Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Brandes et al, 2009[104] **Study design:** RCT **Comparison:** Triptan vs Placebo **Setting:** NR (55 sites in Europe and North America) **Duration of follow-up:** 4 months	**Patient group:** Women ≥ 15 years of age with difficult to treat menstrual migraine (MM)*. **Inclusion criteria:** Women aged ≥ 15 years (in USA, France, Sweden and Finland) or ≥ 18 years (in Canada, Norway, Germany , Italy and the UK); had menses occurring at regular and predictable intervals; women using oral contraceptive pills were required to be on a stable regimen maintained for 2 months before screening; documented history of MM for ≥ 12 months and had MM in at least two of their previous three cycles; presence of difficult to treat MM defined as having previous exposure to non-triptan (acute and/or prophylactic) therapy for the treatment of MM and an inadequate response to triptan therapy (determined using Migraine Medication History Questionnaire) for the acute treatment of MM over a minimum of two menstrual cycles. *MM defined as migraine experienced with menstruation as well as at other times of the cycle (menstrually-related migraine), or pure MM in which migraine occurred only in association with menstruation on or between day -2 to day +3 of cycle, with day 1 counting as first day of menses. **Exclusion criteria:** Pregnant or breastfeeding women; had more than three migraines per month that were not MM attacks or ≥ 15 headache days per month; a history of myocardial infarction, heart disease, coronary vasospasm, peripheral vascular disease, uncontrolled hypertension or cerebrovascular disease (including basilar or hemiplegic migraine); severe renal or hepatic dysfunction or any serious illness that would interfere	**Group 1** - Frovatriptan 2.5 mg tablets once daily **Group 2 -** Frovatriptan 2.5 mg tablets twice daily **Group 3 -** Placebo (tablets) Patients randomised to treat three perimenstrual periods (PMP) over a 4 month period if they experienced MM in one of two single-blind run-in phases of two consecutive PMPs of 6 days which were treated with placebo. Medication commenced 2 days before anticipated onset of an MM and continued for 6 days. Both frovatriptan groups received loading dose of 5mg frovatriptan on day 1 of treatment; Group 2 received 5mg both in morning and evening and Group 1 received 5mg in the morning and placebo in the evening.	**Change in headache days** Total number of days with headache pain over a standardized 28-day cycle	**Group 1:** -0.4; n=149 **Group 2**: -0.5; n=101 **Group 3:** +0.5; n=160 **P value:** 2vs3, p=0.05	**Funding:** Vernalis Development Ltd, and Endo Pharmaceuticals Inc. **Limitations:** Frovatriptan also used as a rescue medication (may limit sensitivity of the study). Some patients inaccurately anticipated MM onset. 35% of patients in placebo group, 30% in the frovatriptan once daily group and 24% in the twice daily group were using oestrogen containing contraceptives. **Additional outcomes:** Time to first migraine. Incidence of intercurrent migraine. Ratio of severe to mild attacks. Ratio of severe vs mild functional impairment. Previous medication tried: Non triptan therapy (medications not
			Use of acute pharmacological treatment % of patients using rescue medication	**Group 1:** 67% (99/149) **Group 2:** 68% (68/101) **Group 3:** 86% (137/160)	
			Incidence of serious adverse events: Reported as severe adverse events	**Group 1:** NR **Group 2:** NR **Group 3:** 2 (inguinal hernia, prolonged chest discomfort for 8 days - Patient had taken frovatriptan as rescue medication 1 day before chest pain occurred)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	with study participation; or received any investigational medications (within 30 days or 5 half-lives);had a history of allergy to triptans; had participated in a previous trial of frovatriptan for the prevention of MM. **All patients** **N:** 587 (screened); 427 (randomised) **Average MM attacks over previous three cycles:** 2.9±0.4 **Group 1 Frovatriptan 2.5 mg once daily** **N:** 155 (randomised); 149 (mITT) **Age (mean, SD):** 37.8±7.9 **Drop outs:** 31(20%) **Group 2 Frovatriptan 2.5 mg twice daily** **N:** 104 (randomised); 101 (mITT) **Age (mean, SD):** 38.9±7.6 **Drop outs:** 24 (23%) **Group 3 Placebo** **N:** 168 (randomised); 160 (mITT) **Age (mean, SD):** 37.9±7.2 **Drop outs:** 23 (14%)	Additional open label frovatriptan 2.5mg tablets were provided (nine per cycle in a separate non-blinded container) for treatment of breakthrough MM and for non-menstrual (intercurrent) migraine.			specified). Triptans previously used: Almotriptan (19%), Eletriptan (24%), Frovatriptan (11%), Naratriptan(19%), Rizatriptan (36%), Sumatriptan (52%), Zolmitriptan (35%). **Notes:** Study was conducted among refractory patients and may not be generalisable to all. Includes pure menstrual and menstrually related migraine. The modified ITT population included all patients who received at least one dose of study medication and provided data for the primary efficacy end-point (number of headache free PMPs out of three treated PMPs).

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, mITT= modified Intention to treat analysis, PMP=Perimenstrual period, MM=Menstrual migraine

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Newman et al, 2001[587] **Study design:** RCT **Comparison:** Triptan vs Placebo **Setting:** Outpatient clinics (18 study sites in USA) **Duration of follow-up:** 4 months	**Patient group:** Adult females with history of migraine with/without aura. **Inclusion criteria:** Women > 18 years of age; at least 6 month history of migraine with/without aura as defined by IHS criteria; had regular menstrual cycles and could predict within 1 to 2 days the onset of menstrual flow; had at least 1 migraine attack during the last peri-menstrual period (PMP)* at a predictable time relative to the onset of menstrual flow. *PMP defines as beginning 2 days before the onset of menses and ending 4 days after the onset of menstrual flow (6 days in total). **Exclusion criteria:** 15 days or more of tension type headache or more than 6 migraines per month during either of the two months before screening; uncontrolled hypertension (diastolic blood pressure ≥95mmHg or systolic blood pressure≥160 mmHg); confirmed or suspected ischaemic heart disease, Prinzmetal angina, Raynaud syndrome; peripheral vascular, cardiovascular, or cerebrovascular disease, cardiac arrhythmias requiring medication; Basilar or hemiplegic migraine or evidence or history of abuse of alcohol or other drugs including ergotamine in the past year; history of epilepsy; contraindication to naratriptan; pregnant or breastfeeding, sexually active but not using contraception. **All patients** **N:** 372 (screened), 220 (enrolled), 206 (ITT), 171	**Group 1 - Naratriptan 2.5 mg twice daily orally** **Group 2 - Naratriptan 1 mg twice daily orally** **Group 3 - Placebo tablets twice daily orally** Baseline phase: Patients documented their headaches daily through the end of their next PMP in a diary. 2nd visit: Patients who documented a menstrually associated migraine (MAM) in baseline phase were randomised and given study medication for one PMP. Instructed to begin treatment 2 days prior to expected onset of MAM and continue for a total of 5 days. MAM was defined as migraine occurring within the perimenstrual period. Instructed not to use serotonin agonists or medications containing	**Change in patient reported headache intensity** Peak headache severity; on a 4-point scale :0=no pain to 3=severe pain; Reported for breakthrough MAMs in treated PMPs (Baseline and final values, mean) **Headache specific QOL** Migraine Specific Questionnaire **Incidence of serious adverse events**	**Group 1**: n=70 Baseline PMP: 2.3 Mean over 4 treated PMPs†: 2.3 **Group 2:** n=70 Baseline PMP: 2.3 Mean over 4 treated PMPs†: 2.1 **Group 3:** n=66 Baseline PMP: 2.2 Mean over 4 treated PMPs†: 2.2 No significant difference between groups **Group 1:** 0 n=71 **Group 2:** 0 n=71 **Group 3:** 0 n=68	**Funding:** Glaxo Wellcome Inc. **Limitations:** Unclear randomisation and allocation concealment. Difference in baseline characteristics. Difference in proportion of patients using concomitant long term prophylactic medication. Concomitant use of oral contraceptives 39% in Group 3, 35.7% in Group 2 and 38.5% in Group 1. Unclear if attacks of migraine occurred with aura. **Additional outcomes:** Number of MAMs that occurred over 4 PMPs. Number of MAM days over four PMPs. Total hours of migraine pain/symptoms per attack. **Previous medication tried:**

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	(completed study) **Drop outs**: 39 **Group 1Naratriptan 2.5 mg** **N:** 70 **Age (mean):** 36.3 **Drop outs:** 16 **Group 2 Naratriptan 1 mg** **N:** 70 **Age (mean):** 38.0 **Drop outs:** 10 **Group 3 Placebo** **N:** 66 **Age (mean):** 36.4 **Drop outs:** 13	ergotamine or ergot type medications 24 hours before or after using study medication 3rd visit: 1 to 7 days after treatment of first PMP; study medication given for next three PMPs; instructed to come to clinic after treatment of fourth PMP.			Chronic prophylactic medications (not specified) remained unchanged throughout study **Notes:** †Adjusted by the number of peri-menstrual days at risk 96 days per pmp) and standardised to four PMPs . Nb. Patients not diagnosed with menstrual or menstrually related migraine.

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, MAM= Menstrually associated migraine, PMP= Peri-menstrual period, IHS=International Headache Society

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Author & Year: Tuchman et al, 2008[807] **Study design:** RCT **Comparison:** Triptan vs Placebo **Setting:** NR (27 sites in the US) **Duration of follow-up:** 3 months	**Patient group:** Adult females with menstrual migraine (MM)* **Inclusion criteria:** Women aged ≥18 years who had regular menstrual periods; established diagnosis of menstrual migraine headache according to the IHS criteria; migraine attacks occurring during the defined time window in at least 75% of previous menstrual cycles; at least three menstrual migraine headaches of moderate or severe intensity within the previous three months; a history of 15 or fewer days of non-migraine headache per month; any preventative treatment of migraine was to be discontinued prior to study inclusion and randomisation, with a washout interval of at least five half lives of the longest acting agent. *MM defined as occurring exclusively within 2 days before the expected onset of menses through to the end of menses, but not at other times of the menstrual cycle. **Exclusion criteria:** Any medical or psychiatric condition that any interfere with data collection; a history of symptoms or of significant risk factors for cardiovascular disease; uncontrolled hypertension; a history of basilar, ophthalmoplegic or hemiplegic migraine; any serious neurological condition associated with headache; use of monoamine oxidase A inhibitors or treatment with SSRIs; pregnancy and lactation; history of poor compliance with treatment regimens. **All patients** **N:** 253 (randomised); 217 (completed study); 244 (ITT population, provided post treatment efficacy data) **Drop outs:** 36 **Group 1 Zolmitriptan 2.5 mg 3x/day** **N:** 85(randomised); 83 (ITT)	**Group 1 Zolmitriptan 2.5 mg 3x/day** **Group 2 Zolmitriptan 2.5 mg 2x/day and placebo tablet once daily** **Group 3 Placebo 3x/day** Patients were instructed to treat three consecutive menstrual cycles, starting treatment 2 days prior to expected onset of menses and continuing through to 5 days after the onset of menses (i.e. 7 days treatment in total) Use of escape medication was to be recorded in diary cards. It could be taken any time after the onset of breakthrough migraine	**Responder rate** % of patients achieving ≥50% reduction in frequency of MM attacks over three consecutive cycles	**Group 1:** 58.6% (49/83) **Group 2:** 54.7% (44/80) **Group 3:** 37.8% (31/81) **P values:** 1vs 3, p=0.0007 2vs 3, p=0.002	**Funding:** AstraZeneca, **Limitations:** Unclear allocation concealment and blinding of investigators. Study assumes that patients would not experience migraine attacks between menses and overlooks the fact that preventative therapy could delay attacks until after the treatment period. Some patients experienced aura with attacks (which does not fit IHS description of pure menstrual migraine). **Previous medication tried**: No patient was receiving preventative treatment for migraine prior to study inclusion and randomisation. **Notes:** Study was conducted in two phases; first phase evaluated the efficacy of
			Use of acute pharmacological treatment % of breakthrough attacks requiring use of escape medication	**Group 1:** 61.6% (77/125) **Group 2:** 60.7% (102/168) **Group 3:** 74.4% (154/207) **P values:** 1vs 3, p=0.0004 2vs 3, p=0.0055	
			Incidence of serious adverse events	**Group 1:** 2 **Group 2:** 2 **Group 3:** 1	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Age (mean, SD): 39.4 , 7.0 **Drop outs:** 13 **Group 2 Zolmitriptan 2.5 mg 2x/day** **N:** 83 (randomised); 80 (ITT) **Age (mean):** 38.1, 6.3 **Drop outs:** 10 **Group 3 Placebo 3x/day** **N:** 85 (randomised); 81 (ITT) **Age (mean):** 39.2, 6.3 **Drop outs:** 14				zolmitriptan in the treatment of acute menstrual migraine. Findings reported here are of the second phase. None of the serious adverse events were considered treatment related. NB. Pure menstrual migraine only

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard deviation, SE=Standard error, ITT=Intention to treat analysis, MM= Menstrual migraine, IHS=International Headache Society