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CSF in helper T-cells. The study showed that GM-CSF was secreted by CNS-invading autoaggressive helper T cells and that its production correlated with the pathogenic ability of these autoaggressive helper T cells. Importantly, the cytokine GM-CSF was necessary and largely sufficient for the induction of neuroinflammation.[6] The neutralization of GM-CSF has been shown to cure MS in a mouse model.[5,6] Therefore, targeting GM-CSF in MS patients is a promising novel approach.

MOR103 is a fully human HuCAL antibody directed against GM-CSF and is being developed for inflammatory diseases such as MS, as well as rheumatoid arthritis. Preclinical studies of the compound were performed in a rat EAE model. Rats that were treated with MOR103 showed a significant decrease in EAE score. Due to the promising preclinical data of MOR103 in MS animal models, MOR103 is expected to enter a Phase 1b safety study in MS in the fourth quarter of 2011.

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▶ The Promise of TNX-102 in Fibromyalgia Syndrome

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Fibromyalgia (FM) is a common pain disorder that predominantly affects women. The prevalence of FM in the United States has been estimated at 2%; occurring in approximately 3.4% of females and 0.5% of males.[1] In addition to diffuse pain, FM is characterized by multiple tender points in specific anatomic regions, chronic fatigue, psychological distress, and disturbed or unrefreshing sleep.[2] Sleep disturbance is not an isolated symptom, but also has the potential to exacerbate pain and other FM symptoms. Therefore, improving sleep quality is a key goal of therapies to improve daytime FM symptoms. TONIX Pharmaceuticals is targeting unrefreshing sleep by developing TNX-102 for bedtime administration for the maintenance of FM patients.

TONIX recently reported Phase 2a data for bedtime very-low dose (VLD) cyclobenzaprine (immediate-release capsules) compared to placebo in an 8 week randomized, double-blind, placebo-controlled trial.[5] Cyclobenzaprine, even at low doses, induces somnolence, which is recognized as a common side-effect. The rationale for testing bedtime VLD cyclobenzaprine was to improve sleep quality, but limit the side-effects of cyclobenzaprine that may limit efficacy or mask benefits at higher dosages. The study found that bedtime treatment with VLD cyclobenzaprine reduced pain and improved other symptoms.

In addition, bedtime VLD cyclobenzaprine improved sleep quality.[5] The sleep disturbance of FM has been studied by sleep EEG and a non-rapid-eye-movement (non-REM) arousal rhythm was identified: the "alpha-EEG sleep anomaly".[2] Subsequently, this FM sleep anomaly has been further characterized as increases in the nocturnal alarm signals termed the cyclic alternating pattern (CAP) types A2 and A3.[3] A different experimental treatment that improves

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FM symptoms was also shown to decrease CAP A2 and A3.[4] In the Phase 2a study, bedtime VLD cyclobenzaprine increased the number of subjects who experienced nights of normalized CAP A2 and A3 sleep over a threshold. The improvement of restorative sleep by bedtime VLD cyclobenzaprine correlated with improvements in fatigue and other FM symptoms.[5]

The results from studying VLD cyclobenzaprine in a primitive immediate-release formulation support development of more elegant formulations designed for bedtime use. The immediate-release forms of cyclobenzaprine developed as Flexeril have variable absorption and prolonged plasma half-life (~18.5 hr).[6] Therefore, bedtime use has unpredictable next-morning effects and can be associated with "hangover." To address these problems, TONIX is developing TNX-102, a gelcap formulation of VLD cyclobenzaprine that has a more predictable absorption and possibly a decreased risk of hangover.

TONIX's next human clinical study will test the blood levels of cyclobenzaprine in approximately 30 healthy adult volunteers after they ingest either a TNX-102 or a control immediate-release cyclobenzaprine product. After the completion of two successful efficacy studies in FM, it is expected that TNX-102 would be registered with the U.S. Food and Drug Administration (FDA) through the provisions of Section 505(b)(2) of the Food, Drugs and Cosmetic Act. This regulatory pathway could abbreviate product development. The 505(b)(2)-based product development plan for TNX-102 is designed to leverage the safety data that has been generated by other manufacturers for cyclobenzaprine-containing products and accepted by the FDA in support of their product registration.

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▶ First-In-Class EP4 Receptor Antagonist for the Treatment of Migraine

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Migraine headache is estimated to affect 11% of the world population. It accounts for an estimated 30 million days of lost productivity at a cost of up to $17 billion per year in the United States alone. During migraine attacks, the pain is frequently accompanied by nausea, sometimes vomiting, and/or photophobia, phonophobia, and osmophobia. The most commonly used therapies in the treatment of acute migraine are non-steroidal anti-inflammatory drugs (NSAIDs) and triptans (5-HTIB/1D agonists). However, many migraine sufferers do not experience relief from current treatment options or cannot tolerate their gastrointestinal, cardiovascular, and other side effects.[1] Thus, new treatments are needed.

While the precise cause of migraines is not fully understood, changes in vascular tone and inflammatory processes appear to be key contributing factors. Prostaglandins are integral components of vascular and inflammatory reactions in the central and peripheral nervous systems. Prostaglandin E2 (PGE2) is well known to be a mediator of pain and inflammation and a wealth of evidence demonstrates that PGE2 binding to the EP4 receptor can stimulate inflammatory pain mechanisms, including production of pain-related peptides, such as calcitonin gene-related peptide (CGRP).[2] PGE2 signaling via EP4 receptors also causes dilation of small blood vessels in the brain, while leaving coronary and pulmonary arteries unaffected.

Ariel Pharmaceuticals is developing AP-1531, a first-in-class, orally available, potent and selective EP4 receptor antagonist that specifically targets PGE2-EP4 binding.[3] AP-1531 has been shown to be safe in preclinical and clinical settings, to effectively reverse acute pain in humans,