Neurotech Insights™

THE NEUROTECHNOLOGY INDUSTRY NEWSLETTER

MARKET HIGHLIGHTS: INVESTORS PLACE THEIR BETS AHEAD OF THE STORM

By Carla Lema Tome. PhD

Private investors made moves prior to the Brexit vote and were equally generous to neuropharmaceutical and neurodevice companies. **Annexon** closed a $44 million Series B financing led by New Enterprise Associates securing funds to advance their antibodies targeting complement activation. Currently in their pipeline, Annexon is focusing on development of disease-modifying treatments for neurodegenerative and ophthalmic disorders.

CVRx raised $46 million that will support US pivotal trials of neurostimulation therapy *Barostim Neo*. The first two patients in the trial were treated this month and CVRx has secured Expedited Access Pathway designation from the FDA. The device has already secured CE mark for the treatment of heart failure.

Earlens secured $51 million to claim its stake in the hearing aid market. Their novel device received FDA approval via the de novo pathway at the end of September 2015. The Earlens device uses a laser diode and direct vibration of the eardrum with an implanted component that is custom-molded to the patient's eardrum and directly stimulates the eardrum by direct contact, resulting in functional sound amplification.

Neurotech Winners & Losers	Symbol	1 mo. return	3 mo. return	1 yr. return
Transition	TTHI	69%	15%	-30%
Nymox Pharma	NYMX	38%	37%	152%
Anavex Life Sciences	AVXL	38%	25%	239%
StemCells	STEM	-29%	-87%	-94%
EnteroMedics	ETRM	-45%	-70%	-97%
Marinus Pharma	MRNS	-77%	-76%	-89%

In the public markets, Brexit was not the only factor bringing down stocks this month. **Biogen (BIIB)** lost $8 billion in market value after its multiple sclerosis candidate opicinumab (anti-LINGO-1), a fully human monoclonal antibody, failed to meet the primary endpoint in a Phase II study of relapsing multiple sclerosis. The stock has not yet recovered and was trading at $240 at the end of the month compared to $290 prior to the results announcement.

INSIDE THIS ISSUE

THERAPEUTIC OPTIONS OPENING UP IN THE ADHD PIPELINE

By Carla Lema Tome, PhD, and Casey Lynch

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurobehavioral disorder of childhood affecting between 5 and 10% of children. It is characterized by developmentally inappropriate and impairing inattention, motor hyperactivity, and impulsivity, as well as executive dysfunction, lack of emotional self-control and motivation, with difficulties often continuing into adulthood. Indeed, a significant number of affected children (65%) continue manifesting symptoms into adulthood, and hence adult ADHD prevalence is estimated to range between 2.5 and 5%. However, the predominant features of ADHD in adults differ from ADHD in children, with adults showing less obvious hyperactivity or impulsivity and more inattentive symptoms. Children from families with low socioeconomic status and children with public insurance are diagnosed with ADHD at higher rates than their peers. Among children, males are diagnosed more often than females, while in adults, the diagnosis ratio is closer than 1:1. This fact may be a function of male children exhibiting more hyperactivity, which leads to referral bias.

ADHD is a complex and heterogeneous disorder and its etiology is not yet completely understood. Despite evidence that environmental factors have an important role in its etiology, twin and adoptions studies of ADHD have supported a strong genetic etiology for the disorder, with a heritability ranging from 60% to 90%. Genetic studies have primarily implicated at least 2 candidate genes, the dopamine transporter gene *(DAT1)* and a particular form of the dopamine 4 receptor gene *(DRD4),* in the development of ADHD. Additional genes that might contribute to ADHD include *DOCK2* associated with a pericentric inversion 46N inv(3)(p14:q21) involved in cytokine regulation, a sodium-hydrogen exchange gene, other dopaminergic genes *(DRD5),* serotonergic genes *(5HTT, HTR1B),* and the synaptosomal-associated protein, SNAP-25. However, the behaviors associated with the dysfunction of neuroanatomical circuits at the basis of attention and cognitive functions, is probably the result of the confluence of many genetic and environmental risk factors.

ADHD, continued on page 18

Tracking Index	1 mo. Return	3 mo. return	1 yr. Return
NeuroInsights Neurotech Index*	-4%	2%	-16%
NASDAQ Biotech Index (^NBI)	-7%	0%	-29%
S&P 500 Index (^SPX)	0%	2%	2%

*see p23 for info on the NeuroInsights' Neurotech Index

Product and Clinical Trial Updates

RETROTOPE'S RT001 GAINS ORPHAN DRUG DESIGNATION FOR FRIEDREICH'S ATAXIA

June 1, 2016

The FDA granted **Retrotope** orphan drug designation to RT001 for Friedreich's ataxia (FA). RT001 is an orally available modified fatty-acid therapeutic that stabilizes mitochondrial and cellular membranes against attack and restores cellular health. Recent results indicate RT001 is well tolerated with no serious adverse events or dose limiting toxicities in the first cohort of its Phase I/II clinical trial in FA patients. The Phase I/II is still ongoing and completion is anticipated by the end of July 2016.

BIOGEN TO RECEIVE EMA SUPPORT THROUGH ADUCANUMAB PRIME PROGRAM

June 1, 2016

Biogen's (BIIB) aducanumab was accepted into the EMA's PRIority MEdicines (PRIME) program, which will grant Biogen access to enhanced support from EMA, including its advice at key development milestones and the potential for accelerated assessment of a marketing authorization application (MAA). Aducanumab is a human recombinant monoclonal antibody that targets aggregated forms of beta amyloid. Biogen licensed aducanumab from Neurimmune under a collaborative development and license agreement. The antibody is currently in Phase III trials with completion anticipated in 2022.

GENEURO BEGINS DOSING IN RRMS PHASE IIB

June 1. 2016

GeNeuro (GNRO) dosed the first patients with GNbAC1, in a Phase IIb study in relapsing-remitting multiple sclerosis (RRMS). GNbAC1 is a monoclonal antibody designed to neutralize MSRV-Env, a protein linked to the inflammatory and neurodegenerative components of the disease. The study will enroll 260 patients in 69 clinical centers in 13 European countries. The primary endpoint will examine the cumulative number of active brain lesions determined by MRI after 6 months, followed by additional MRI and clinical measures at 12 months. Topline results are expected by Q4 2017.

STEALTH ADVANCES ELAMIPRETIDE TO PHASE II

June 1, 2016

Stealth BioTherapeutics initiated a Phase II study evaluating the topical eye drop delivery of elamipretide (previously *Ocuvia*) for the treatment of Leber's hereditary optic neuropathy. Elamipretide is a cardiolipin peroxidase inhibitor and mitochondria-targeted peptide. The study will enroll 12 patients with a specific genetic mitochondrial DNA mutation (m.11778G>A), who were 18-50 years of age at the time of vision loss in the second eye, and experienced this vision loss within the last 10 years. Participants will be randomized to receive one drop of elamipretide twice daily for 12 weeks in either one or both eyes. The study's primary endpoints are safety and tolerability. Secondary endpoints include change in visual function and electrical response of retinal ganglion cells. Findings for this trial are anticipated in the second half of 2017.

FDA AND EMA GRANT ORPHAN DRUG DESIGNATION TO PROQR'S OLIGONUCLEOTIDE DRUG

June1, 2016

ProQR Therapeutics' (PRQR) QR-110 received FDA and EMA orphan drug designation for the treatment of Leber's congenital amaurosis Type 10. QR-110 is a first-in-class oligonucleotide, designed to address the underlying cause of LCA10 due to the p.Cys998X mutation. QR-110 is designed to restore wild-type, or normal CEP290 mRNA by binding the pre-mRNA and thereby restoring normal splicing of the pre-mRNA leading to the expression of wild-type CEP 290 protein. QR-110 is designed to be administered through intravitreal injections in the eye. QR-110 is expected to enter clinical trials by the end of 2016.

X2 INTRODUCES NEW BRAIN DAMAGE ASSESSMENT SYSTEM

June 1, 2016

X2 Biosystems introduced the *X2 Head Impact Management System*, includes the *X-Patch Pro* next-generation wearable impact sensor, *X2* Impact Data Management (IDM) app, and Integrated Concussion Evaluation (ICE) app. ICE is already used for baseline testing, post-impact sideline assessments, and return-to-play monitoring by the NFL, NHL and Major League Soccer. The X-Patch is currently being used to help study cumulative brain damage due to repetitive sub-concussive head impacts, and to develop more comprehensive and personalized remove-from-play thresholds in athletic and military training.

GENMAB TAKES ATUMUMAB TO PHASE III FOR RELAPSING MULTIPLE SCLEROSIS

June 2, 2016

Genmab (GEN) and **Novartis (NVS)** will start Phase III studies of ofatumumab for relapsing multiple sclerosis (RMS), with enrolment of patients expected to start in September 2016. The studies will compare subcutaneous ofatumumab with teriflunomide in 900 RMS patients. The primary endpoint of the studies is annualized relapse rate, which is the number of confirmed relapses in a 12-month period.

PROMIS IDENTIFIES NEW MONOCLONAL ANTIBODY CANDIDATES FOR ALZHEIMER'S DISEASE

June 2, 2016

ProMIS Neurosciences identified multiple therapeutic candidates that have successfully completed the screening stage of validation, and will be further developed as potential treatments for Alzheimer's disease. These monoclonal antibody therapeutics selectively bind to distinct epitope targets specific for misfolded amyloid beta.

NOVARTIS' GILENYA DEMONSTRATES GREATER PATIENT RETENTION AND SATISFACTION IN RRMS

June 3, 2016

Novartis (NVS) obtained data from a Phase IV open-label study that demonstrated patient retention rate (81%) with *Gilenya* (fingolimod) was significantly higher than the patient retention rate (29%) with injectable interferon ß or glatiramer acetate therapies at 12 months, in patients with early relapsing-remitting multiple sclerosis (RRMS). At enrollment, patients with RRMS were treatment-naïve or had received only one injectable disease-modifying therapy (IFNß-1a, IFNß-1b or glatiramer acetate). A total of 875 patients were randomized (1:1) to *Gilenya* 0.5 mg or to a pre-selected injectable disease-modifying therapy, and followed up quarterly for 12 months. After a minimum of 3 months of treatment, a single on-study treatment switch was allowed, however, switches due to efficacy or safety were allowed at any month following randomization. Compared to injectable disease-modifying therapies, *Gilenya* also improved clinical and MRI outcomes and was associated with greater patient satisfaction.

ENDO CONFIRMS BELBUCA SAFE IN LONG TERM STUDY AFTER APPROVAL

June 3, 2016

Endo Pharmaceuticals (ENDP) and **BioDelivery Sciences (BDSI)** achieved results that support the safety and tolerability of *Belbuca* (buprenorphine) buccal film for the long-term management of chronic pain, in patients requiring around-the-clock opioids. *Belbuca* is a buprenorphine formulation, a mu-opioid receptor partial agonist and a potent analgesic, developed with a dissolving film that is absorbed through the inner lining of the cheek for chronic pain management. The Phase III, open-label study enrolled 506 patients with moderate to severe chronic pain requiring continuous opioid treatment. Patients underwent a dose titration period of up to six weeks followed by a long-term treatment phase (48 weeks). Among these patients, 435 patients went on to receive long-term treatment (<48 weeks) with *Belbuca* 300 µg (n=52), 450 µg (n=45), 600 µg (n=141), 750 µg (n=62) or 900 µg (n=135); administered every 12 hours. Many patients receiving treatment with *Belbuca* twice daily reported a low incidence of typical opioid-like side effects such as nausea and vomiting during treatment titration and for up to 48 weeks of daily therapy. The study also found that *Belbuca* was effective during long-term treatment and provided sustained pain relief throughout the treatment phase (48 weeks) as measured on the numeric rating scale. In the safety analysis, AEs (> 3%) occurred in 43.1% and 54.0% of patients during dosing (n=506) and long-term treatment (n=435) phases, respectively. The most common AEs included nausea (10.3%), constipation (5.9%) and headache (3.6%) during the titration phase, and nausea (8.3%), vomiting (5.1%) and upper respiratory tract infection (4.8%) during long-term treatment.

HIGHLAND MEETS PRIMARY ENDPOINT IN SECOND PHASE III ADHD TRIAL FOR HLD-200

June 6, 2016

Highland Therapeutics achieved positive data in a second Phase III trial *Benjorna* (HLD-200, delayed release and extended-release methylphenidate capsules) for ADHD. The study included 161 pediatric patients (ages 6-12). The group randomized to receive HLD-200 achieved a statistically significant improvement (44%) in ADHD symptom scores compared to placebo group (p=0.002), based on the ADHD-RS-IV Rating Scale. The treatment group also demonstrated improved functioning scores during the morning routine as measured by two separate scales. On the Before School Functioning Questionnaire (BSFQ), the treatment group achieved a 59% improvement in functioning compared with the average baseline score, a statistically significant difference relative to the placebo group (p<0.001). The PREMB-R (Parent Rating of Evening and Morning Behavior-Revised) morning subscale revealed that the treatment group showed a 66% improvement compared with baseline, significantly different from the placebo group (p<0.001). The treatment group achieved a 44% improvement in functioning in the evening as measured by the PREMB-R evening subscale (p=0.002, relative to the placebo group). These positive results, from the early morning through to the evening time period, have now been observed in three separate Phase III trials.

CVRX INITATES PHASE III WITH BAROSTIM NEO STIMULATION THERAPY

June 6, 2016

CVRx, treated the first two patients with the *Barostim Neo* system in a pivotal trial evaluating the therapy for heart failure. The Phase III trial of *Barostim* will randomize 480 patients who suffer from heart failure with a reduced ejection fraction and who have no additional treatment alternatives available. *Barostim Neo* system is designed to electrically activate the baroreflex, the body's natural mechanism to regulate cardiovascular function. By activating this afferent pathway, *Barostim Neo* reduces sympathetic activity and increases parasympathetic activity, ultimately restoring autonomic balance. Completion of the pivotal trial is expected in 2021.

CARA THERAPEUTICS RESUMES PATIENT RECRUITMENT FOR PHASE III OF CR845

June 6, 2016

Cara Therapeutics (CARA) resumed patient recruitment after the FDA removed a clinical hold on its adaptive Phase III trial of I.V. CR845 for postoperative pain. The primary outcome measure of the trial is the change in pain intensity over time using the Numeric Rating Scale. Secondary endpoints include Post Surgical Nausea and Vomiting (PONV) scores, use of rescue medication and Patient Global Assessment of study drug. Completion of the trial is now expected in mid-2017.

FDA CLEARS CEREVE TECHNOLOGY FOR TREATING INSOMNIA

June 6, 2016

Cereve received FDA clearance for the *Cereve Sleep System,* a prescription device that reduces latency to Stage 1 and Stage 2 sleep for people with insomnia. The inspiration behind the Cereve System came from functional brain imaging studies that confirmed that the frontal cortex stays active in people with insomnia during sleep, preventing them from getting deeper, more restorative sleep. The Cereve System cools the forehead within a precise, clinically-proven therapeutic range in order to reduce this activity in the frontal cortex. Three independent clinical studies conducted on more than 230 patients over 3,800 research nights demonstrated the safety and efficacy of this device.

AXONICS RECEIVES CE MARK FOR SACRAL NEUROMODULATION SYSTEM

June 6, 2016

Axonics Modulation Technologies received CE mark for its rechargeable implantable Sacral Neuromodulation System (SNM) for the treatment of urinary and fecal dysfunction, to treat overactive bladder, fecal incontinence and urinary retention. Axonics has also received ethics committee approval from select centers in Western Europe to start a 65 patient post-market clinical follow up study.

FDA REQUESTS MORE DATA FROM SAREPTA AS IT CONTINUES TO EVALUATE ETEPLIRSEN

June 6, 2016

The FDA requested additional data from **Sarepta Therapeutics (SRPT)** related to dystrophin, as measured by western blot, from biopsies already obtained from the ongoing confirmatory study of eteplirsen. The company plans to submit data from thirteen patient biopsy samples, at baseline and Week 48, to the FDA over the coming weeks to facilitate a prompt decision on the NDA by the agency.

SAGE REPORTS POSITIVE TOP-LINE RESULTS FROM PHASE I STUDY OF SAGE-217

June 7, 2016

Sage Therapeutics (SAGE) achieved positive top-line results in a Phase I study of SAGE-217, a compound intended to enhance GABA receptor mediated inhibition in the brain. Sage is developing SAGE-217 for the treatment of several GABAA dysfunction related disorders, including essential tremor and seizures associated with rare epilepsy disorders. In the trial, SAGE-217 was found to be generally well tolerated with no serious AEs reported during the treatment and follow-up periods. Assessment using EEG showed clear evidence of target engagement starting at the lowest dose tested (15 mg). The observed EEG effect was sustained throughout the 7 day dosing period without diminution. In addition, rates of moderate to deep sedation defined by a structured rating scale (MOAA/S < 3) were comparable to placebo until the maximum tolerated dose was reached, in both the single and multiple ascending dose phases of the study. The presence of sedation was associated with maximum drug exposure. SAGE-217 is also under evaluation for potential use in postpartum depression.

BIOGEN MISSES PRIMARY ENDPOINT IN PHASE II OF OPICINUMAB IN MULTIPLE SCLEROSIS

June 7, 2016

Biogen (BIIB) missed the primary endpoint in its Phase II study evaluating opicinumab (anti-LINGO-1), a fully human monoclonal antibody being developed as a potential neuroreparative therapy. Opicinumab was examined in 418 participants with relapsing forms of multiple sclerosis (RMS), over 72 weeks. All study participants received concurrent treatment with 30 mcg interferon beta-1a intramuscular injection once weekly. In the study, opicinumab missed the primary endpoint, a multicomponent measure evaluating improvement of physical function, cognitive function, and disability (Timed 25-Foot Walk; T25FW).

Evidence of a clinical effect with a complex, unexpected dose-response was observed. Opicinumab did not meet the secondary efficacy endpoint, which evaluated the slowing of disability progression (Expanded Disability Status Scale; EDSS). Safety and PK measures were also assessed as secondary endpoints. Opicinumab was generally well-tolerated and the safety profile was consistent with what has been observed in prior studies. Opicinumab showed a linear, well-behaved PK profile over the studied dose range. The company continues to analyze the results to inform the design of the next study.

AT 81 WEEKS, PARKINSON'S PATIENTS SHOW DISEASE REVERSAL WITH NTCELL

June 7, 2016

The four patients who took part in **Living Cell Technologies**'s Phase I/IIa study of *NTCell* for Parkinson's disease show reversal of the progression of Parkinson's disease at 81 weeks as measured by the Unified Parkinson's Disease Rating Scale (UPDRS). *NTCell* is an alginate coated capsule containing clusters of neonatal porcine choroid plexus cells. After transplantation *NTCell* functions as a biological factory producing factors to promote new central nervous system growth and repair disease induced nerve degeneration. A clinically and statistically significant improvement in the patients' neurological scores from their pre-implant baseline. The company initiated a larger Phase IIb study this year. Living Cell Technologies aims to obtain provisional consent and launch *NTCell* as the first disease modifying treatment for Parkinson's disease in 2017.

RELMADA RECEIVES ORPHAN DRUG DESIGNATION FOR D-METHADONE

June 7, 2016

Relmada Therapeutics (RLMD) received FDA orphan drug designation for REL-1017 (d-Methadone), a N-methyl-d-aspartate receptor antagonist for the management of postherpetic neuralgia. The compound is in development as a treatment for both depression and chronic neuropathic pain.

COLUCID ON TRACK TO COMPLETE LASMIDITAN PHASE III IN Q3 2016

June 7, 2016

CoLucid Pharmaceuticals (CLCD) completed enrollment in the first Phase III study evaluating oral lasmiditan as an acute treatment for migraines. CoLucid is developing oral lasmiditan as a first line therapy for migraine sufferers who are contraindicated from using triptans. CoLucid expects to report topline data from this study in Q3 2016.

TREVENA INITIATES PHASE III PROGRAM WITH OLICERIDINE FOR PAIN

June 8, 2016

Trevena (TRVN) enrolled the first patients in the two Phase III studies of oliceridine in patients suffering moderate to severe acute pain following bunionectomy and abdominoplasty, respectively. The first study will evaluate pain for 48 hours following bunionectomy, and the second study will evaluate pain for 24 hours following abdominoplasty. Oliceridine is the first mu receptor G protein pathway selective modulator.

In each trial, patients will be randomized to receive placebo, morphine, or one of three regimens of oliceridine by patient-controlled analgesia device for the management of their post-operative pain. Each study will enroll approximately 375 patients, allocated equally across study arms. The primary objective in each study is to evaluate the analgesic efficacy of oliceridine compared to placebo. Secondary endpoints will include comparisons of oliceridine efficacy, safety, and tolerability to morphine. The company continues to expect to report top-line data from both studies in Q1 2017, and to file an NDA for oliceridine in the H2 2017.

NOVARTIS' AMG 334 SIGNIFICANTLY REDUCES NUMBER OF MIGRAINE DAYS PER MONTH

June 8, 2016

Novartis (NVS) demonstrated positive first results in a Phase II study investigating the fully human monoclonal antibody AMG 334 (erenumab) in chronic migraine prevention. The study evaluated AMG 334 at two doses, 70 mg and 140 mg, administered subcutaneously once a month, with both doses meeting the study's primary endpoint of a statistically significant reduction in the number of monthly migraine days versus placebo. Overall, patients had a mean baseline of 18 migraine days per month. Patients experienced a mean 6.6-day reduction from baseline in monthly migraine days in both treatment groups. The results were statistically significant compared with 4.2 days observed in the placebo group. The safety and tolerability profile of AMG 334 was similar to placebo in both treatment groups. No AEs were reported in greater than five percent of patients treated with AMG 334; the most commonly reported AEs included injection site pain, infection of the upper respiratory tract and nausea.

ACURA CONFIRMS ORAL ABUSE DETERRENCE CAPABILITIES WITH LIMITX TECHNOLOGY

June 8, 2016

Acura Pharmaceuticals' (ACUR) reported topline results from cohort 2 of their study of AP-LTX-400 confirming that the hydromorphone immediate-release tablets, using their LIMITX oral abuse deterrent technology, successfully slowed the release of the active opioid ingredient when four, six and eight intact tablets were ingested. They studied 4, 6 and 8 tablet dosage subgroups of LTX-04P against the marketed comparator product, *Dilaudid*. All subjects in cohort 2 had extent of drug absorption (measured by AUC) for LTX-04P comparable to *Dilaudid* when the same number of tablets were ingested. Likewise, the Tmax was comparable at all doses. Doses were generally well tolerated with no serious AEs reported. Acura expects to resume clinical testing of a new formulation of LTX-04 in the Q4 2016 following completion of ongoing reformulation work and a discussion with the FDA regarding the results of this study.

FDA GRANTS FAST TRACK DESIGNATION TO REMEDY'S CIRARA

June 8, 2016

Remedy Pharmaceuticals received Fast Track designation for *Cirara* for the treatment of large hemispheric infarctions. *Cirara* is a high affinity inhibitor of Sur1-Trpm4 channels, which are upregulated following ischemia and trauma. Opening of these channels can lead to edema, midline shift, increased intracranial pressure and brain herniation, *Cirara* is currently in Phase III trials.

ACORDA'S CVT-427 SUCCESSFUL IN PHASE I FOR MIGRAINES

June 9, 2016

Acorda Therapeutics (ACOR) demonstrated increased bioavailability and faster absorption compared to oral and nasal administration of CVT-427 (inhaled zolmitriptan) in a Phase I study in healthy adults. The study enrolled 21 healthy adults; 17 completed all treatments. Each subject first received successively, single doses of the zolmitriptan reference formulations, a 5 mg oral tablet and a 5 mg nasal spray. Subjects then received four individual pre-metered doses of CVT-427. There were no serious adverse events, dose limiting toxicities, or study discontinuations due to adverse events reported for CVT-427.

UPSHER-SMITH GRANTED TENTATIVE FDA APPROVAL OF QUDEXY XR FOR MIGRAINE

June 9, 2016

The FDA granted tentative approval to **Upsher-Smith Laboratories** for its supplemental new drug application (sNDA) for *Qudexy XR* (topiramate) extended-release capsules for use as prophylaxis of migraine headache in adults. *Qudexy XR* is currently approved for use as initial monotherapy in patients two years of age and older with partial-onset or primary generalized tonic-clonic seizures and adjunctive therapy in patients two years of age or older with partial-onset or primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut syndrome. *Qudexy XR* has been available in the US since June 2014.

ADAMAS SUCCESSFUL IN STUDY OF ADS-5102 FOR TREATMENT OF MS WALKING IMPAIRMENT

June 13, 2016

Adamas Pharmaceuticals (ADMS) demonstrated positive findings from its Phase II study evaluating ADS-5102 (amantadine HCl) extended-release capsules in individuals with multiple sclerosis (MS), who have impaired walking. The study evaluated ADS-5102 340 mg in an MS population for four weeks. Efficacy analyses were based on a modified intent-to-treat population (n=56). A key walking assessment was the timed 25-foot walk (T25FW) test, and an approximately 15 percent placebo-adjusted improvement ($p < 0.05$) in walking speed was observed in the T25FW group.

The type of AEs reported with ADS-5102 were consistent with the known safety profile of amantadine. The majority of study participants experienced at least one AE (17 in ADS-5102 group and 19 in placebo group); of these patients, the recorded AE intensity was mild or moderate in the majority of patients (88 percent in the ADS-5102 group; 100 percent in the placebo group). Five patients discontinued study drug due to an AE; all of these patients were in the ADS-5102 group. Of these patients, one patient experienced a serious AE, which was deemed study related. The most common AEs were: dry mouth, constipation, insomnia, abnormal dreams, agitation, ataxia, dehydration, fall, hallucination, nausea, and pollakiuria. Data from the study suggest that ADS-5102 is well tolerated in the MS patient population and has a significant positive impact on walking speed.

FDA ACCEPTS CHARLESTON AND DAIICHI SANKYO'S NDA FOR CL-108

June 13, 2016

The FDA accepted an NDA submitted by **Charleston Laboratories** and **Daiichi Sankyo** for CL-108 for the relief of moderate to severe pain while preventing or reducing the associated opioid-induced nausea and vomiting. CL-108 is a fixed-dose, immediate-release bi-layered tablet with a rapid release layer containing 12.5 mg of promethazine and a second layer containing 7.5 mg of hydrocodone and 325 mg of acetaminophen. The FDA has set a PDUFA target action date of January 31, 2017. The NDA is supported by two Phase III studies, one following oral surgery and the other after bunionectomy surgery, as well as by an additional Phase III open-label, actual use safety study in patients with moderate-to-severe acute pain, associated with osteoarthritis of the knee or hip.

MARINUS MISSES PRIMARY ENDPOINT IN PHASE III TRIAL IN ADULT FOCAL ONSET SEIZURES

June 13, 2016

Marinus Pharmaceuticals (MRNS) top line results from its Phase III trial in adults with drug-resistant focal onset seizures indicate that the study missed its primary endpoint of percent change in the 28-day seizure frequency from baseline (p=0.1537). The median percent reduction of focal onset seizures in the ganaxolone group was 21.28% compared to 10.25% with placebo, during the titration and 12-week treatment period. Consistent with previously conducted studies, ganaxolone was generally safe and well tolerated. Marinus plans to discontinue its program in adult focal onset seizures and focus its efforts on advancing ganaxolone in status epilepticus and pediatric orphan indications.

CELL CURE NEUROSCIENCES RECEIVES APPROVAL TO START SECOND COHORT IN TRIAL FOR DRY-AMD

June 13, 2016

BioTime (BTX) and subsidiary **Cell Cure Neurosciences** received authorization to move forward with enrollment and dose escalation to the second cohort for their Phase I/IIa trial of *OpRegen*. *OpRegen* is comprised of retinal pigment epithelial cells designed for the treatment of the advanced form of dry age-related macular degeneration. Recruitment for the second cohort will begin immediately, with patients receiving a higher, more clinically significant dose of 200,000 cells of *OpRegen*.

MALLINCKRODT TO INITIATE CLINICAL WORK WITH SYNACTHEN DEPOT FOR DMD

June 13, 2016

Mallinckrodt (MNK) submitted an IND application for *Synacthen Depot* to the FDA. The company will pursue an indication for the drug in treatment of Duchenne muscular dystrophy (DMD). *Synacthen Depot* is a depot formulation of *Synacthen* (tetracosactide), a synthetic 24 amino acid melanocortin receptor agonist. *Synacthen Depot* is approved and marketed outside of the US for certain autoimmune and inflammatory conditions, but has never been approved for use in patients in the US.

JAZZ GETS MIXED RESULTS IN HUMAN ABUSE LIABILITY STUDY OF WAKE-PROMOTING JZP-110

June 14, 2016

The results from a human abuse liability study conducted by **Jazz Pharmaceuticals (JAZZ)** with JZP-110, a wake-promoting agent in Phase III development for the treatment of excessive sleepiness in adult patients with narcolepsy or with obstructive sleep apnea, were mixed. The study compared JZP-110 relative to the Schedule IV stimulant phentermine, in 43 adults with a recent history of recreational polydrug use including stimulants. Subjects were randomized to one of six test sequences, in which they received a single treatment with one of the six study drugs (JZP-110 at 300 mg, 600 mg, and 1200 mg; phentermine at 45 mg and 90 mg; and placebo), with a two-day washout period between each treatment. The primary endpoint was liking at the moment across the first 12 hours after drug administration based on a subject-reported 100-point bipolar liking/disliking VAS. All doses of JZP-110 had significantly lower ratings of peak (Emax) Liking at the Moment compared to 90 mg of phentermine ($P<0.05$) but had significantly greater ratings of peak Liking at the Moment compared to placebo ($P<0.001$). Key secondary endpoints were retrospective VAS ratings at 24 hours after drug administration for overall next day drug liking. JZP-110 at 600 mg and at 1200 mg had significantly lower measures compared to both doses of phentermine ($P<0.05$).

FLEX PHARMA INITIATES PHASE II EFFICACY STUDY IN MULTIPLE SCLEROSIS

June 15, 2016

Flex Pharma (FLKS) initiated a Phase II study in MS patients in Australia. The study is designed to evaluate FLX-787, a TRP ion channel activator, in approximately 50 patients who suffer from cramps, spasms and/or spasticity as a consequence of MS.

THERAPIX REQUESTS ORPHAN DRUG DESIGNATION FOR CANNABINOID FOR TOURETTE

June 15, 2016

Therapix Biosciences (THXBY) requested orphan drug designation from the FDA for THX-RS01, developed based on the entourage technology, which combines cannabinoid substances in treating Tourette syndrome. The entourage technology is based on the combination of cannabinoid substances or cannabinoid analogs with existing drugs.

ELECTROCORE'S VAGUS NERVE STIMULATION THERAPY EFFECTIVE IN CLUSTER HEADACHE

June 15, 2016

Studies with **electroCore**'s non-invasive vagus nerve stimulation (nVNS) therapy, *gammaCore*, demonstrated its effectiveness at preventing both cluster headache and menstrual migraine. One study found that two weeks after adding *gammaCore* therapy to the standard of care, patients had a significant and sustained reductions in cluster headache attack frequency. This was also associated with significantly greater >25%, >50%, and 75%, response against standard of care. A second study found that prophylaxis with nVNS was effective in significantly reducing the number of menstrual migraine/menstrually related migraine days per month as well as pain intensity, analgesic use, and migraine disability.

VANDA SECURES EXPANDED EXCLUSIVITY FOR FANAPT UNTIL 2019

June 16, 2016

The FDA extended **Vanda Pharmaceuticals' (VNDA)** marketing exclusivity for the changes related to the sNDA approved on May 26, 2016, which modified and expanded the prescribing information for the use of *Fanapt* as a maintenance treatment of schizophrenia in adults. The FDA added this entry to the *Fanapt* Orange Book listing providing exclusivity until May 26, 2019 based upon three years from the sNDA approval date.

PERNIX THERAPEUTICS ACHIEVES POSITIVE RESULTS IN SILENOR VS. ZOLPIDEM STUDY

June 16, 2016

Pernix Therapeutics (PTX) demonstrated positive final results from a Phase IV Study assessing the effects of nighttime administration of insomnia treatments, *Silenor* 6 mg and zolpidem 10 mg, as well as placebo, on arousability, gait, balance, and cognitive performance after going to sleep. The study was performed using healthy male volunteers (n=52), and assessed the effects of a single dose of *Silenor* 6 mg compared with matching placebo and a single dose of zolpidem 10 mg compared to its matching placebo at the respective Tmax (time the maximum serum concentrations are observed). The results of the study demonstrated that *Silenor* 6 mg was statistically superior to zolpidem 10 mg on the measures of arousability, gait, balance, and memory, and that subjects taking Silenor 6 mg did not have impairment on arousability, gait, balance, and cognitive performance, and were comparable to placebo.

Further, in addition to *Silenor* 6 mg, both placebo groups were also statistically superior to zolpidem on the measures evaluated, indicating that zolpidem subjects had statistically significant difficulty in waking up, with walking and balance and with memory. Finally, there were no differences in efficacy measures between zolpidem 10 mg and Silenor 6 mg, while several measures were significantly improved with Silenor 6 mg versus placebo.

FDA APPROVES NLS PHARMA'S IND FOR STUDY OF MAZINDOL IN ADHD

June 16, 2016

The FDA accepted an IND submitted by **NLS Pharma** for a Phase II proof-of-concept clinical trial evaluating the use of NLS-1 (mazindol) in adults with attention deficit hyperactivity disorder (ADHD). NLS-1 (Mazindol) is a norepinephrine and dopamine reuptake inhibitor which was previously approved as an immediate release formulation in Europe and in the US for the short term treatment of obesity. Enrollment of patients will begin during the summer of 2016.

BLUEWIND EARNS CE MARK FOR OVERACTIVE BLADDER MINITURE NEUROSTIMULATOR DEVICE

June 16, 2016

Bluewind Medical received CE-Mark for its OAB-1000 System, a miniature wireless neurostimulator to treat overactive bladder. The Bluewind Medical OAB-1000 is a wireless, battery-less neurostimulator which is 90% smaller than typical neurostimulators in the market. The miniature device will allow physicians to treat OAB with a minimally invasive simple procedure lasting only 30 minutes, placing it near the tibial nerve, in the lower leg. The device electrically stimulates the tibial nerve, which influences urinary function, and is powered wirelessly by an external control unit, worn by the patient. Patients wear the external control unit for only 30 minutes, and can use it while performing their daily tasks without interruption. Earlier this year, BlueWind Medical successfully completed a thirty-six patient clinical study in four medical centers in the Netherlands and United Kingdom to study the safety and performance of the OAB-1000.

ST. JUDE LAUNCHES INFINITY DBS IN EUROPE

June 16, 2016

St. Jude Medical (STJ) launched the *Infinity* Deep Brain Stimulation (DBS) System and directional DBS lead in Europe. The system, which received CE Mark approval late in 2015, will support the treatment of patients with the three most common movement disorders in the world: Parkinson's disease, tremor and dystonia.

ZOSANO ENROLLS FIRST SUBJECT PIVOTAL ZP-TRIPTAN PATCH PROGRAM FOR MIGRAINE

June 17, 2016

Zosano Pharma enrolled the first subject in a pivotal efficacy trial of its *ZP-Triptan* patch treatment for acute migraine. *ZP-Triptan* is a proprietary zolmitriptan-coated microneedle patch that is applied to a subject's upper arm to deliver zolmitriptan during a migraine attack. The pivotal efficacy study is a multicenter, randomized, placebo-controlled trial comparing three doses of *ZP-Triptan* (1.0 mg, 1.9 mg, and 3.8 mg) to placebo for the treatment of a single migraine attack. Three hundred and sixty subjects are expected to be enrolled at approximately 35 centers across the US. Based on the company's discussions with the FDA and the FDA's Oct 2014 Draft Guidance--"Migraine: Developing Drugs for Acute Treatment," the co-primary endpoints of this study are (i) pain freedom at 2 hours post dosing and (ii) freedom from each subject's most bothersome symptom at 2 hours post-dosing.

MEDGENICS COMMENCES PHASE II/III IN MGLUR+ ADHD

June 17, 2016

Medgenics (MDGN) enrolled the first patient into a Phase II/III trial to evaluate adolescent patients with mGluR mutation positive (mGluR+) attention deficit disorder (ADHD). The trial is a parallel group Phase II/II study of NFC-1 versus placebo in adolescent patients with ADHD who have genetic disorders impacting the mGluR network. The trial will enroll 90 patients (12 to 17 years old). The primary and key secondary endpoints in the trial will be the change from baseline in the ADHD-rating scale Total Score and change from baseline in Clinical Global Impression - Global Improvement Scale. Patients will be randomized 1:1 to receive either a six-week course of NFC-1 or placebo, with a one-week follow-up.

FDA APPROVES SANGAMO'S IND FOR MPS II

June 20, 2016

The FDA cleared **Sangamo BioSciences' (SGMO)** IND for SB-913, a zinc finger nuclease (ZFN)-mediated approach designed as a single treatment with the potential to provide a long-lasting therapy for mucopolysaccharidosis Type II (MPS II, Hunter syndrome). SB-913 is a ZFP Therapeutic® based on Sangamo's IVPRP approach and is a single treatment strategy designed to produce continuous, durable therapeutic levels of IDS, the enzyme that is missing or defective in patients with MPS IIThe IND is now active and enables Sangamo to initiate a Phase I/II clinical trial (SB-913-1602) to assess the safety, tolerability and potential efficacy of SB-913 in adults with MPS II. Initiation of the clinical program is expected in H2 2016. The study will begin enrolling up to nine subjects, with the possibility of expanding to 12 subjects, to evaluate the safety, tolerability and efficacy of a single administration of SB-913. SB-913 is formulated as adeno-associated virus (AAV) vector preparations encoding the therapeutic hIDS enzyme and ZFNs specific for the albumin locus, and will be administered as a single intravenous infusion.

MITSUBISHI SUBMITS NDA FOR EDARAVONE FOR ALS

June 20, 2016

Mitsubishi Tanabe Pharma (TYO: 4502) submitted an NDA for edaravone (MCI-186) for the treatment of amyotrophic lateral sclerosis (ALS). The edaravone NDA is supported by a clinical research program in patients diagnosed with ALS in Japan. In 2015, edaravone was approved for use as a treatment for ALS in Japan and South Korea. In the same year, the FDA and the EC granted orphan drug designation for edaravone. It is not currently approved by the FDA for any use in the US.

OPHTHOTECH COMPLETES RECRUITMENT IN PHASE III PROGRAM FOR FOVISTA IN AMD

June 20, 2016

Ophthotech (OPHT) completed patient recruitment in its Phase III trial of *Fovista* (pegpleranib), anti-PDGF therapy, in combination with *Eylea* (aflibercept) or *Avastin* (bevacizumab) for the treatment of wet age-related macular degeneration (AMD). Ophthotech also announced that it has achieved a $30 million enrollment milestone from **Novartis (NVR)** as part of the ex-US licensing and commercialization agreement between the two companies focused on the treatment of wet AMD. The Phase III program consists of three clinical trials to evaluate the safety and efficacy of *Fovista* in combination with multiple anti-VEGF agents for the treatment of wet AMD. The company completed enrollment in its two other Phase III trials of *Fovista* in combination with *Lucentis* (ranibizumab) last year, and expects to announce initial, topline data from these two studies in Q4 2016.

WAVE RECEIVES ORPHAN DRUG DESIGNATION FOR SNP TARGETTING THERAPEUTIC FOR HD

June 20, 2016

WAVE Life Sciences (WVE) received orphan drug designation for its candidate WVE-120101, under development for Huntington's disease (HD), WVE-120101 targets rs362307, a Single Nucleotide Polymorphism (SNP) that is associated with the disease-causing mutation in the huntingtin (HTT) gene. The company plans to file an IND for this candidate in late 2016.

AXON NEURO BEGINS PHASE II WITH TAU VACCINE

June 21, 2016

AXON Neuroscience initiated a Phase II study with the first patient having been vaccinated with the active tau vaccine. AXON's vaccine, AADvac1, is intended to be the first disease-modifying tau vaccine for Alzheimer's disease. The 24-month study will assess AADvac1 applied to patients with mild Alzheimer's disease. The primary objective is to confirm the positive phase I results on a larger patient population with mild Alzheimer's disease. The secondary objective is to evaluate the AADvac1 vaccine in slowing down or halting cognitive decline in patients over a period of 24 months. The study will enroll 185 patients across Europe.

POLYGANICS SECURES CE MARK FOR NERVE CAPPING DEVICE

June 21, 2016

Polyganics received CE mark for *Neurocap,* its nerve capping device and plans to launch the product in several European countries later this year. *Neurocap* is an absorbable implant for the treatment and reduction of symptomatic neuroma in peripheral nerves. The device was cleared for sales in the United States in January 2016. Polyganics is conducting a trial to evaluate *Neurocap*'s ability to isolate the nerve end, and its effectiveness with respect to the reduction of pain from the symptomatic neuroma and prevention of pain reoccurrence.

GW PHARMACEUTICALS REVEALS EPIDIOLEX DEVELOPMENT PROGRAM IN INFANTILE SPASMS

June 21, 2016

GW Pharmaceuticals (GWPH) has selected infantile spasms (IS) as the fourth target indication for its *Epidiolex* (cannabidiol or CBD) pediatric epilepsy development program. In addition, the FDA has granted Orphan Drug Designation for *Epidiolex* for the treatment of IS. GW expects to commence a two-part pivotal Phase III study in Q4 2016. *Epidiolex* is already being developed in Dravet syndrome, Lennox-Gastaut syndrome and Tuberous Sclerosis Complex.

ANAVEX RECEIVES SECOND ORPHAN DRUG DESIGNATION FOR ANAVEX 2-73

June 22, 2016

The FDA granted Orphan Drug Designation to **Anavex Life Sciences (AVXL)** for *Anavex 2-73* for the treatment of infantile spasms. The candidate already has Orphan Drug Designation for the treatment of Rett syndrome. *Anavex 2-73*, is currently in a Phase IIa clinical trial for Alzheimer's disease. *Anavex 2-73* is an orally available drug candidate that targets sigma-1 and muscarinic receptors and successfully completed Phase I with a clean safety profile.

MARINUS PHARMACEUTICALS DOSES FIRST SUBJECT IN STUDY OF GANAXOLONE IV

June 22, 2016

Marinus Pharmaceuticals (MRNS) dosed the first subject in its Phase I trial of ganaxolone IV, an intravenous formulation of their CNS-selective GABAA modulator, for the treatment of status epilepticus. The Phase I study will include a dose escalation of a bolus dosage of ganaxolone IV and a bolus dose of ganaxolone IV, followed by a continuous infusion. Data is anticipated in H2 2016.

FRONTIER BIOTECH REPORTS PRIMARY ENDPOINT MET IN STUDY OF AB001 IN CHRONIC BACK PAIN

June 22, 2016

Frontier Biotechnologies reported that a Phase II trial for its patch product AB001 met its primary endpoint at week 2, demonstrating statistically significant (p=0.023) pain relief against placebo. One hundred forty-six subjects applied 2 patches to their lower back once daily in the morning for 14 days. AB001 achieved statistically significant analgesia against placebo at week 1 (p=0.024), greater reduction than placebo in the mean Roland-Morris Disability Questionnaire score at week 2 (p=0.006), and more subjects were satisfied with study medication than that in the placebo group at week 1 (p=0.035) and week 2 (p=0.045). On average, 75% of the patients treated with AB001 experienced 34.1% reduction in pain from baseline at week 2, 50% of patients reduced 58.3% of pain, and 25% patients reduced 78.5% of pain. No drug-related serious AEs were observed and the most common TEAEs were application site AEs, which occurred in 7 subjects (9.6%) in the AB001 group and 5 subjects (6.9%) in the placebo group.

NEUROMETRIX APPLIES FOR CE MARK FOR QUELL

June 22, 2016

NeuroMetrix submitted a CE Technical File Application for *Quell*. This regulatory filing seeks Quell CE certification in the EU as a class IIa medical device. The company plans to market the device directly to consumers in the EU.

FURTHER DATA SUPPORTS ADAMAS' CANDIDATE AS A TREATMENT FOR PD-LID

June 22, 2016

Adamas' (ADMS) further analysis of data from its Phase III study in levodopa-induced dyskinesia associated with Parkinson's disease (PD-LID) revealed a positive treatment effect for the ADS-5102-treated patients across all subgroups including: age, gender, renal function, and severity of motor complications (as measured at baseline). As previously reported, the Phase III study met its primary endpoint with a highly statistically significant reduction in dyskinesia at week 12. The study also met all five pre-specified key secondary endpoints. Improvement in LID was observed at the first post-baseline assessment at week 2 and durable throughout the study (week 24 observation). The efficacy of ADS-5102 was achieved without worsening the underlying PD. ADS-5102 was generally well tolerated, and the types of adverse events (AEs) reported were consistent with the known safety profile of amantadine.

In addition, interim results from a second Phase III of ADS-5102 in PD-LID revealed AEs reported in this study were consistent with the known safety profile of amantadine and previous Adamas-sponsored randomized studies.

VOYAGER'S PHASE IB SURGICAL RESULTS SHOW PROMISE

June 22, 2016

Voyager Therapeutics interim surgical results from an ongoing Phase Ib study of VY-AADC01 in patients with advanced Parkinson's disease demonstrate the continued safety of VY-AADC01 in all 10 patients treated from Cohorts 1 and 2 of the ongoing dose escalation trial, The Phase Ib, open-label study will include up to 20 patients with advanced Parkinson's disease and disabling motor fluctuations, treated with a single administration of VY-AADC01. VY-AADC01 is a gene therapy product to replace AADC (L-amino acid decarboxylase).

The primary objective of the study is to assess the safety and surgical coverage of the putamen at ascending dose levels of VY-AADC01. Five patients enrolled in Cohort 1 in this study received a single administration of VY-AADC01 using an infusion volume of up to 450 µL per putamen. Five patients enrolled in Cohort 2 received a single administration of VY-AADC01 using an infusion volume of up to 900 µL per putamen. The surgical procedure was successfully completed in all 10 patients and infusions of VY-AADC01 have been well-tolerated with no treatment-related serious adverse events in nine of the patients. One patient experienced two SAEs. MRI compatible measures have been added to prevent blood clots. Following a planned meeting of the data and safety monitoring board, investigators may begin dosing a third cohort this summer.

RETROPHIN TO ADVANCE RE-024 FOR PKAN

June 23, 2016

Retrophin's new data from physician-initiated treatment with RE-024, the company's investigational replacement therapy for pantothenate kinase-associated neurodegeneration (PKAN) suggest RE-024 was safe and well tolerated in two adults with PKAN who experienced clinically meaningful improvements, followed by stabilization of disease progression over 47 weeks of treatment. Data describe the experiences of two sibling males with PKAN who received physician-initiated treatment with RE-024. In both patients, treatment with RE-024 was associated with clinically meaningful improvements, including the regained ability to walk unassisted for short distances. These improvements were demonstrated on Parts II and III of the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) assessing activities of daily living and neurological impairment, respectively. After 47 weeks of treatment with RE-024, mean improvements of 13.0 points (40.6 percent) on Part II, and 17.5 points (26.7 percent) on Part III of the scale were observed. Retrophin is planning to initiate an efficacy trial of RE-024 in patients with PKAN in the H2 2016.

EDISON OBTAINS POSITIVE RESULTS IN PHASE II LEIGH SYNDROME TRIAL

June 23, 2016

Edison Pharmaceuticals achieved positive results in the long-term extension trial of the EPI-743 placebo-controlled Leigh syndrome study. EPI-743 treatment resulted in a marked decrease in the number of pediatric subjects being hospitalized and the overall number of hospitalizations over a 2.5-year period. EPI-743 (vincerinone) contains vatiquinone as an active ingredient. Vatiquinone acts by targeting an enzyme NADPH quinone oxidoreductase1 (NQO1) and synchronize energy generation in mitochondria with the need to counter cellular redox stress.The trial included a six-month placebo-controlled phase, followed by a 30-month extension phase to assess long-term drug safety and impact on disease morbidity. During the extension phase, all subjects received treatment with EPI-743. The study enrolled 35 subjects at four study sites. Treatment with EPI-743 was associated with fewer subjects requiring hospitalizations and experiencing serious adverse events as compared with subjects who received placebo (11.8% vs 42.8%).

GLOBAL KINETICS AND NATIONAL PARKINSON'S FOUNDATION STUDY NEW MONITORING SYSTEM

June 23, 2016

Global Kinetics and the National Parkinson's Foundation kicked off a study evaluating how the *Personal KinetiGraph Movement Recording System* or *PKG* monitor can help in improving the treatment of Parkinson's patients. The PKG provides objective measurement of movement in patients with diseases that affect motor skills. It records motion data automatically over a 6-day period and can also remind patients when it's time to take their medication. A physician can then download a patient's data and base future treatments on trends recorded by the PKG. The FDA cleared it in 2014.

The study will involve more than 400 Parkinson's patients. The project is part of the NPF's Parkinson's Outcomes Project Registry Study, the largest clinical study of Parkinson's disease. The duo aims to assess how technology, particularly the continuous measurement of mobility, can be leveraged to inform clinical decisions and achieve better patient outcomes.

ZYNERVA TO ADVANCE CBD GEL IN THE CLINIC

June 27, 2016

Zynerba Pharmaceuticals (ZYNE) obtained positive top line results in a Phase I multiple rising dose trial of ZYN002 cannabidiol (CBD) gel in development for the treatment of epilepsy, osteoarthritis and Fragile X Syndrome (FXS). The Phase I study evaluated the pharmacokinetic (PK) profile and tolerability of several dose levels of ZYN002 (200, 250 and 500 mg) in 24 healthy volunteers and 12 patients with epilepsy. The healthy volunteers and patients were dosed for seven days with either ZYN002 CBD gel or placebo gel. Top line results from the 24 healthy volunteers ranging from 25 to 53 years old and 12 epilepsy patients from 19 to 65 years old demonstrated that ZYN002 CBD gel was safe and well-tolerated at all dose levels. The PK findings are being used to establish the high and low doses for the Phase II studies. The twice daily dosing provided a more favorable PK profile with comparable results between healthy volunteers and epilepsy patients. The results from these Phase I trials will inform the doses to be evaluated in the Phase II clinical trial of ZYN002 CBD gel in adult patients with refractory epilepsy. The company expects to randomize patients and begin dosing in Q3 2016.

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GW'S EPIDIOLEX MEETS PRIMARY ENDPOINT IN PHASE III OF LGS

June 27, 2016

GW Pharmaceuticals' (GWPH), Phase III trial of adjunct *Epidiolex* (cannabidiol) for the treatment of Lennox-Gastaut syndrome (LGS) achieved the primary endpoint of a significant reduction in the monthly frequency of drop seizures assessed over the entire 14-week treatment period compared with placebo (p=0.0135). Patients aged 2-55 years with a confirmed diagnosis of drug-resistant LGS currently uncontrolled on one or more concomitant anti-epileptic drugs (AEDs) were eligible.

The trial randomized 171 patients into two arms, where *Epidiolex* 20mg/kg/day (n=86) or placebo (n=85) was added to current AED treatment. The primary efficacy endpoint was a comparison between *Epidiolex* and placebo in the percentage change in the monthly frequency of drop seizures during the 14 week treatment period. *Epidiolex* achieved a median reduction in monthly drop seizures of 44% compared with a reduction of 22% with placebo, and the difference was statistically significant (p=0.0135). *Epidiolex* was generally well tolerated in this trial. GW is conducting a second Phase III trial of *Epidiolex* for the treatment of LGS, which is fully enrolled at 225 patients. This second trial has three treatment arms: *Epidiolex* 20mg/kg/day, 10mg/kg/day and placebo. GW expects to report top-line results from this trial towards the end of Q3 2016. *Epidiolex* has Orphan Drug Designation from the FDA for the treatment of LGS and Dravet syndrome.

COHERUS ACHIEVES PRIMARY ENDPOINT WITH PPAR GAMMA MODULATOR IN RRMS

June 28, 2016

Coherus BioSciences' study with CHS-131 in treatment-naive, relapsing remitting multiple sclerosis (RRMS) subjects demonstrated approximately a 50% decrease in the incidence of new contrast-enhancing (CE) lesions over six months when compared to placebo. CHS-131 was generally well-tolerated and without evidence of immune suppression. CHS-131 is a selective modulator of PPAR gamma, which has anti-inflammatory activity in the CNS and crosses the blood-brain barrier.This Phase IIb trial was a randomized, double-blind, placebo-controlled clinical study that evaluated the efficacy, safety and tolerability of two orally administered doses (3 mg and 1 mg daily) of CHS-131 against placebo for six months in 227 subjects with RRMS. The primary endpoint was the reduction in the cumulative number of total CE lesions determined by MRI from baseline to week 24 of study treatment. Subjects were assessed clinically and by MRI monthly for six months. All MRIs were read in a blinded fashion. Patients on CHS-131 experienced a statistically significant reduction in CE lesions that was dose dependent, with the 3 mg dose resulting in a 46.3% reduction in CE lesions (p-value = 0.01) compared to placebo.

ACELRX SET TO COMPLETE PHASE III PROGRAM IN ACUTE PAIN

June 28, 2016

AcelRx Pharmaceuticals (ACRX) completed patient enrollment in the two remaining Phase III studies of ARX-04 (sufentanil sublingual tablet, 30 mcg). The first study is a single-arm, open-label study that enrolled 76 adult patients who presented in the emergency room with moderate-to-severe acute pain associated with trauma or injury. The primary endpoint is the time-weighted summed pain intensity difference (SPID) to baseline over the first hour, or SPID1. The second study is a multicenter, open-label study that enrolled 139 patients 40 years and older who had moderate-to-severe acute pain following a surgical procedure with general anesthesia or spinal anesthesia (except those who received intrathecal opioids). The primary efficacy endpoint of this study is SPID over the 12-hour study period, or SPID12. Data from both studies are currently being analyzed, and top-line results are expected in Q3 2016.

AURIS COMPLETES RECRUITMENT FOR PHASE III TINNITUS PROGRAM

June 28, 2016

Auris Medical (EARS) completed patient enrollment in the Phase III trial with *Keyzilen* (AM-101) in acute and post-acute inner ear tinnitus. The trial enrolled more than 300 patients during the acute tinnitus stage (Stratum A) and approximately 330 patients during the post-acute tinnitus stage (Stratum B). The primary endpoint is the change in tinnitus loudness from baseline to Day 84. The change in the Tinnitus Functional Index, which measures tinnitus burden, is a secondary efficacy outcome. Top-line results are expected in Q4 2016.

SHIRE READY TO FILE NDA FOR NEW STIMULANT SHP465

June 29, 2016

Shire (SHPG) achieved positive topline results from a four-week Phase III study of SHP465 in 275 adults aged 18-55 years with attention-deficit/hyperactivity disorder (ADHD). SHP465 (triple-bead mixed amphetamine salts) is an oral stimulant. The primary efficacy analysis of study showed that SHP465 12.5mg and 37.5 mg administered as a daily morning dose, were superior to placebo with respect to the change from baseline on a clinically administered ADHD rating scale (ADHD-RS) total score.

Shire plans to file a Class 2 Resubmission of the NDA by the end of 2016; the program is on track for potential US approval in the H2 2017. Shire expects that SHP465, following potential FDA approval, will have three years of Hatch-Waxman exclusivity and at least three patents listed in the FDA Orange Book expiring as late as May 2029.

Deals, Alliances and Financings

SECOND SIGHT SECURES $19.4 MILLION ISSUING 6 MILLION SHARES

June 1, 2016

Second Sight Medical Products (EYES) completed an oversubscribed rights offering and will retain $19.8 million of the subscriptions received, with subscriptions over that amount being returned to investors. Second Sight will issue approximately 6.0 million shares of the company's common stock at $3.315 per share. Net proceeds, are approximately $19.4 million. Proceeds will continue funding the ongoing post-market clinical study of the *Argus II Retinal Prosthesis Systems*, to assess the safety and efficacy of the Argus II for the treatment of dry age-related macular degeneration and to further expand domestic and international markets for the Argus II. In addition, funds will support going development of the *Orion I Visual Cortical Prosthesis*, a visual prosthesis for cortical stimulation to treat nearly all forms of blindness.

NEURORX WINS ISRAEL'S VENTURE COMMUNITY PRIZE

June 1, 2016

NeuroRx was awarded first prize in the annual startup competition of the Israel Advanced Technology Industry (IATI) BIOMED forum. The company is developing *Cyclurad,* an oral-fixed dose combination of two FDA-approved drugs: D-cycloserine, an NMDA receptor modulator; and lurasidone (*Latuda*), a 5-HT2a receptor antagonist. NeuroRx has completed a pre-investigational new drug meeting with the FDA for a planned pivotal study expected to commence in Q3 2016. The prize includes financial support from Israel's venture community.

ANTHROTRONIX AND CAMBRIDGE COGNITION JOIN FORCES TO COMMERCIALIZE MEDICAL APP

June 1, 2016

AnthroTronix and **Cambridge Cognition Holdings (COG)**, executed a distribution agreement to sell *DANA*, AnthroTronix's FDA-cleared mobile brain health assessment app, to markets in the US and Europe. In the US, Cambridge Cognition will distribute *DANA* for use in academic research, clinical trials, and pharmaceutical development. In the UK and portions of Europe, *DANA* will be marketed for use in militaries, academic research, clinical trials, pharmaceutical development, and occupational health screenings. *DANA* is a mobile medical app that administers game-like tests to assess a person's brain/cognitive health. The app can help track cognitive function over time and during treatment for conditions as depression, dementia/Alzheimer's disease, and post-traumatic stress disorder.

CLEARSIDE RAISES $58 MILLION IN IPO

June 2, 2016

Clearside Biomedical priced an initial public offering of 7,200,000 shares of its common stock at a public offering price of $7.00 per share. In addition, Clearside granted the underwriters a 30-day option to purchase up to an additional 1,080,000 shares of common stock at the public offering price. The shares began trading on the NASDAQ Global Market on June 2, 2016 under the ticker symbol "CLSD." At this price the entire offering is valued up to $57.96 million. The company is developing first-in-class drug therapies to treat blinding diseases of the eye.

AMARANTUS SELLS DIAGNOSTICS SUBSIDARY

June 3, 2016

Amarantus BioScience Holdings (AMBS), closed the sale of its wholly-owned subsidiary Amarantus Diagnostics to **Avant Diagnostics (AVDX)**. Amarantus received 80 million shares of Avant common stock valuated at $25.6 million. Amarantus' equity stake in Avant represents approximately 38% of the fully-diluted shares. The company plans to continue development of their engineered skin substitute for severe burns and continues to evaluate value-building strategic options for all of its therapeutic assets, including ESS, *Eltoprazine* and MANF.

NEVRO SECURES FUNDS TO CONTINUE SENZA COMMERCIALIZATION AND FOR R&D

June 6 and 13, 2016

Nevro (NVRO) raised $172.5 million aggregate principal amount of 1.75% convertible senior notes due 2021, which included the exercise in full of the underwriters' over-allotment option. Nevro intends to use approximately $21.0 million of the net proceeds to repay in full an existing term loan agreement and to continuing commercialization of its *Senza* spinal cord stimulation system and funding research and development.

SKYEPHARMA LICENSES ABUSE DETERRENT TECHNOLOGY FROM LUCIDEON

June 7, 2016

Skyepharma (SKP) signed an exclusive feasibility, development and license agreement with **Lucideon**, giving Skyepharma access to Lucideon's *iCRT-deter* abuse deterrent controlled release technology. Skyepharma intends to develop an abuse deterrent formulation of a major opioid for the US market. The companies will collaborate to assess the feasibility of using the technology in this novel way. Skyepharma will fund this development work. Lucideon will provide specialist and Skyepharma's oral business will formulate the product and complete an abuse deterrence challenge study. The investment by Skyepharma is expected to be about $4.5 million over four years.

CRISPR AND ANAGENESIS TO COLLABORATE ON CELL THERAPY FOR DMD

June 8, 2016

CRISPR Therapeutics and **Anagenesis Biotechnologies** executed a strategic in-licensing and collaboration agreement, which grants CRISPR Therapeutics exclusive worldwide license to Anagenesis' proprietary Paraxial Mesoderm Multipotent Cells (P2MCs) technology for cell therapy for all human muscle diseases. The P2MC technology allows for the efficient, reproducible and chemically defined differentiation of pluripotent cells into skeletal muscle stem cells, also known as satellite cells. The agreement will support the advancement of CRISPR-based cellular therapies for the treatment of musculoskeletal diseases. Initial research will focus on Duchenne muscular dystrophy.

LILLY TO SUPPORT HEADACHE REGISTRY WITH $1 MILLION GRANT

June 9, 2016

Eli Lilly (LLY) will provide a $1 million grant to the **American Migraine Foundation** to sponsor the development of the American Registry for Migraine Research (ARMR), a large-scale, publicly-accessible headache registry and biological repository that will contain clinical, biologic and neuroimaging data to further advance the research and discovery of new treatments for migraine.

THE MESO-BRAIN CONSORTIUM TO BUILD 3D NEURAL NETWORKS

June 9, 2016

The MESO-BRAIN consortium received $3.7 million in funding from the European Commission as part of its Future and Emerging Technology scheme. The project aims to develop 3D human neural networks with specific biological architecture, and the inherent ability to interrogate the network's brain-like activity both electrophysiologically and optically. The project will use human induced pluripotent stem cells (iPSCs) that have been differentiated into neurons upon a defined and reproducible 3D scaffold to support the development of human neural networks that emulate brain activity.The investigation will launch in September 2016 and research will be conducted over three years.

SAREPTA TO RAISE $37.5 MILLION IN PUBLIC OFFERING

June 9, 2016

Sarepta Therapeutics (SRPT) will sell an amount of its common stock equal to approximately $37.5 million in gross proceeds for use in product and commercial development, manufacturing, any business development activities and other general corporate purposes.

CELL CURE NEUROSCIENCES SECURES NEW FUNDING FOR OPREGEN CELL THERAPY

June 10, 2016

BioTime's **(BTX)** subsidiary **Cell Cure Neurosciences** was awarded a new grant for 2016 of $2.2 million from the Israel Innovation Authority. The grant provides continuing funding for the development of *OpRegen*, a cell-based therapeutic product that consists of animal product-free retinal pigment epithelial (RPE) cells. *OpRegen* is currently in a Phase I/IIa dose-escalation clinical study evaluating the safety and efficacy of *OpRegen* for geographic atrophy.

MERCK LICENSES COGNITIVE REMEDIATION TRAINING PROGRAM FROM HAPPYNEURON

June 13, 2013

Merck (MRK) entered into an agreement with **HAPPYneuron**, a subsidiary of SBT Group of France, in which Merck will receive an exclusive license to the company's cognitive remediation training program for people living with multiple sclerosis (MS). HAPPYneuron's cognitive remediation program will be available for inclusion in Merck's MSdialog platform. HAPPYneuron is designed to improve cognitive skills through brain training by repeated cognitive game training exercises. HAPPYneuron's suite of cognitive training games are designed to address the cognition challenges that people living with MS face, and the games automatically adjust skill to match the need of the individual. MSdialog is a multi-tenant cloud-based software system for the management of MS that captures and presents patient outcome data to enable better decision-making by patients and providers. The software system provides patients with reminders to take their *Rebif* (interferon beta-1a) medication, synchronizes with the new *RebiSmart* auto-injector, monitors patient's adherence information to their treatment and monitors clinical data.

TITAN RECEIVES $15 MILLION MILESTONE FROM BRAEBURN

June 13, 2016

Titan Pharmaceuticals (TTNP) received a $15 million milestone payment from development and commercialization partner **Braeburn Pharmaceuticals** following FDA approval of *Probuphine*. Braeburn will pay Titan tiered royalties on net sales in the US and Canada at rates ranging from the mid-teens to low-twenties, and additionally, Titan is eligible for up to $165 million in milestone payments based on achievement of certain annual sales targets.

MJFF OFFERS $2 MILLION FOR A-SYN PET TRACER

June 14, 2016

The Michael J. Fox Foundation (MJFF) announced a $2 million prize for development of a PET tracer to visualize the protein alpha-synuclein. Academic and industry researchers, MJFF funded or not, are eligible to apply for the prize. Contestants must provide pre-clinical and clinical data showing selectivity and viability of their alpha-synuclein radiotracer. Importantly, contestants must also agree to make their radiotracer available for use by the Foundation and MJFF awardees through a nonexclusive license or other MJFF-approved mechanism.

NINDS GRANTS SOTERIX $2.5 MILLION FOR PHASE II OF TDCS TO TREAT APHASIA AFTER STROKE

June 15, 2016

Soterix Medical received award of a $2.5 million grant from the National Institute of Neurological Disorders and Stroke to support a Phase II trial aimed at establishing the effectiveness of individualized High-Definition transcranial Direct Current Stimulation (HD-tDCS TM) for adjunctive treatment of anomia in chronic post-stroke aphasia. The multi-center, randomized, sham-controlled, double-blind trial includes collaborators from Georgetown University, University of North Carolina, Medstar Research Institute, The City College of New York, and University of South Carolina.

OTSUKA AND IBM LAUNCH JOINT VENTURE OTSUKA DIGITAL HEALTH

June 15, 2016

Otsuka Pharmaceutical (TYO: 4578) and **IBM Japan** executed an agreement to establish Otsuka Digital Health, a joint venture independent of Otsuka's pharmaceutical business, in order to start a digital health solutions business for psychiatry in Japan. **Otsuka Digital Health** will market *MENTAT*, which was developed based on Otsuka's knowledge and expertise in the central nervous system and on IBM's Watson-based technology. The company will integrate and analyze a large volume of data held by medical institutions. Solutions will be provided for medical issues such as improving the quality of treatment and sharing useful information among hospital medical staff.

EARLENS SECURE S $51 MILLION TO LAUNCH NEW HEARING AID

June 16, 2016

Earlens raised $51 million in debt and equity to back the launch of its light-driven hearing aid. Investors include New Enterprise Associates, Aisling Capital and Lightstone Ventures. includes $34 million in new venture capital investment, in addition to $17 million in outstanding convertible bridge notes.

The *Earlens Contact Hearing Device* (CHD) includes both a tympanic membrane transducer, which is placed deeply into the ear canal on the eardrum without surgery, and a behind-the-ear audio processor that sits on the outer ear and is connected to an ear tip that is placed in the ear canal. Sound waves are converted by the system to electronic signals, which are digitally processed, amplified and sent to the ear tip. A laser diode converts the signals into pulses of light, which shine onto a photodetector in the tympanic membrane transducer. This then converts the light back into electronic signals to transmit sound vibrations directly to the eardrum. In a 48-subject trial over 30 days, *Earlens* offered a 33% average improvement in word recognition. Users also gained function in higher frequencies, which is typically not found with conventional air-conduction hearing aids. The FDA cleared the device via its de novo premarket review pathway last September. The company will use the funds to execute a limited launch of the technology.

CVRX RAISES $46 MILLION TO SUPPORT PIVOTAL STUDIES OF BAROSTIM NEO NEUROMODULATOR

June 18, 2016

CVRx raised $46 million from unnamed investors in support of its implantable neuromodulator to treat high blood pressure and heart failure, bringing its total equity funding to $237 million over 5 rounds. The CE-marked *Barostim Neo* system is designed to electrically activate the baroreflex, the body's natural mechanism to regulate cardiovascular function. By activating this afferent pathway, *Barostim Neo* reduces sympathetic activity and increases parasympathetic activity, ultimately restoring autonomic balance. The device is currently in a pivotal 310 patient trial is slated to conclude in September 2017. In addition, another trial to test the device on heart failure patients is recruiting subjects. Its primary endpoint of (the rate of cardiovascular mortality and heart failure morbidity) is scheduled to report in 2021.

DOD FUNDS LPATHOMAB DEVELOPMENT FOR PAIN FOLLOWING NEUROTRAUMA

June 20, 2016

Lpath, (LPTN) received a $1.45 million two-year grant from the Defense Medical Research and Development Program (DMRDP), an agency of the US Department of Defense (DoD). This grant will support the study of Lpathomab for the treatment of neuropathic pain associated with traumatic brain injury. This DoD grant will fund preclinical studies designed to evaluate the ability of Lpathomab to alleviate pain following neurotrauma, and to confirm the potential efficacy of Lpathomab as previously demonstrated by Stanford University researchers in an animal model of TBI pain.

FERRER AND ALEXZA FINALIZE MERGER FOR FORMATTING

June 20, 2016

Spain-based **Grupo Ferrer** acquired **Alexza Pharmaceuticals,** which will become a wholly owned of Ferrer. Alexza's products and development pipeline are based on the *Staccato* system, a hand-held inhaler designed to deliver a pure drug aerosol to the deep lung, providing rapid systemic delivery and therapeutic onset, in a simple, non-invasive manner. Active pipeline product candidates include AZ-002 (*Staccato* alprazolam) for the management of epilepsy in patients with acute repetitive seizures and AZ-007 (*Staccato* zaleplon) for the treatment of patients with middle of the night insomnia.

YUMANITY TAPS NYSCF TO GENERATE IPSC CELLS

June 22, 2016

Yumanity Therapeutics and the New York Stem Cell Foundation (NYSCF) Research Institute entered into a discovery collaboration. The immediate aim of the partnership is to generate induced pluripotent stem cell (iPSC) lines for use in support of Yumanity Therapeutics' discovery efforts focused on new medicines for neurodegenerative diseases. The New York Stem Cell Foundation's automated technology, the NYSCF Global Stem Cell Array, systematically and consistently produces high-quality iPSCs at a scale that enables discovery, which Yumanity hopes will accelerate their discovery efforts.

ANNEXON RAISES $44 MILLION IN SERIES B TO SUPPORT CLINICAL PROGRAM

June 23, 2016

Annexon Biosciences closed a $44 million Series B financing led by new investor New Enterprise Associates, with participation by Correlation Ventures and existing Annexon investors, including Novartis Venture Fund, Clarus and Satter Investment Management. The Series B funding will be used to advance Annexon's lead drug programs, including monoclonal antibodies ANX005 for CNS and autoimmune disorders, and ANX007 for ophthalmic disorders. These lead therapeutics inhibit C1q, the initiating molecule of the classical pathway, and block complement activation involved in neurodegeneration.

MEDTRONIC AND WORLD STROKE ORGANIZATION PARTNER UP TO RAISE STROKE AWARENESS

June 23, 2016

The World Stroke Organization and **Medtronic (MDT)** established a global partnership to increase stroke awareness. The partnership will focus on continued growth of stroke awareness through the Stroke is Treatable World Stroke Day campaign; implementation of the WSO's new global stroke services guidelines: The Roadmap to Delivering Quality Stroke Care; and, supporting WSO's global clinical educational programs including the World Stroke Academy and teaching courses.

TAKEDA RETURNS NGF ANTIBODY TO AMGEN

June 24, 2016

Takeda Pharmaceutical (TYO: 4502) returned to **Amgen (AMGN)** the rights to develop and commercialize multiple molecules / products from Amgen's pipeline for the Japanese market, including AMG403 and AMG386. AMG403 contains fulranumab, a fully human recombinant nerve growth factor monoclonal antibody with potential analgesic activity. The collaboration with other candidates will proceed as established.

NEUROMETRIC AND SCRIPPS TO CONDUCT STUDY OF NEUROSTIMULATION IN CANCER PAIN

June 27, 2016

NeuroMetrix (NURO) and the Scripps Translational Science Institute will partner in a study of *Quell* wearable pain relief technology in patients with cancer related pain. *Quell* utilizes neurostimulation technology to provide relief from chronic pain. The study will enroll 40 adult patients with metastatic breast, prostate or colorectal cancer and who use at least one opioid medication on a daily basis. The primary endpoint is a reduction in daily opioid use assessed at weeks 2, 4, 6, 8 and 10 of the study. A 20% change in opioid consumption will be deemed clinically relevant. The study will also examine the potential benefits of *Quell* as a digital health intervention. The device integrates with a smartphone app that includes electronic pain tracking and provides objective feedback to the subject about their therapy utilization and sleep.

NEUROVISION RAISES $10 MILLION SERIES B TO ADVANCE RETINAL ALZHEIMER'S DIAGNOSTIC

June 29, 2016

NeuroVision Imaging raised a $10 million Series B led by a $5 million investment from Wildcat Capital Management. A portion of the Series B financing has been reserved for strategic investors. The funds will support NeuroVision's efforts as it seeks advanced validation and regulatory approval for its retinal imaging technology in connection with the early detection and monitoring of amyloid pathology related to Alzheimer's disease.

OPKO TO ACQUIRE TRANSITION THERAPEUTICS IN $60 MILLION DEAL

June 29, 2016

OPKO Health (OPK) and **Transition Therapeutics (TTHI)** signed a definitive agreement under which OPKO will acquire Transition Transition security holders will receive approximately 6.4 million shares of OPKO common stock. The transaction is valued at approximately US$60 million.

Company Spotlight

NLS PHARMA SPRINTS AHEAD IN THE RACE FOR NOVEL ADHD TREATMENTS

Based in the biotech-friendly Canton of Nidwalden in Switzerland, **NLS Pharma** group is still a newcomer to the neurotechnology space. It was founded last year with the purpose of addressing unmet medical needs in behavioral and cognitive disorders. This month, NLS Pharma announced the acceptance of an IND for a Phase IIb trial of mazindol in adult ADHD. NeuroInsights spoke with Alex Zwyer, a co-founder of NLS Pharma and the company's CEO.

The concept that sparked the formation of NLS Pharma dates back to the year 2000, when Dr. Eric Konofal, co-founder of the company and a neurologist and sleep specialist, involved in sleepiness disorders and neurobehavioral diseases, published a manuscript that described a relationship between sleep, deficit of alertness and ADHD. Alex Zwyer shares that "At that time, the study did not create too much noise. And last year, at the world ADHD Congress in Glasgow, one of the main topics actually was on sleep and ADHD, so sometimes, things take time to evolve."

The discovery began when one of Dr. Konofal's colleagues was abroad and he volunteered to help out with their ADHD patients. He started noticing overlap in their symptoms with his usual narcoleptic patients. He had been treating his narcoleptic patients with Sandoz's mazindol, which was approved and marketed as a treatment for obesity in the US and Europe. However, around 2000, the drug was withdrawn from the market due to commercial reasons and not due to safety. Numerous studies have been published on the use of mazindol to treat sleep disorders and many physicians use the drug off-label for this purpose. Hence, Dr. Konofal, after drawing the parallels between his narcoleptic patents and the ADHD patients, undertook a short-term clinical trial in pediatric ADHD patients that responded poorly to methylphenidate. In the study, conducted between 2008 and 2009, twenty-four children received a daily mazindol dose of 1 mg for 7 days and were followed for 3 additional weeks. The results demonstrated a 90% improvement from baseline as measured by the mean change in score in ADHD RS-IV.

Dr. Konofal recognized the need for safer alternatives to amphetamine salts and different methylphenidate formulations for the treatment of ADHD. Armed with the success from the small clinical trial, he started looking for a way to bring this solution to the patients. He sought help to develop a business case and secure funding for his venture. Zwyer comments, "That effort took time, as he still had a full time academic appointment. When I came onboard, we created the business structure, wrote the business plan and searched for funds." It was in 2015 when a group of Swiss private investors came to the table to fund their venture. The company's Series A financing was successfully completed for $8.5 million in August 2015.

Zwyer is proud of what they have been able to accomplish in a short amount of time and candidly shares, "In 10 months, we have developed the API, optimized it, completed the formulation work, developed a protocol, completed a pre-IND meeting with the FDA and now we got the go-ahead from the FDA to proceed with a Phase II proof of concept trial."

The upcoming Phase II trial will have seven US sites involved and will seek to enroll about 100 adult patients. Zwyer is cautious as previous experience with the drug is limited to the off label use in narcolepsy and the small pilot in pediatric ADHD. There is no prior data for the compound in the adult ADHD population that they can work from. From his personal point of view, Zwyer believes that there is a lot of potential for mazindol. The first patient is expected to enroll in July 2016 and if everything goes according to plan, as it seems thus far, top-line results would be available within 6-9 monhs. Zwyer comments, "Assuming that this would be a valid treatment for ADHD, then this would represent an attractive value proposition for a potential partner as it is a novel approach. Maybe it would open a new way or create a trend for other wake promoting agents to follow. Maybe we are at the brink of seeing a disruptive market strategy."

In addition to mazindol, NLS Pharma has other promising candidates in the pipeline, including NLS-3 (phacetoperane) a catecholaminergic drug structurally different from methylphenidate and pipradol but showing similar activity; and NLS-4 (lauflumide), a selective dopaminergic reuptake inhibitor, in development for cognitive impairment.

NLS Pharma group operates in a different way than most startups as it encompasses three companies, including NLS Pharma Inc., where the IP is held. Once a compound is ready and there are funds to support the projects, a spinoff is created. Currently, there are two spinoffs, NLS-0 and NLS-1, which will execute a specific strategy according to the asset and goal. According to Zwyer, they will continue to look for innovative and cost-effective ways to treat CNS disorders and bring those in to the parent company until they can replicate the model. NLS-1 is open to many possibilities and would be interested in talking to potential partners.

Zwyer discusses their patient-centric approach, and hopes that current trends in device development continue to complement efforts from the pharmaceutical industry. He states, "ADHD is poorly understood and there is a huge burden on society due to adult ADHD. As technology and devices are developed,

knowledge evolves, will help us come up with more effective treatments."

Future efforts will continue to seek de-risked assets to tackle CNS disorders, and Zwyer defends their approach of repurposing and repositioning candidates that may have been abandoned, failed at other indications or have an interesting side effect profile. The approach is working for NLS Pharma as they have leaped ahead in the race to bring a safer ADHD treatment to market.

Feature, Continued from page 1

In addition to the genetic component, there are also possible risk factors including in utero tobacco/drug exposure or hypoxia, low birth weight, prematurity, pregnancy, lead exposure, family dysfunction, low socioeconomic status and brain injury as 20% of children with severe traumatic brain injury are reported to have subsequent onset of substantial symptoms of impulsivity and inattention. Evidence also supports possible association between dietary factors (e.g., refined sugar, food additives) and ADHD in a small percentage of patients. A causal link between environmental toxins and ADHD has not been clearly established.

Structural and functional abnormalities have been identified in children with ADHD without preexisting identifiable brain injury. These include dysregulation of the frontal subcortical circuits, small cortical volumes in this region, widespread small-volume reduction throughout the brain, and abnormalities of the cerebellum, particularly midline/vermian elements. Abnormalities in neural networks or circuits have been identified with functional MRI.

Currently, three clinical subsyndromes have been delineated in children. First, combined hyperactivity, impulsivity, and inattention, which describes approximately 75% of affected children; Secondly, a predominantly inattentive syndrome; and finally a small group that display only hyperactivity. In adults, motoric hyperactivity is less common, but restlessness, edginess, and difficulty relaxing are often seen. Disorganization and difficulty completing tasks are other common complaints.

Diagnosis of ADHD after a thorough evaluation, including a careful history and clinical interview to rule in or to identify other causes or contributing factors; completion of behavior rating scales by different observers from at least 2 settings (e.g., teacher and parent); a physical examination; and any necessary or indicated laboratory tests which arise from conditions suspected based on history and/or physical examination.

CURRENT TREATMENTS

Medication therapy is the most common treatment, although behavioral therapy is the recommended first-line approach in younger children. Reports indicate that the use of ADHD medications among Americans has experienced double digits growth in the past 8 years and that about 75% of children diagnosed with ADHD are on medication. According to the CDC since 2011, there has been a 50% increase in the number of preschool children, between the ages of 4 and 5, who take ADHD medications.

Stimulants.

The most commonly used pharmacological interventions for ADHD are stimulant medications. Stimulants are sympathomimetic drugs, which increase intrasynaptic catecholamines (mainly dopamine) by inhibiting the presynaptic reuptake mechanism and releasing presynaptic catecholamines. Whereas methylphenidate specifically blocks the dopamine transporter protein, amphetamines also release dopamine stores and cytoplasmic dopamine directly into the synaptic cleft. Stimulants appear to work in all age groups of individuals with ADHD. However, there may be a higher side effect burden in younger children compared to other age groups.

The stimulants include short- and long-acting methylphenidate (*Ritalin, Concerta, Metadate, Focalin*, and others), dextroamphetamine (*Dexedrine, Adderall*), and dextroamphetamine/amphetamine combinations (mixed amphetamine salts). A methylphenidate patch (*Daytrana*) is available, as is a pro-drug form of dextroamphetamine, lisdexamfetamine (*Vyvanse*), which is designed to limit the abuse potential, and a long-acting oral suspension of methylphenidate (*Quillivant XR*). Many patients will switch between stimulant medications until an appropriate treatment is found.

In 2015, revenues for **Shire**'s *Vyvanse* reached sales of $1.7 billion, which represents 19% growth compared to the previous year. Revenues from **Novartis'** *Ritalin/Focalin* franchise continued to drop, down to $365 million as more generics reached the market. **Janssen's** *Concerta* bounced back reaching $821 million in sales compared to $599 million in 2014 and $782 million in 2013. **Pfizer's** *Quillivant XR*, which reached the market in the US at the beginning of 2013, also grew its revenues and gained $37 million in 2015, up from $32 million in 2014.

In May 2015, **Rhodes Pharmaceuticals** launched *Aptensio* XR, an extended-release formulation of methylphenidate capsule with an onset of effect of 1 hour and a 12-hour duration of effect with approximately 40% of the active ingredient released immediately and approximately 60% delivered later in the day.

This year, **Neos Therapeutics'** new formulation of extended-release amphetamine, *Adzenys XR-ODT* received FDA approval and was launched in the US. The approval followed the 505(b)(2) regulatory pathway. The clinical program demonstrated that *Adzenys XR-ODT* is bioequivalent to *Adderall XR1*.

Nonstimulants.

Lilly's *Strattera* (atomoxetine) is the most commonly prescribed non-stimulant ADHD medication. Atomoxetine hydrochloride is a propylamine derivative anxiolytic agent with antidepressant activity. It acts by selectively inhibiting the reuptake of norepinephrine, thus facilitating noradrenergic neurotransmission. In 2015, *Strattera* sales reached $784 million, a 6% growth from 2014. The drug will lose patent protection in 2017.

The alpha2 agonists, clonidine and guanfacine are primarily used as adjunctive to stimulants or for patients who developed tics with stimulants or did not otherwise tolerate stimulants. In 2009 the FDA approved **Shire's** *Intuniv* (guanfacine XR, once-daily formulation) and in 2010 **Shionogi's** *Kapvay* (long-acting clonidine), for treatment of children and adolescents with ADHD. *Intuniv* reached peak sales of $335 million with 16% annual growth in 2013, but in 2015, despite receiving approval in the EU, after generics had eroded its market share, revenues were down to $65 million. *Kapvay* is currently marketed by **Concordia Pharmaceuticals** and had sales in 2015 of $36 million.

A subgroup of antidepressants are second-line drugs of choice for ADHD. The tricyclic antidepressants (TCAs) as well as bupropion (*Wellbutrin*) block the reuptake of neurotransmitters including norepinephrine. In contrast, the serotonin reuptake inhibitors are not useful for ADHD. The TCAs are effective in controlling abnormal behaviors and improving cognitive impairments associated with ADHD, but less so than the majority of stimulants.

TREATMENTS IN DEVELOPMENT

The number of open interventional clinical studies for ADHD has remained steady over the past two years, currently there are 181 open studies for ADHD, 17 of which involve devices and 79 of which include a behavioral component (alone or in combination with a drug or device therapeutic). Pharmaceutical companies continue to search for non-stimulant drugs with improved safety and lower potential for abuse and diversion. These attributes are becoming more critical as the ADHD drug use has risen sharply in the adult population, with college aged patients (19-25 years old) being the fastest growing group and also being a group in which abuse and diversion are of most concern.

Monoamine modulators.

The brain circuits associated with ADHD are rich in monoamines, which are involved in the mechanism of action of psychostimulants and other medications used to treat this disorder. Pharmacological treatments of ADHD all optimize catecholamine signaling in the prefrontal cortex and new compounds that can increase concentrations of dopamine, norepinephrine, and serotonin in the synaptic cleft, mimicking the effect of amphetamines, represent an attractive avenue in the development of novel ADHD therapies.

In March 2015, **Alcobra** completed a Phase II study of a single administration of MDX (Metadoxine Extended Release) in adolescent patients. MDX is a nonstimulant monoamine-independent modulator of GABA transmission, and does not directly affect dopamine or norepinephrine. MDX demonstrated good tolerability and no safety concerns were identified, with an adverse event profile showing no differences from the placebo. A total of 83 patients aged 13-17 with predominantly inattentive ADHD were enrolled. Three dosage levels of MDX were administered as a single dosing and were assessed on a follow up visit. The most common side effects were headache, nausea, and fatigue. Analyses of secondary cognitive measures did not produce statistically significant findings. MDX is in Phase III development for adults with ADHD. A first Phase III trial was completed in 2014 and using a modified intent-to-treat population analysis there was a mean change on the CAARS-INV from baseline to the final visit of 11.6 in the MDX treated group as compared with a mean change of 8.7 in the placebo treated group ($p < 0.03$). MDX also showed a statistically significant impact on the inattention subscale of the CAARS-INV ($p < 0.05$). Patients with both predominately inattentive (PI) ADHD and combined type (CT) ADHD subtypes appeared to benefit similarly in this trial. The company is currently conducting a second, pivotal Phase III study of MDX in adults with ADHD for which completion is expected in December 2015. In the design of this trial, the company is aiming to address the high placebo response and wide response variability observed in the first Phase III study and that prompted the mITT analysis. Alcobra is also planning a registrational Phase II/III pediatric ADHD trial to begin this year.

Sunovion and **Dainippon Sumitomo** are pursuing development of dasotraline (SEP-225289), a norepinephrine/dopamine reuptake inhibitor for ADHD and binge-eating disorder. The drug increases the levels of norepinephrine, serotonin and dopamine by inhibiting their reuptake. In May 2014, Sunovion completed a Phase II study, and a Phase III study was initiated in June 2014 investigating SEP-225289 in adults with ADHD. The results of this Phase III are expected in the last quarter of 2016. The companies also have ongoing pediatric studies that are expected to run until November 2016. In January 2016, the companies completed a Phase I human liability study and found that dasotraline single doses of 8 mg, 16 mg and 36

mg were not significantly different compared to placebo on the primary endpoint and most secondary endpoints, assessing potential for abuse. All doses were associated with significantly lower "drug liking"* compared to 40 mg and 80 mg single doses of methylphenidate. The companies expect to file an NDA for dasotraline in 2017.

According to clinicaltrials.gov, **Neurovance** recently completed a three-week Phase IIb crossover trial of centanafadine SR, a triple reuptake inhibitor that preferentially modulates norepinephrine and dopamine, and to a lesser degree, serotonin. The results of this Phase IIb have not yet been disclosed. The company had previously successfully completed a Phase IIb study in May 2014, demonstrating a statistically significant improvement in ADHD symptoms on the ADHD- Rating Scale-IV. In addition to this trial, Neurovance is conducting a Phase I imaging study and a Phase I pharmacokinetics study evaluating several once-daily formulations. Together, the studies will measure brain transporter occupancy, clinical efficacy in ADHD, onset and duration of action, guidance on optimal dosing and formulation selection. These trials will lay the groundwork for Phase IIb/IIIa trials beginning in 2016.

Lundbeck is conducting a proof of concept trial using *Trintellix* (previously *Brintellix*) to treat adult ADHD patients. *Brintellix* is currently approved and commercialized for major depressive disorder, and preclinical and clinical observations supported the potential benefit on attention and executive functions.

Supernus has two candidates in late stage development: SPN812, a selective norepinephrine reuptake inhibitor in Phase II/III development for ADHD; and SPN810 (molindone hydrochloride) as a treatment for impulsive aggression in ADHD patients. In April 2016, Supernus initiated an open-label, single-group-assignment, extension Phase III trial in the US, to assess long-term safety and efficacy of SPN-812 ER when administered alone or in conjunction with an FDA-approved ADHD medication in 200 pediatric subjects. Subjects aged 6-12 years will be treated with SPN-812 ER followed by dose optimization. The subject will be given a choice to extend their participation in the study every 6-months for up to 36 months. Completion of this study is expected in mid-2019 while initial Phase III data for SPN-810 is expected to be available by mid-2017. The program consists of three studies evaluating the compound in the treatment of impulsive aggression in pediatric patients with ADHD in conjunction with standard ADHD treatment. The program was initiated in January 2016 will recruit over 1000 patients and will extend until 2019.

Development of **Lilly**'s LY2216684, a norepinephrine reuptake inhibitor for ADHD was terminated in September 2015. The compound was also in development for major depressive disorder, however it did not meet the primary endpoint in the Phase III trials and hence Lilly abandoned its development for both indications.

New amphetamine formulations.

At the end of 2015, **Neos Therapeutics** received a complete response letter from the FDA regarding the company's NDA for *Cotempla* XR-ODT (methylphenidate extended release orally disintegrating) tablets. The CRL for *Cotempla* XR-ODT requires the company to conduct a bridging study to demonstrate bioequivalence between the clinical trial material and to-be-marketed drug product, including an assessment of food effect, and to provide validation and three months of stability data. The company has set as two milestones for 2016 to announce the results of the bioequivalence study for Cotempla XR-ODT in Q3 2016 and to resubmit the NDA in Q4 2016.

In April 2016, **Ironshore Pharmaceuticals**, a subsidiary of **Highland Therapeutics** achieved positive results in the first of two Phase III trials of *Benjorna* (delayed-release and extended-release methylphenidate capsules designed to be dosed in the evening). In the first study of 153 pediatric patients in a classroom setting, *Benjorna* demonstrated a statistically significant improvement compared to placebo ($p=0.01$), based on a composite measure from 8am through to 8pm on the Swanson, Kotkin, Agler, M-Flynn and Pelham Rating Scale, the study's primary endpoint. Patients randomized to *Benjorna* also demonstrated improved functioning during the morning routine as measured by the Parent Rating of Evening and Morning Behavior-Revised morning subscale, the study's key secondary endpoint ($p<0.001$). This month, Highland released results from a second Phase III study of *Benjorna* in 161 pediatric patients (ages 6-12) outside of the classroom setting. In this study, the group randomized to receive *Benjorna* achieved a 44% improvement in ADHD symptom scores, a highly statistically significant positive difference compared to the placebo group ($p=0.002$), based on the ADHD-RS-IV Rating Scale, the study's primary endpoint. Secondary endpoints were also achieved, with improved functioning scores during the morning routine as measured by two separate scales. In the Before School Functioning Questionnaire (BSFQ), the treatment group achieved a 59% improvement in functioning compared with the average baseline score, a highly statistically significant difference relative to the placebo group ($p<0.001$). In the PREMB-R (Parent Rating of Evening and Morning Behavior-Revised) morning (AM) subscale, the treatment group showed a 66% improvement, compared with baseline; also a highly statistically significant result compared with the placebo group ($p<0.001$). The company is now working towards registering the drug.

Shire's *Adderall XR2* (SHP465) achieved positive topline results in a four-week Phase III study in children and adolescents aged 6-17 years with ADHD. SHP465 (triple-bead mixed amphetamine salts) is an investigational oral stimulant

medication. The primary efficacy analysis demonstrated that SHP465, administered as a daily morning dose, was superior to placebo on the change from baseline in ADHD-RS-IV (ADHD rating scale) total score, with a Least Squares mean difference from placebo at Week 4 of -9.9 (95% CI: -13.0 to -6.8, p<0.001), suggesting a significant improvement in ADHD symptoms. SHP465 was also superior to placebo in the key secondary efficacy analysis on the clinical global impression improvement scale (CGI-I), with an LS mean difference from placebo at Week 4 of -0.8 (95% CI: -1.1 to -0.5, p<0.001), indicating a significantly higher proportion of patients were rated improved on the CGI-I rating scale. The completion of SHP465-305 addresses an FDA requirement to evaluate the safety and efficacy of SHP465 in children and adolescents prior to filing a resubmission for approval. Once the pharmacokinetic study and an additional safety and efficacy Phase III trial in adults currently under way are complete later this year, Shire plans to add these study results to its existing SHP465 data set to submit a Class 2 resubmission for FDA approval.

Highland Therapeutics is developing HLD100, a novel formulation of dextroamphetamine sulfate. The compound has completed Phase II trials and a Phase III is expected in the second half of 2016.

Other mechanisms.

This month, **Medgenics**, enrolled the first patient into a Phase II/III trial to evaluate NFC-1 in adolescent patients with mGluR mutation positive (mGluR+) ADHD. NFC1 is a non stimulant agonist of multiple metabotropic glutamate receptors (mGluRs) 1, 3, 5, 7, 8 and also upregulates GABAB receptors. The trial will enroll 90 patients between the ages of 12-to-17 years old. The primary and key secondary endpoints in the trial will be the change from baseline in the ADHD-rating scale Total Score (ADHD-RS-5) and change from baseline in Clinical Global Impression - Global Improvement Scale (CGI-I). Results are expected at the end of the year.

NLS Pharma Group (*see Spotlight page 17*) will enter Phase II trials with NLS1, a controlled release formulation of mazindol (MZD), which is a norepinephrine reuptake inhibitor. The IND, which had been submitted in May 2016, is now approved and seven clinical sites in the US will participate in the study.

Diagnostic, Devices and Neurosoftware

Diagnosis of ADHD involves behavioral observations by parents and teachers. Several companies are seeking to take the bias out of the diagnosis and have developed new tests to evaluate potential ADHD patients.

In April 2016, the FDA cleared **Qbtech**'s ADHD test, QbCheck. The test aids in the assessment and evaluation of treatment interventions in patients with ADHD. QbCheck is an online test that provides objective and unbiased decision-making support when diagnosing and treating ADHD in children, adolescents and adults. The device has also received the CE Mark.

CogCubed has experienced some delays in the development of *Groundskeeper*, a video game used as an assessment for ADHD. The technology consists of small cube computers that contain multiple sensors, which allow children to hold and play with the cubes as they solve problems posed in the game. A pilot study in 52 children and adolescents has been completed and currently two clinical trials recruiting participants for both pediatric and adult ADHD are ongoing. The expected completion date for these studies was in 2015, however at this time the pediatric study is still recruiting participants and the adult study has completed recruitment but is still ongoing.

As alternative to pharmaceutical interventions, a growing number of companies are developing device and software interventions to manage ADHD without the bothersome side effects of drug therapies.

In November 2015, **NeuroSigma** received CE Mark approval for its *Monarch* eTNS System as treatment for ADHD in adults and children age 7 and older. This CE Mark is the first for any non-drug treatment of ADHD in the EU. Currently, a 90-subject double-blind trial of eTNS for ADHD is being conducted at UCLA with funding from the NIH. The Monarch eTNS system is composed of a cell-phone sized pulse generator and a single-use electric patch that is applied to the forehead. Signals are transmitted through lead wires to the patch in order to stimulate the trigeminal nerve in the skin of the forehead; triggering these nerve fibers sends signals to targeted brain regions and changes the activity there. Patients may conveniently self-administer the Monarch eTNS system at home and typically use the device while sleeping.

In April 2016, **Posit Science** released results from an initial study of its brain exercises used by children with ADHD, demonstrating steady and significant improvements on the study's primary outcome measure, the ADHD rating scale (RS IV, a parent-reported symptom severity measure), over the course of the six-month study period and in the six-month post-study follow-up. The results were significant both against baseline (within group) and against the control group, which engaged in 30 hours of video game play. Improvements were also noted on secondary measures. Through randomization, 10 children were assigned to a control group using video games and 21 were assigned to the novel intervention of computerized brain exercises developed at Posit Science. Children engaged in the intervention or control activity for a total of 30 hours over a period that extended as long

as six months (at a frequency of 3-5 times per week and 30 minutes per session). A majority (52%) of children completely adhered to the 30-hour requirement for brain exercises, while the remainder partially adhered, including ten children who completed less than half of the 30 hour training (1-13 hours, mean 4.5± 3.6 hours). at the six-month follow-up evaluations, there was no significant difference on the primary outcome measure between the healthy group and the group that had completed the brain exercises, suggesting renormalization of behaviors.

Akili Interactive Labs released data from the Akili-001 pediatric ADHD pilot study of Project: EVO, its lead therapeutic product candidate. The study confirmed Project: EVO's safety and feasibility. Additionally, exploratory outcome measurements demonstrated that Project: EVO improved attention, inhibition and working memory in children with ADHD. The study enrolled 80 children between the ages of 8 and 12 years, 40 of whom were diagnosed with ADHD and not taking a medication, and 40 of whom had no psychiatric diagnosis. The regimen consisted of using the digital intervention delivered through an action video game interface on a tablet device at home for approximately 30 minutes per day, five times a week over the span of four weeks. The primary aims of the study were to confirm feasibility and safety of the at-home intervention, as well as to measure the difference in baseline attentional functioning between the two groups. Exploratory measures of attention, impulsivity, and working memory were also assessed at one month. Improvement was seen across these domains in the ADHD group. Statistically significant improvements were observed in the ADHD group on multiple outcome measures. Akili plans to initiate a large, randomized, controlled pivotal study in the coming months to further validate the efficacy and safety of Project: EVO as a treatment for pediatric ADHD.

Pharmaceutical clinical trials for ADHD

Company	Compound	MOA	Phase
Shire	SHP465 (*Adderall XR2*)	Mixed amphetamine salts	Class 2 resubmission
Neos Therapeutics	Contempla XR-ODT	Methylphenidate extended release	CRL 11/2015
Alcobra/ Teva	MG01CL (metadoxine SR)	Increases GABA and acetylcholine	Phase III
Sunovion/ Dainippoin Sumitomo	Dasotraline (SEP225289)	Norepinephrine/dopamine reuptake inhibitor	Phase III complete
Highland Therapeutics (Ironshore Pharma)	*Benjorna*	Methylphenidate extended release	Phase III complete
Medgenics	NFC01	Metabotropic glutamate receptor modulator	Phase III
Supernus	SPN 810 (molindone Hcl)	Low dose antipsychotic	Phase III (aggression in ADHD)
Highland Therapeutics (Ironshore Pharma)	HLD100	Dextroamphetamine	Phase II
Supernus	SPN 812	NE reuptake inhibitor	Phase II/III
Neurovance	Centanafadine SR (EB-1020)	NE, DA preferring triple reuptake inhibitor (1:6:14)	Phase IIb complete
Lundbeck	*Trintellix*	5-HT reuptake inhibitor	Phase II
Amarantus Psychogenics	Eltoprazine	5HT1A/B agonist	Phase II (development on hold)
NLS Pharma	NLS-1	Mazindol	Entering Phase II
BioLite	BLI-1008	Dextroamphetamine	Phase II
EMER Pharma	ASP-2905	BEC1/KCNH3 Potassium channel inhibitor	Phase I complete (no dev. Reported)
Integrative Research Laboratories	IRL752	Cortical enhacer	Phase I
P2D Bioscience	PD9475 (betahistine)	H3 antagonist	Phase Ib (no further development since 2009)
NLS Pharma	NLS-3	levofacetoperane	Phase I

NeuroInsights Neurotech Index

Company	Symbol	1 mo Return (%)	3 mo Return (%)	1 yr return (%)	Market Cap ($M)	Ave. Daily Vol (Shares)	Last Price	52 Week Low	52 Week High
ACADIA Pharmaceuticals	ACAD	-8	16	-22	3,673.2	2,974,115.68	32.46	16.64	51.99
AcelRx Pharmaceuticals	ACRX	-22	-13	-37	121.89	485,680.86	2.69	2.4	5.88
Acorda Therapeutics	ACOR	-10	-4	-23	1,174.9	547,381.00	25.51	23.85	43.63
Alcobra	ADHD	-16	18	-31	123.74	82,779.27	4.49	3.15	9.5
Alexza Pharmaceuticals	ALXA				0		0.94	0	0
Alkermes	ALKS	-7	26	-33	6,533.3	943,986.09	43.22	27.14	80.71
Amarantus Bioscience	AMBS	-20	-7	-99	3.48	523,000.73	0.05	0.03	7.19
Amicus Therapeutics	FOLD	-23	-35	-61	693.69	2,549,242.86	5.46	4.98	18.83
Anavex Life Sciences	AVXL	38	25	239	218.19	631,116.55	6.11	1.7	14.84
Arena Pharmaceuticals	ARNA	-6	-13	-63	415.61	1,497,511.14	1.71	1.3	5.12
AxoGen	AXGN	24	28	119	206.98	283,414.73	6.88	3.04	6.88
Axovant Sciences	AXON	-3	12	-37	1,273.0	482,692.59	12.84	8.86	22.88
Biogen	BIIB	-17	-7	-40	52,971.	2,416,411.05	241.8	223.02	412.24
BioLine Rx	BLRX	-16	-22	-70	45.14	199,538.14	0.8	0.71	2.8
bluebird bio	BLUE	-4	2	-74	1,599.2	1,046,866.59	43.29	35.37	171.24
Catalyst Pharmaceuticals	CPRX	15	-39	-83	58.84	1,454,834.32	0.71	0.51	5.8
Cerecor	CERC	-6	-41		19.03	51,988.95	2.2	1.94	5.19
Cynapsus Therapeutics	CYNA	19	41	3	206.3	56,340.14	16.75	10.54	17.33
Depomed	DEPO	-4	41	-9	1,198.7	1,122,551.27	19.62	12.25	33.74
Durect	DRRX	4	-10	-49	167.58	508,019.86	1.22	0.99	2.87
Endo International	ENDP	-1	-45	-80	3,471.3	10,045,062.7	15.59	12.56	88.54
EnteroMedics	ETRM	-45	-70	-97	2.68	291,803.32	0.29	0.27	12.45
EPIRUS	EPRS	-26	-83	-92	11.84	1,490,440.50	0.45	0.39	8.75
GW Pharmaceuticals ADR	GWPH	3	27	-25	1,993.0	629,789.95	91.57	35.83	131.25
Horizon Pharma	HZNP	-4	-1	-53	2,641.0	4,284,795.32	16.47	12.86	39.49
Integra Lifesciences	IART	7	18	31	2,969.3	367,578.41	79.78	54.75	79.85
Jazz Pharmaceuticals	JAZZ	-7	8	-20	8,538.2	908,499.45	141.3	108.5	194.73
LivaNova	LIVN	3	-7	-16	2,464.7	872,802.95	50.23	46.79	77
Marinus Pharmaceuticals	MRNS	-77	-76	-89	24.78	507,579.41	1.27	1.19	20.72
Minerva Neurosciences	NERV	-17	66	76	285.29	1,312,455.59	10.21	3.45	15.84
Natus Medical	BABY	17	-2	-11	1,251.7	350,112.32	37.8	29.34	51.05
Neos Therapeutics	NEOS	-11	-14		148.91	152,961.95	9.28	7.15	28.99
Neuralstem	CUR	-13	-61	-85	26.79	519,465.14	0.29	0.25	2.02
Neurocrine Biosciences	NBIX	-8	15	-5	3,938.5	1,456,509.36	45.45	31.25	58.46
NeuroDerm	NDRM	-13	15	6	351.16	86,238.45	16.25	11.76	26.5
NeuroMetrix	NURO	-2	-9	-54	7.29	128,946.86	1.66	1.35	4.96
Nevro	NVRO	6	31	37	2,089.0	631,348.41	73.76	36.51	77.94
Nymox Pharmaceutical	NYMX	38	37	152	150.04	462,118.14	3.35	1.13	4.37
Orexigen Therapeutics	OREX	8	-24	-91	62.59	2,720,096.68	0.43	0.35	5.04
Pain Therapeutics	PTIE	-6	-2	27	101.05	63,055.05	2.19	1.53	2.63
Palatin Technologies	PTN	-16	-18	-50	30.03	226,104.36	0.44	0.36	1.18
Prana Biotechnology	PRAN	25	67	-32	42.2	84,171.73	4.74	2.7	7.68
Raptor Pharmaceutical	RPTP	-3	17	-66	458.1	647,133.27	5.37	2.94	16.28
RespireRx Pharmaceuticals	RSPI	-15	-21	2	11.48	257,581.45	0.02	0.01	0.04
Sage Therapeutics	SAGE	-8	-6	-59	966.07	614,734.68	30.13	26.28	77.48
Sarepta Therapeutics	SRPT	-9	-2	-37	872.93	5,542,777.59	19.07	8	41.97
Second Sight Medical	EYES	-8	-26	-74	129.01	483,141.91	3.58	3.17	15.82
Shire PLC	SHPG	-1	7	-23	36,333.	3,724,448.55	184.0	147.6	270.63
StemCells	STEM	-29	-87	-94	4.71	892,066.09	0.4	0.33	7.56
Supernus Pharmaceuticals	SUPN	4	34	20	1,006.7	587,552.32	20.37	9.51	23.3
Titan Pharmaceuticals	TTNP	-22	14	24	109.87	738,375.09	5.47	2.57	10
Transition Therapeutics	TTHI	69	15	-30	57.16	123,585.36	1.47	0.66	2.75
Valeant Pharmaceuticals	VRX	-29	-23	-91	6,908.6	28,672,023.7	20.14	18.55	263.81
Vanda Pharmaceuticals	VNDA	8	34	-12	482.88	624,180.00	11.19	6.91	14.5
VIVUS	VVUS	-12	-20	-53	116.58	1,069,716.91	1.12	0.92	2.44
Xenon Pharmaceuticals	XENE	-15	-16	-49	84.99	19,733.09	5.9	5.65	11.78
XenoPort	XNPT	-1	56	15	447.23	721,039.45	7.04	3.35	7.86
Zogenix	ZGNX	-20	-13	-40	199.41	171,971.73	8.05	7.33	21.65