DEBATE: THE ENDPOINTS USED IN HEADACHE DRUG TRIALS ARE CLINICALLY RELEVANT – NO

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Migraine is a common episodic brain disorder with protean manifestations including head or neck pain, aura symptoms, distortions of sensation and perception, impairments in cognition and affect, and/or disturbances of autonomic function. Any of these myriad migraine symptoms, either alone or in combination, may lead to significant patient disability and reduced global functioning. That is, the burden of migraine is typically not due to headache alone, and in some instances may not be due to headache at all. Accordingly, drug therapies developed for migraine treatment ought to be directed to relieving and/or preventing the multiple sources of disability and harm that are clinically relevant and meaningful to patients with the disorder.

However, clinical trials for acute and preventive therapies for migraine have historically included primary endpoints primarily or exclusively focused on the relief or freedom from *headache* frequency, severity, or duration. Patients have been polled repeatedly as to their preferences for ideal migraine drugs with such surveys consistently emphasizing questions about headache parameters. Unsurprisingly, results of these surveys show that complete (headache) pain relief, no pain recurrence, rapid onset of pain relief, and no drug side-effects are particularly sought-after acute migraine drug attributes. Consequently, for migraine studies focused on alleviating headache, the composite endpoints of "sustained pain-free" response from 2 to 24 hours (SPF) or SPF with no adverse events (SNAE) would seem to be more clinically relevant and preferable to previously employed endpoints (e.g. pain relief, or pain free). In practice, however, such controlled trials using these composite endpoints often yield a low percentage of successfully treated trial subjects necessitating large study enrollments to demonstrate statistically significant results versus placebo, which may not reflect an absolute risk reduction large enough to be clinically meaningful.

Recent United States Food and Drug Administration (FDA) registration trials for acute agents for migraine have sought to recognize and address migraine symptoms in addition to headache, including photophobia (light sensitivity), phonophobia (sound sensitivity), and nausea. A new standard has now been set by FDA for the approval of acute agents for migraine; a potential drug must now meet statistical significance for 4 co-primary endpoints (headache, photophobia, phonophobia, nausea) in pivotal trials to be considered migraine specific. This more stringent standard appears to be predicated on a mistaken assumption that these 4 classes of symptoms are nearly universally found in all migraine study subjects. In fact, by including all 4 classes in a combined primary endpoint, a significant new barrier has been created to drug approvals. Given the variability of symptoms across individuals with migraine, drug approvals ought to require the statistical significance of single primary endpoints.

Some recent clinical trials for acute migraine medications have also included single endpoints that incorporate multiple migraine symptom assessments in order to capture a more complete treatment of migraine attacks. Examples of these endpoints include (a) SPF response from 2 to 48 hours, (b) pain-free (PF) response at 2 hours with relief of nausea, photophobia, and phonophobia in subjects with these symptoms at baseline ("migraine-free"), and (c) "migraine-free" plus relief from sinus and neck pain at 2 hours in subjects with these additional symptoms at baseline. The migraine-free endpoint is particularly powerful statistically compared to 4 separate but co-primary endpoints since most migraine subjects do not report all these migraine symptoms and these symptoms are not necessarily independent. However, composite trial endpoints such are migraine-free have often been even

more challenging to meet in trials of recently studied acute migraine drugs than for the endpoint of SPF alone.

New primary endpoints are needed that align with an expanded diagnostic understanding of the disorder of migraine and better capture the diversity of migraine symptoms that lead to disability most meaningful to patients. Potential examples of such new primary endpoints addressing health-related quality of life in FDA sanctioned controlled trials of prophylactic migraine drugs might be the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36), Migraine Disability Assessment Score (MIDAS), Migraine-Specific Quality of Life Questionnaire (MSQ), measures of sustained concentration, and the impact of concurrent mood and anxiety (e.g. Patient Health Questionnaire (PHQ-4).

Development of drug clinical trial protocols and their analyses must also be based on an understanding that migraineurs are often more prone to treatment-related side effects and adverse events than are patients with other conditions who might use a similar drug (e.g. topiramate trials for migraine vs. epilepsy), perhaps due to the generalized hypersensitivity that is characteristic of the migraine brain state.

Finally, migraine is a disease with vulnerability that may last for decades, though it may take different forms at different ages. Therapeutic needs for migraine may change over time and research is lacking that addresses meaningful and sustained control of migraine from attack to attack and over decades. Currently, fewer than 30% of migraine patients receive consistent efficacy of acute therapies across multiple attacks of migraine.

In conclusion, the development of migraine drugs should be directed towards alleviating the symptoms that cause disability of greatest importance to patients. While currently available medications may meet trial endpoints reflecting a limited measure of migraine impact, they may not meet trial endpoints that are most meaningful to patients. Future migraine drug development should strive to successfully meet these needs.