawal (Eur J Pharmacol Oct 09) ; Ibudilast attenuates TLR4 signalling (Watkins, Johnson 08)

- Ibudilast (AV411) is well-tolerated in combination with opioids in clinical trials

Drug and Alcohol Dependence 102 (2009) 166–169

Glial cells and drugs of abuse in the nervous system☆

Roger G. Sorensen*, Diane M.P. Lawrence

Division of Basic Neuroscience and Behavioral Research, National Institute on Drug Abuse, National Institutes of Health,

Hutchinson, M.R., Bland, S.T., Johnson, K.W., Rice, K.C., Maier, S.F., Watkins, L.R., 2007. Opioid-induced glial activation: mechanisms of activation and implications for opioid analgesia, dependence, and reward. ScientificWorldJournal 7, 98–111.

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Preclinical Efficacy of Ibudilast in Opioid Addiction

Attenuates Opioid Withdrawal in Rats

- Morphine or Oxycodone
- Spontaneous or precipitated withdrawal
- Reduced opioid withdrawal correlates with reduced brain microglial and astrocytic activation.

Reduces Opioid-increased Dopamine levels in rat Nucleus Accumbens

(neurochemical marker/mediator of reward)

Suppresses Morphine Reward in Rat Conditioned Place Preference

Ongoing Phase 1b/2a Opioid Withdrawal & Analgesia (OWA) Trial

* NIDA-sponsored

Objective: Assess MN-166 safety/tolerability/PK and preliminary efficacy for opiate withdrawal (and analgesia potentiation) in heroin-dependent subjects

Trial Design/Endpoints (N = 10 completers/cohort)			
Week	**1**	**2**	**3**
Treatment	Morphine (30 mg QID) and Placebo BID	Morphine (30 mg QID) and Placebo/20 mg/40 mg MN-166 BID	Placebo/20 mg/40 mg MN-166 BID
Endpoints	Tolerability, CPT*, PK#, PET	Tolerability, CPT, PK, PET	Withdrawal scores, Tolerability

Status:
- Well-tolerated
- Anticipate completion in 3Q10

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Ibudilast-based, lead optimization-drived NCEs

1st Gen. Dev. Candidate – AV1013

No Significant PDE Inhibition
In vitro cytokine regulation

Glial Regulation *in vivo* enabling oral efficacy in rat models
Neuropathic & Inflammatory Pain, Opiate Withdrawal

Favorable ADME
High Oral Bioavailability (Rat & Dog), QD or BID Dosing, CNS Penetration, Limited hepatic metabolism

No Safety issues at 4x efficacious dose/exposure
14-Day Rat Tox, Rotorod, Acute dog tolerability

2nd Generation

dual Glial attenuator – Kinase inhibitor Family
Lead(s) with confirmed target activities, selectivity, oral efficacy

Patent/Commercial Overview

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MN-166 Program Partnering Objectives

Medicinova is seeking partners to participate in the development and commercialization of MN-166 and analogues

- Global partnership preferred

Medicinova expectations/needs from a partner are

- Strategic strength/interest in CNS
- Established commercial capability
- Strong regulatory/clinical capabilities
- Financial commitment

Potential Medicinova role in a partnership

- Collaborate where beneficial on non-clinical, CMC, clinical development, and US regulatory activities
- Transition support
- Jointly fund defining Phase 2(b)