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**Efficacy of almotriptan in early intervention for treatment of acute migraine in a primary care setting: the START\* study**

\* Standardized sTudy with Almotriptan in eaRly Treatment of migraine

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## Disclosures

MLM has received personal compensation for activities (consulting, clinical research) with Allergan, Almirall SAS, AstraZeneca Pharmaceuticals, Glaxo-Smith Kline Inc, Grunenthal, Eli Lilly & Company, Johnson & Johnson, Medtronic, Menarini, Merck, Pierre Fabre, Pfizer Inc, Sanofi-Aventis, UCB, Zambon.

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ML has received personal compensation for activities (consulting, clinical research) with Almirall SAS, Medtronic

**Abstract**

**Aims**

The benefits of taking almotriptan early for acute migraine when pain is mild have clearly been demonstrated in the neurology setting. The aim of this study was to determine whether similar benefits with early intervention of almotriptan can be achieved in everyday general practice, where most migraineurs are managed.

**Methods**

In this European, prospective, observational study, patients were asked to treat up to 3 migraine attacks over a 2-month period with almotriptan 12.5 mg administered within 1 hour of pain onset and when pain was mild ( early + mild intervention group).

**Results**

A total of 501 patients were enrolled in primary care centers across Spain, France and Italy. The intention-to-treat analysis involved 454 patients who reported 1174 migraine attacks, with early intervention being used in 138 of these attacks.

A greater proportion of patients who took almotriptan early + mild for their first migraine attack (n=42) were pain free at 2 hours compared with those in the non-early + mild intervention group (n=410) (62% vs 35%;  $p<0.001$ ). Similar results were obtained for all migraine attacks comparison (65% (n= 138) vs 38% (n= 1036);  $p<0.001$ ). Other secondary endpoints were also significantly in favour of early+mild treatment, including sustained pain free (SPF), SPF with no adverse events (SNAE), and time lost due to migraine (all  $p<0.001$ ). Almotriptan was well tolerated with no serious adverse events reported.

**Conclusions**

In the primary care setting, early intervention with almotriptan for treatment of migraine provides significant clinical benefits compared with delaying treatment and/or waiting until pain intensity has progressed beyond mild.

ClinicalTrials.gov number: NCT00725140

### What's known?

- In a randomized, placebo-controlled study, almotriptan 12.5 mg taken early for acute migraine, within 1 hour of pain onset and when pain was still mild, significantly improved outcomes in patients in a neurology setting
- However, most migraineurs are diagnosed and treated in the primary care setting

### What's new?

- The present study was undertaken to evaluate the benefits of almotriptan 12.5 mg taken early + mild for acute migraine (within 1 hour of onset and when pain is still mild) in patients in the primary care setting by employing an appropriate study design (observational) to make data applicable to everyday clinical practice
- Early + mild intervention with almotriptan 12.5 mg significantly improved outcomes in migraine patients in the primary care setting
- Greater effort is required to overcome the obstacles which prevent more patients taking their almotriptan early in an acute migraine attack when the pain is mild

**Introduction**

Migraine is a common, chronic and disabling neurovascular disorder. The World Health Organization (WHO) estimates that there are around 77 million migraine sufferers in Europe. It is ranked as the third most prevalent disease worldwide, after anaemia and hearing loss, and the large numbers of patients involved place an enormous burden on healthcare systems and society (1).

Triptans are the treatment of choice for most patients requiring specific therapy for acute migraine (2). In traditional clinical trials undertaken during the clinical development of triptans, migraine patients recruited in neurology clinics were instructed to initiate therapy when the severity of their headache pain was moderate to severe (3). Major reasons for this approach were to provide a higher baseline level of pain against which to measure change, to minimize the influence of a placebo response, and to allow patients to distinguish migraine from non-migraine headaches (e.g. tension-type headache) (3). However, recent data have demonstrated that migraineurs are able to accurately identify a migraine attack at onset, thus facilitating development of newer approaches to migraine management (4).

Indeed, a growing body of clinical experience and evidence demonstrates that early treatment of migraine with triptans results in significantly improved patient outcomes (5). The multicentre, multinational, double-blind, placebo-controlled Act when Mild (AwM) study showed that patients who took almotriptan 12.5 mg within 1 hour of migraine onset and while pain was still mild achieved statistically significant and clinically relevant improvement in outcomes compared with patients who delayed treatment until headache severity has progressed to moderate/severe (6).

An important aspect of the AwM study was that it was a placebo controlled clinical trial undertaken in a secondary care setting (neurology clinics) which make it very reliable, but also makes it difficult to extrapolate the results to everyday clinical practice. Most patients with migraine are diagnosed and treated in the primary care setting (7,8). Headache is the most common new neurological

symptom (9) and the most frequently reported pain symptom presented to a general practitioner (GP), and GPs are usually the only point of contact for the majority of migraineurs (10). For example, in the UK between 1992 and 2000, 4.4% of all GP consultations each year were for headache; yet only 2% of these patients were referred to a specialist (11). In the US, headache was found to be the primary reason for  $\geq 7\%$  of GP consultations (12). Similarly high consultation rates for migraine headache have been reported in German (13) and French (14) populations, and in the French survey only 18% of migraineurs were being medically followed for their headaches. Many patients who present to their GP with headache have a high level of disability which impacts on their quality of life (15) and, worryingly, only about half of those with migraine are diagnosed correctly (16). The difficulties in diagnosing and managing different types of headache were recently re-emphasized in a large survey of European physicians (17).

The European Medicines Agency (EMA) guidelines for studies investigating the acute treatment of migraine state that "migraine sufferers attending specialist clinics may not be representative of the larger number of patients seen by primary care physicians". The guidelines recommend that, while early migraine trials can be conducted in specialist centres, later studies should include patients from primary care with as few restrictions as possible (18).

A placebo arm is used in clinical studies as a comparator from which to assess a drug's relative efficacy. However, the placebo response can strongly influence how the results of a clinical trial are interpreted. This is particularly the case for diseases which have "more subjective" symptoms, such as pain, as an endpoint. The evolution of pain is based on the patients' interpretation and input, and not on specific disease measures such as (e.g.) blood glucose levels in patients with diabetes. The placebo response rate varies with the choice of study design, primary outcome measure, patient characteristics and the cultural setting in which the trial is conducted. In migraine trials, variable placebo response rates of up to 50% have been reported (19,20). Placebo has been shown to act on 5HT-dependent hormone secretion mimicking the effects of triptans (20). Furthermore,

placebo not only demonstrates an efficacy response in patients with migraine, it also has a ‘nocebo’ effect which is an association between placebo and adverse events (21). In migraine studies, adverse events have been reported in more than 30% of patients receiving placebo (22).

The purpose of the current study, Standardized study with Almotriptan in early Treatment of migraine (START), was to confirm the benefits of almotriptan taken early after pain onset (within 1 hour) and when pain is still mild, as was demonstrated in the randomized, placebo-controlled AwM clinical trial (6). This prospective study was undertaken in the primary care setting and employed an open-label, observational design to obviate the placebo effect and to make the results more relevant to real-life clinical practice.

**Methods**

This European, prospective, open-label, observational study was approved by the appropriate Ethics Committees and conducted in accordance of Good Clinical Practice guidelines (23) and the Declaration of Helsinki. The study was undertaken to determine the efficacy of early intervention with almotriptan 12.5 mg (within 1 hour of onset and when pain was still mild) for the treatment of acute migraine in everyday, primary care clinical practice.

**Patients**

Patients were recruited in primary care centers in Spain, France and Italy. Male and female subjects aged 18 to 65 years presenting with a diagnosis of migraine with or without aura, according to International Headache Society (IHS) diagnostic criteria, were enrolled into the study (24). Patients were required to provide written informed consent before they were allowed to participate in the study.

*Inclusion criteria:* Patients were required to have at least a 1-year history of migraine headache which progressed from mild to at least moderate intensity with a frequency of 2 to 6 attacks per month during the previous 3 months, and to

be able to distinguish migraine from other headaches. In addition, patients were required to be either currently using almotriptan 12.5 mg to treat their migraine attacks or to demonstrate at baseline that a change from their current treatment was required using, for this second possibility, the French National Agency for Accreditation and Evaluation in Health (ANAES) scale (8,25).

*Exclusion criteria:* Patients currently treating their migraine attacks with almotriptan 12.5 mg who demonstrated the need to change medication according to the ANAES scale were excluded from the study. Other exclusion criteria included contraindications to almotriptan following the approved and distributed to participants Summary of Product Characteristics document, or a history of discontinuing almotriptan; chronic daily headache; migraine frequency of more than 6 episodes per month during the last 3 months; headache predominantly occurring on waking; onset of migraine after the age of 50 years; plans to initiate non-pharmacological management during the study period; and pregnant or breastfeeding women.

In addition, overuse of the following medications was defined and prohibited: non-steroidal anti-inflammatory drug (NSAIDs; including acetylsalicylic acid > 325 mg/day), COX<sub>2</sub> inhibitors, acetaminophen, benzodiazepines (except for anxiolytic/hypnotic purposes), and anti-emetics for >3 days per week; opioids, ergotamine-related medications and triptans for >2 days per week.

### **Treatment and assessments**

All patients were assessed at baseline by their primary care physician. Eligible patients were provided with 3 almotriptan 12.5 mg tablets to treat up to 3 consecutive migraine attacks (1 tablet/ attack) during the subsequent 2-month period. Patients were asked to treat their migraine within 1 hour of pain onset and when pain was still mild (early intervention), and to record the characteristics of their migraine attack in a personal diary.

Concomitant use of migraine prophylactic treatment was permitted if the dose had been stable for 1 month prior to enrollment and remained stable throughout the duration of the study.

Rescue medication, if required, was preferably paracetamol (acetaminophen), an NSAID (including acetylsalicylic acid), or another drug deemed appropriate by the investigator and had to be reported. Use of ergotamine-related agents or triptans as rescue medication was not permitted. Patients were asked to delay the possible intake of rescue medication and any other medications (e.g. anti-emetic) until at least 2 hours after taking almotriptan 12.5 mg.

In order to assess the impact of basic patient education regarding early treatment of migraine, half of the centers in each country randomly received patient leaflets promoting the benefits of treating migraine early when the pain was still mild.

**Endpoints**

The primary endpoint of the study was the percentage of patients who were pain free at 2 hours after taking almotriptan 12.5 mg for their first migraine attack. Secondary endpoints included the percentage of patients pain free 2 hours after taking almotriptan 12.5 mg across all attacks, those achieving sustained pain free (SPF) status (pain free at 2 hours with no return of pain within 24 hours without the use of rescue medication), SPF with no adverse events (SNAE), relapse at 24 hours, use of rescue medication, evolution of migraine symptoms, duration of pain, functional disability (defined as time lost due to the migraine attack), tolerability, and the influence of an educational intervention regarding the early treatment of migraine.

**Statistical analyses**

Sample size calculations were based on the findings of the Act when Mild clinical trial which reported that 53.5% of patients treated early would be pain free at 2 hours (6). For the current trial it was estimated that to achieve the same endpoint

500 patients would provide a 95% power using a 2-sided test and a precision of 4.4%.

The safety analysis was undertaken in all patients included in the study who had taken at least one almotriptan tablet (this represented the safety population).

Analyses of primary and secondary endpoints were undertaken in the intention-to-treat (ITT) population which comprised patients in the safety population who had at least one measure of efficacy. Supportive analyses were also undertaken in the per-protocol (PP) population which comprised patients in the ITT population who did not violate the protocol.

The Chi-squared test with a significance level of 0.05 was used in bivariate analyses of categorical data. If conditions for application of the Chi-square were not fulfilled, the Fisher exact test was used.

For bivariate analyses of continuous data, the Student's t test or ANOVA was used to compare mean values. If the variable did not fulfill the normality hypothesis using the Kolmogorov-Smirnov normality test or through QQ plots of the residues, then the Mann-Whitney or Kruskal-Wallis tests were used.

Pearson's correlation coefficient was used to analyze the relationship between two quantitative variables except when the assumption of normality was not fulfilled, in which case the Spearman correlation coefficient was used.

**Results**

**Patients**

501 patients were enrolled into the study across 63 primary care centres in Spain (n=228), France (n=145) and Italy (n=128) between April 2008 and March 2009. The mean age of patients was 42 years; the majority were female (78%) and considered well educated with almost half (45%) having reached at least high school level education.

The study populations are defined in Figure 1. After excluding the 45 patients who reported not taking almotriptan during the study period, the safety population comprised 456 patients. A further 2 patients did not have adequate data available to assess efficacy and were excluded from the ITT analysis (n=454, 1147 attacks). 436 patients completed the study.

A total of 151 enrolled patients violated study protocol requirements in some manner, including some with more than one reason. Failure to comply with inclusion/exclusion criteria was documented in 74 patients: 32 with migraine frequency outside the defined range of 2–6 attacks per month during the previous 3 months; 26 who were initiated on almotriptan despite a baseline ANAES score indicating that a change in medication was not necessary; 17 with onset of migraine after the age of 50 years; and 5 outside the specified age range of 18 to 65 years. 86 patients took or overused medications that were either not permitted or had their use restricted during the study, including 65 patients who overused NSAIDs, acetaminophen, benzodiazepines and opioids. 74 patients failed to complete their personal migraine diaries correctly, including not noting pain intensity at 2 and at 24 hours or whether they had relapsed or used rescue medication within 24 hours. 15 patients were lost to follow up. The PP population thus consisted of 303 patients and 773 attacks.

**Efficacy**

As similar results for efficacy were obtained in both the ITT and PP analyses, data are presented for the ITT population, which is the approach that better reflects what occurs in everyday practice. Clinically meaningful differences between the two populations are detailed below.

Overall 86% of attacks were treated within 1 hour of migraine onset. However, only 9.3% (42/452) of first migraine attacks and 11.7% (138/1174) of all attacks during the study period were treated within 1 hour of onset and when the pain was still mild and thus represented the early intervention groups. For the remainder of attacks, the patient's had allowed the pain intensity to reach moderate (49%) or severe (25%) within 1 hour of onset before almotriptan treatment was taken or the attacks were treated more than 1 hour after pain onset, but when pain was still mild (1.3%) or had become moderate to severe (13.1%). These compromised the comparator non-early intervention group.

Analysis of the primary efficacy variable showed that 62% of patients who took almotriptan for their first migraine attack within 1 hour of onset and when pain was still mild were pain-free at 2 hours, compared with 35% of those in the non-early intervention group ( $p<0.001$ ; Figure 2). Similar results were found across all attacks, with 65% and 38% of patients, respectively, being pain free at 2 hours ( $p<0.001$ ; Figure 2).

#### *Sustained pain free with and without adverse events*

Across all attacks, significantly more patients who took their almotriptan early + mild achieved SPF status compared with those who did not (59% vs 33%;  $p<0.001$ ) (Figure 3). Likewise, significantly more patients in the early intervention group achieved SNAE status: 55% vs 31%;  $p<0.001$  (Figure 3).

#### *Use of rescue medication*

Only 15% of patient who took almotriptan early + mild required rescue medication compared with 27% ( $p=0.003$ ) of patients in the non-early intervention group.

*Duration of migraine and functional disability*

Early intervention with almotriptan significantly reduced the duration of migraine as well as time lost as a result of migraine. Across all attacks, migraine duration was 2 hours 10 minutes in the early intervention group, compared with 5:00 hours in the non-early intervention group ( $p<0.001$ ). Likewise, time lost due to migraine was 51 minutes and 1 hour 46 minutes, respectively, in these treatment groups ( $p<0.001$ ) (Figure 4).

*Relapse within 24 hours*

In the ITT population, no statistically significant differences were found in the number of patients who were pain free at 2 hours and who relapsed within 24 hours either for the first attack or across all attacks between early + mild and non-early + mild groups, although it should be noted that fewer patients in the non-early intervention group were pain free at two hours. Furthermore, analysis of this endpoint in the PP population showed a significant reduction in the number of relapses among patients in the early intervention group compared with patients in the non-early intervention group (5.9% vs 15.3%;  $p<0.041$ ).

*Migraine-associated symptoms*

Patients who treated their migraine early experienced significantly fewer migraine-associated symptoms at the time of treatment than those who delayed treatment, and this difference remained significant at 2 hours post-treatment for the symptoms of nausea, photophobia and phonophobia (Table 1).

*Educational intervention*

Approximately 40% of enrolled patients received educational leaflets promoting the benefits of early intervention for migraine. No significant differences were

found between 'educated' and 'non-educated' patients in terms of the numbers who took almotriptan within 1 hour of pain onset and when pain was still mild for at least one attack (19.9% vs 22.7%;  $p=NS$ ).

### Adverse events

A total of 65 treatment-emergent adverse events were reported during the study, none of which was serious or led to drug discontinuation. Only 2 adverse events were considered to be possibly related to study medication (1 case of dizziness and 1 case of tremor). Both of these were mild and resolved with no consequences. There were no statistically significant differences in the incidence and nature of adverse events between the early and non-early intervention groups ( $p=0.202$ ).

Discussion

In this European, prospective, observational study conducted in the primary care setting, early intervention with almotriptan 12.5 mg significantly improved clinical outcomes in patients with an acute migraine attack. A significantly greater proportion of patients who took almotriptan within 1 hour of migraine onset and when pain was still mild were pain free at 2 hours, achieved SPF status and SNAE status compared with patients who delayed treatment for more than 1 hour and/or waited until pain had progressed beyond mild. The early intervention group also achieved significantly greater reductions in the duration of their migraine attack and in time lost due to an attack. Furthermore, patients who took almotriptan early experienced significantly fewer migraine-associated symptoms immediately after treatment and this was maintained at 2 hours post dose for nausea, photophobia and phonophobia. Almotriptan was well tolerated in this study with no differences noted in either the type or number of adverse events associated with early intervention. The results of the START study indicate that early intervention with almotriptan is an effective therapeutic strategy for migraineurs who are managed in primary care facilities.

The START study was undertaken to ‘mirror’ the placebo-controlled AwM study previously conducted in neurology clinics (6), but with appropriate changes to the study design (i.e. open-label/observational) to ensure that findings were more applicable to everyday clinical practice. Both studies demonstrated significant improvements in outcomes when almotriptan was given early within 1 hour of migraine onset and when the pain was mild. However, the percentage of patients pain free at 2 hours was higher in migraineurs treated early when mild in the START study compared with a similar group treated early when mild in the AwM trial (65 vs. 53%). Likewise, the percentage of patients free from pain for 2-24 hours was higher in the early when mild treatment group in the START study compared with those in the AwM trial (59 vs. 46%). Although further studies are required to fully understand the physiological process behind this benefit, it is thought that early intervention

may help prevent the cascade of factors (vascular, neuronal, etc) that are responsible for the evolution of migraine.

Despite patients having been instructed to take their medication early (i.e. within 1 hour of migraine onset and when pain was still mild), only 9.3% (42/452) of first migraine attacks and 11.8% (138/1174) of all attacks during the study period were eligible for the early intervention analyses; this compares with 90% of patients who followed dosage instructions in the AwM study (6). Although 85% of migraine attacks in the present study were in fact treated within an hour of migraine onset, 74% of attacks had already progressed to moderate or severe intensity at the time of treatment. Similar findings were noted in the Almotriptan Time Versus Intensity Migraine Study (AIMS) which was designed to determine whether early treatment with almotriptan (within 1 hour of onset regardless of pain intensity) was superior to 'standard' treatment (treatment when pain intensity had reached moderate/severe) (26). In the AIMS study, pain intensity at time of treatment was mild in 17% of patients, moderate in 60% and severe in 23%. Likewise, a cohort study that set out to determine the evolution of migraine found that 48 to 60% of patients' with mild pain at onset progressed to moderate/severe pain within 1 hour and that 11-19% of patients already had moderate/severe pain at onset (27).

These data clearly highlight some of the practical difficulties encountered in day-to-day clinical practice, e.g. the 'time window' in which patients can take medication in order to achieve maximum benefit may be relatively short or patients may be 'caught out' without medication at hand. Based upon the results of this study and the AIMS study, there is evidence that the emphasis for patient treatment initiatives should be "treat as soon as you experience migraine pain/prodromal symptoms". Since migraineurs are generally able to accurately identify a migraine attack at onset (4) this would assist such an approach to migraine management.

It is acknowledged that, while the educational intervention used in the START study to inform patients about the benefits of early intervention in the treatment of migraine using hand-outs highlighting the benefits of early intake, was exploratory at best, it did highlight a number of issues. What are the obstacles to early intervention? Are patients reluctant to ‘waste’ treatment on a headache that may not be migraine or may turn out to be only mild? This shouldn’t be the reason, as patients have proven to be able to differentiate migraine from other headaches, and there is no such thing as “mild migraine”. When the cascade starts, it does not stop without treatment, and pain grows indefectibly until a later self resolution. Should the window of time when treatment is to be initiated be shortened further and/or further emphasized? Are there cost considerations? Should there be greater emphasis on physician education? Clearly, treatment of acute migraine attacks is complex where there may be a level of discordance between physicians and their patients in terms of expectations of therapy relative to efficacy, safety, costs, etc. What seems certain however, if we can increase the proportion of individuals who treat their disease when it is mild, we will decrease the overall burden of acute migraine attacks from a healthcare and societal perspective.

The major limitation of the current trial is its open, observational design, but this was intentional so as to better understand the benefits, limitations and difficulties with an early intervention strategy in everyday clinical practice.

In conclusion, the START study performed in a primary care setting confirmed the efficacy and safety of almotriptan taken early after migraine onset and when the pain was still mild, as was previously demonstrated in patients in the neurology setting (6). Further study needs to be dedicated towards identifying and overcoming the obstacles, real and perceived, which deter patients from taking their almotriptan early in order to gain maximum therapeutic benefit from this strategy.

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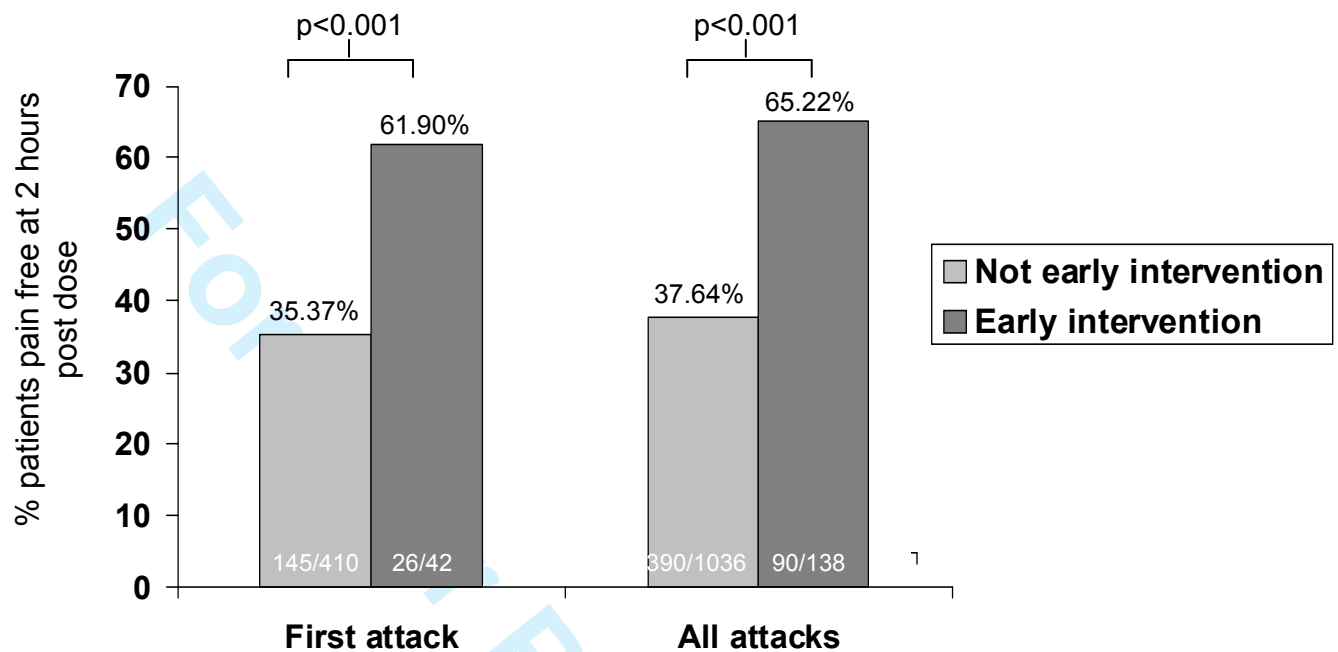
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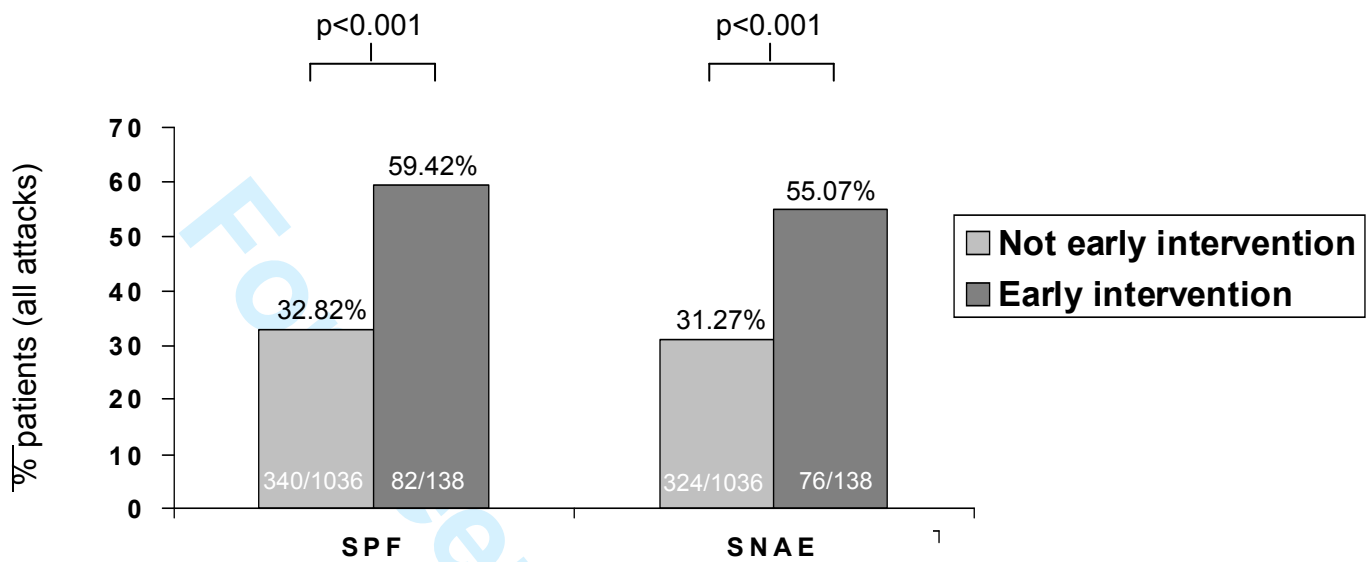
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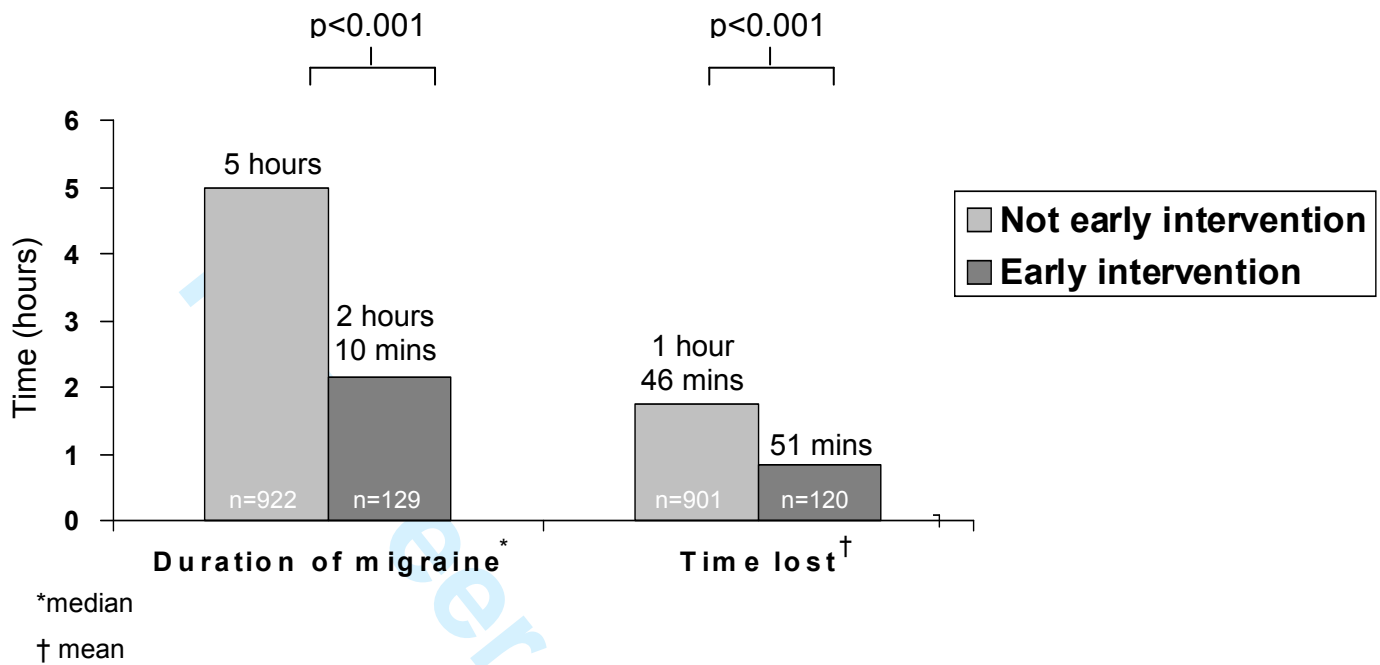
**Figure 2** Percentage of patients pain-free 2 hours after early + mild intervention with almotriptan 12.5 mg (within 1 hour of pain onset and when pain was still mild) compared with those who delayed treatment beyond 1 hour and/or until pain had progressed to moderate/severe (non-early + mild intervention).

\*\*\*p<0.001

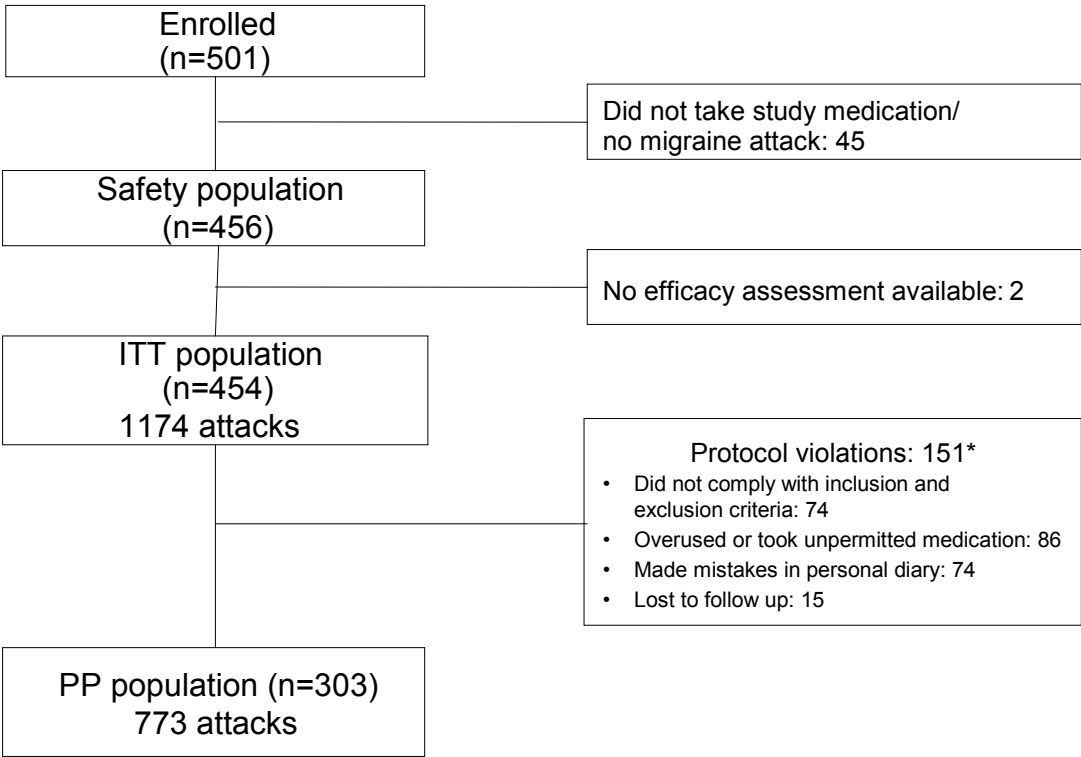


SPF: sustained pain free; SNAE: SPF with no adverse effects

**Figure 3** Percentage of patients who achieved sustained pain free status (SPF: pain free at 2 hours with no return of pain within 24 hours and without the use of rescue medication) and SNAE (SPF with no adverse events) status after early + mild intervention (within an hour of pain onset and when pain was still mild) and non-early + mild intervention (treatment delayed beyond 1 hour and/or until pain had progressed to moderate/severe) with almotriptan 12.5 mg. \*\*\*p<0.001



**Figure 4** Duration of migraine and time lost as a result of migraine between patients taking almotriptan 12.5 mg within 1 hour of onset and when pain was still mild (early + mild intervention) and those who did not (non-early + mild intervention). \*\*\* $p<0.001$



**Figure 1** Disposition of subjects

\* patients could have more than one protocol violation

**Table 1** Percentage of patients experiencing migraine-associated symptoms at baseline and at 2 hours post-dose across all attacks (n=1174 attacks).

Symptom	Early intervention*		Non-early intervention†		P-value
	Baseline*	2 hours	Baseline*	2 hours	
Nausea	31.4%	7.5%	45.5%	19.2%	P<0.001
Vomiting	2.2%	1.5%	9.7%	3.9%	P=0.218
Photophobia	34.3%	10.5%	51.0%	24.7%	P<0.001
Phonophobia	27.7%	10.5%	48.9%	23.5%	P<0.001

*Symbols:* \* Early intervention = patients who treated migraine with almotriptan 12.5 mg within 1 hour of onset and when pain was still mild. † Non-early intervention = patients who delayed treatment beyond 1 hour and/or pain had progressed to moderate/severe.