

A New Migraine Therapy: Efficacy and Tolerability of a Fixed Single-Tablet Formulation of Sumatriptan RT Technology™ and Naproxen Sodium in the Early Intervention Paradigm

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Objectives: Evaluate the efficacy and tolerability of sumatriptan 85mg formulated with RT Technology™ and naproxen sodium 500mg(SumaRT/Nap)when treating during mild migraine pain.

Background: Utilization of an optimal treatment paradigm (early) and pharmacotherapy that concurrently targets both serotonin dysmodulation and inflammation in migraine may improve migraine treatment outcomes, i.e. providing a more comprehensive migraine treatment.

Methods: Two identical randomized, multi-center, double-blind, placebo-controlled, parallel group, single attack (treating mild pain within 1h of onset) trials of adult migraineurs (ICHD-II) were conducted. Subjects were randomized (1:1) to SumaRT/Nap or placebo (PBO). Therapeutic gain (TG) was calculated (active-PBO) for pain endpoints and incidence of IHS and non-IHS symptoms. Endpoints were evaluated statistically using a hierarchical step down method to control for multiplicity.

Results: Subjects in both studies were demographically similar to other migraine studies. At 2h, SumaRT/Nap pain free (PF) TG was 35% ($p \leq 0.001$; study 1 (S1); $n=576$) and 36% ($p \leq 0.001$; study 2 (S2); $n=535$). SumaRT/Nap was also statistically superior in PF rates compared to PBO at 30 min, 1, and 4h ($p \leq 0.05$) in both studies. SumaRT/Nap 2-24h sustained PF TGs were 45% and 40% in both studies resp. ($p \leq 0.001$). 86% of subjects (S1) and 78% (S2) who were PF at 2h maintained their PF status, without use of rescue medication, to 24h. Rescue medication use was significantly lower with SumaRT/Nap vs PBO (S1: 20% v 47%; $p \leq 0.001$; S2: 16% v 45%; $p \leq 0.001$). Incidence of IHS and non-IHS symptoms was lower at 2h for SumaRT/Nap vs PBO in both studies. Nausea was lower at 2h for SumaRT/Nap vs PBO (S1: 17% v 24%; $p \leq 0.05$; S2: 19% v 31%; $p \leq 0.001$); phonophobia (S1: 26% v 54%; $p \leq 0.001$; S2: 20% v 46%; $p \leq 0.001$); photophobia (S1: 31% v 57%; $p \leq 0.001$; S2: 22% v 55%; $p \leq 0.001$). Baseline neck pain/discomfort was 63% (SumaRT/Nap) and 58% (PBO) in S1 and 63% for both groups in S2. Neck pain/discomfort decreased significantly at 2h for SumaRT/Nap vs PBO (S1: 35% v 44%; $p \leq 0.001$; S2: 28% v 54%; $p \leq 0.001$). Baseline sinus pain/pressure was 43% (SumaRT/Nap) and 42% (PBO) in S1 and 52% and 46%, resp. in S2. Sinus pain/pressure significantly decreased at 2h for SumaRT/Nap vs PBO (S1: 19% v 33%; $p \leq 0.001$; S2: 23% v 38%; $p \leq 0.001$). SumaRT/Nap was well-tolerated vs PBO as evidenced by only nausea and dizziness reported in $\geq 2\%$ subjects (nausea: S1: 3% v 1%; S2: 4% v 2%; dizziness: S1: 1% v 0%; S2: 2% v $< 1\%$).

Conclusions: SumaRT/Nap provides effective pain free response at 2 hours which is maintained to 24 hours. SumaRT/Nap is the first migraine medication to demonstrate effective treatment of neck pain/discomfort associated with migraine. SumaRT/Nap is well-tolerated and effectively relieves pain and IHS and non-IHS symptoms, providing a more comprehensive migraine therapy for patients.

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Productivity and patient satisfaction benefits of a fixed single-tablet formulation of sumatriptan with RT Technology™ and naproxen sodium in an early intervention paradigm

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Objectives: To evaluate the effect of sumatriptan 85mg formulated with RT Technology™ and naproxen sodium 500mg, a fixed-dose, single-tablet formulation (SumaRT/NAP) vs. placebo (PBO) on productivity and patient satisfaction.

Background: Migraine is characterized by painful episodic headache often associated with functional impairment and lost productivity. Pharmacotherapy that concurrently targets serotonin dysmodulation and inflammation in migraine may deliver effective and sustained pain relief leading to reduced productivity loss and increased patient satisfaction.

Methods: Two identical randomized, double-blind, PBO-controlled, parallel group, single attack (treating within one hour of head pain onset and while pain is mild) multicenter-studies of adult migraineurs were conducted. The usual primary and key secondary endpoints (pain, associated symptoms, rescue medication use, etc.) and productivity and satisfaction were evaluated. Lost workplace productivity, lost activity time, and total productivity loss were assessed 24 hours post dosing. Satisfaction was assessed using the 32-item Patient Perception of Migraine Questionnaire – Revised (PPMQ-R) at baseline and 24 hours. PPMQ-R consists of 4 satisfaction subscales, a total satisfaction score, 3 global satisfaction items, and a “Tolerability” subscale assessing whether subjects were bothered by side effects. Scores range from 0 to 100 with higher scores reflecting more satisfaction or higher tolerability. A 5-point score difference is considered clinically relevant.

Conclusions: Treating a migraine attack early with SumaRT/NAP reduced productivity loss and improved satisfaction significantly compared to PBO. Patients reported high tolerability with taking SumaRT/NAP within one hour of head pain onset.

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Long-term Safety and Tolerability of a Fixed Single-Tablet Formulation of Sumatriptan RT Technology™ and Naproxen Sodium in the Acute Treatment of Migraine

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Objectives: Evaluate the safety and tolerability of sumatriptan 85mg formulated with RT Technology™ and naproxen sodium 500mg, a unique fixed-dose, single-tablet formulation (SumaRT/Nap) over 12 months.

Background: Pharmacotherapy that concurrently targets serotonin dysmodulation and inflammation in migraine may improve outcomes over monotherapy. A proof of concept study demonstrated that the combination of sumatriptan and naproxen sodium is more effective than components (Smith 2005); however, the long-term safety and tolerability of acute episodic use in migraine is unknown

Methods: Multicenter open-label study of SumaRT/Nap in migraineurs (18-65 years; ICHD-2 2004). FDA-required exposure to a new acute medication is 300 and 100 subjects for 6 and 12 months respectively. Therefore, > 600 subjects were screened with 1, 2, 3, 6, 9, 12 month visits. Subjects were required to treat ≥2 migraines per month to maintain eligibility and were allowed to take a 2nd dose, if needed. Data (clinical laboratory, physical exam, AEs) were collected by diary and at scheduled visits. Three populations (overall safety, 12-month and 6-month completer populations) are described.

Results: Overall, 565 subjects took 1 dose of SumaRT/Nap; 414 and 362 subjects completed 6- and 12-months treatment respectively, with significantly higher retention over 12 months than planned. Subjects were demographically similar to those in other migraine studies, i.e. migraine without aura (74%), Caucasian (92%) females (86%), ~44 years old, with 20 years of migraine. The overall safety population (> 1 dose of SumaRT/Nap) treated 24,485 attacks; 21,478, 12-month completers; 12,419, 6-month completers. In the 12-month completer population, subjects took study drug to treat a median of 5 migraines/month, 6 days between attacks. Subjects took a 2nd dose in 30% of attacks with no increase in AEs compared to 1 dose. At least 1 AE was reported by 66%, 55%, and 68% of subjects for overall, 6- and 12-month completers, resp. which were mostly mild/moderate; 8%, 3%, <1% withdrew due to an AE, resp. Most commonly reported AEs for 12-month completers were nasopharyngitis (13%), sinusitis (9%), upper respiratory tract infection (6%); most commonly reported AEs judged to be related and within 24 hours of treatment were nausea (4%), dizziness (3%), paresthesia (2%), muscle tightness (2%). 14 subjects reported at least one SAE; 1 was judged as probably related (acute coronary syndrome). Among 12-month completers, no clinically significant laboratory results occurred.

Conclusions: SumaRT/Nap which targets multiple mechanisms exhibits a consistent and uniform clinical safety/tolerability profile over 12 months. No significant trends in safety concerns were identified in this study. Acute episodic exposure over 12-months with SumaRT/Nap was well tolerated.

Superior Efficacy of Combination Therapy over Monotherapy: Results of a Fixed Single-Tablet Formulation of Sumatriptan RT Technology and Naproxen Sodium in the Acute Treatment of Migraine in the Traditional Treatment Paradigm

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Objectives: Evaluate the clinical efficacy and tolerability of sumatriptan 85mg formulated with RT Technology™(SumaRT) and naproxen sodium 500mg when given as a unique fixed single-tablet formulation (SumaRT/Nap) vs components.

Background: Pharmacotherapy that concurrently targets serotonin dysmodulation and inflammation in migraine may improve outcomes over monotherapy. A proof of concept study demonstrated that the combination of sumatriptan/naproxen sodium is more effective than components (Smith 2005).

Methods: Two identical randomized, double-blind, placebo-controlled, parallel group, single attack (moderate/severe) multicenter-studies of migraineurs (18-65 years; ICHD-2 2004) were randomized: SumaRT/Nap, sumatriptan 85mgRT (SumaRT), naproxen sodium 500mg (NAP), or placebo (pbo). Diary data were collected through 24h post-dose. Six FDA-required co-primary endpoints were evaluated (2h pain relief and associated symptoms, SumaRT/Nap v placebo; 2-24h sustained pain free (SPF) response SumaRT/Nap v components). Key secondary endpoints were evaluated statistically using a hierarchical step down method to control for multiplicity.

Results: Subjects enrolled in these 2 studies were demographically similar to other migraine studies, i.e., primarily Caucasian (88%) females (87%), about 40 years old, with 18 years of migraine. Efficacy: All comparisons displayed are statistically significant ($p < 0.01$). Study 1 (n=1470): SumaRT/Nap was more effective compared to SumaRT, NAP, and pbo for 2h pain relief (57%, 50%, 43%, 29%, resp.) and associated symptoms (except nausea), 2-24 h SPF (23%, 14%, 10%, 7%, resp.), 4h pain relief (72%, 62%, 53%, 37%, resp.), rescue medication use (23%, 38%, 39%, 58%, resp.). Study 2 (n=1441): SumaRT/Nap was more effective compared to SumaRT, NAP, or pbo for 2h pain relief (65%, 55%, 44%, 28%, resp.) and associated symptoms, 2-24 h SPF (25% v 16% v 10% vs 8%, resp.), 4h pain relief (78%, 66%, 55%, 37%, resp.), rescue medication use (22%, 32%, 38%, 53%, resp.). Pooled data for nausea indicate a statistically significant reduction with SumaRT/Nap compared to pbo by 2h through 24h. Data suggest increased clinical benefits when treating a moderate vs severe migraine (2h pain relief: study 1: 66% (MOD) vs 45% (SEV); study 2: 75% (MOD) vs 49% (SEV) for SumaRT/Nap). Safety: All treatments were well-tolerated and adverse event profile of SumaRT/Nap was similar to components.

Conclusions: SumaRT/Nap, which targets multiple mechanisms, demonstrates superiority for standard endpoints and sustained efficacy without a significant change in profile of adverse events, compared to monotherapy.

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Long-term clinical and patient-reported benefits of a fixed single-tablet formulation of sumatriptan with RT Technology™ and naproxen sodium in a moderate/severe treatment paradigm

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Objectives: To evaluate efficacy and patient-reported outcomes (PRO) of sumatriptan 85mg formulated with RT Technology™ and naproxen sodium 500mg, a unique fixed-dose, single-tablet formulation (SumaRT/NAP), over 12 months.

Background: Pharmacotherapy that concurrently targets serotonin dysmodulation and inflammation in migraine may improve clinical and patient-reported outcomes over monotherapy.

Methods: A multicenter open-label 12-month study of SumaRT/NAP for acute treatment of moderate/severe migraine with 2nd dose optional was conducted. Subjects recorded usual migraine symptoms in a diary. Patient satisfaction was measured using the 8-item Patient Perception of Migraine Questionnaire (PPMQ) at baseline, month 3, and month 12 or at early termination. Migraine related quality of life (QOL) was measured using the MSQ, version 2.1, at the same visits. The MSQ assesses Role-Function – Restrictive (RR), Role Function – Preventive (RP), and Emotional Function (EF) domains. Each domain is scored on a 0-100 point scale with higher scores indicating better QOL. Minimal clinically important differences for EF, RR, and RP are 5.76, 6.80, and 8.72 points, respectively. PRO are reported for subjects with follow-up assessments.

Results: Overall, 565 subjects took ≥ 1 dose of SumaRT/NAP; 414 and 362 subjects completed 6- and 12-months treatment respectively with similar demographics. Overall subjects treated 24,485 attacks; of these, 81% attacks achieved pain relief and 60% pain free by 2 hours. In the 12-month completer population, subjects took study drug to treat a median of 5 migraines/month, with 6 days between attacks. Subjects took a 2nd dose in 30% of attacks with no increase in AEs compared to 1 dose. The percentage of subjects satisfied/very satisfied increased on all 8 PPMQ items after 3 months of SumaRT/NAP therapy and remained high through 12 months. Importantly, the percent of subjects satisfied/very satisfied with how well SumaRT/NAP relieved migraine pain and associated symptoms increased from 54% at baseline to 89% and 86% at months 3 and 12, respectively. Mean RR (51 at baseline; 65 at months 3 and 12), RP (65 at baseline; 79 and 78 at months 3 and 12), and EF (58 at baseline; 73 and 72 at months 3 and 12) scores showed clinically relevant improvements by month 3 and remained high through 12 months.

Conclusions: SumaRT/NAP which targets multiple mechanisms of migraine provides consistent relief of migraine attacks over 12 months resulting in improved patient satisfaction and migraine-specific quality of life, two important outcomes of quality care.