2. SYNOPSIS

Name of Company: **I.R.I.S.** **6 place des Pléiades** **92415 Courbevoie – France**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product: **VASTAREL® 35 mg -**	**Volume:**	
Name of Active Ingredient: ***Trimetazidine MR 35mg***	**Page:**	

Title of study:

Study of the effect of trimetazidine MR 35 mg (2 tabs/day) on the emergence of choroidal neovascularisation in age-related macular degeneration. A multicenter, randomised, double-blind, placebo-controlled, phase III study in 1100 patients treated for 3 to 5 years – France DMLA 2 – Protocol No.: MC3 - 06790 - 001

Main Coordinator *:*

[redacted]

Coordinator in Belgium:

[redacted]

Coordinator in Spain:

[redacted]

Angiography Reading Committee

[redacted]

Monitoring Committee

[redacted]

Study centres:

417 centres of ophthalmology in 3 countries: 398 in France, 13 in Spain and 6 in Belgium.
324 active centres: 307 in France (1375 patients selected, 991 included), 11 in Spain (107 patients selected, 74 included) and 6 in Belgium (136 patients selected, 127 included)

Publication (reference):

Studied period: Initiation date: **19 March 1999**. Completion date: **31 October 2005**	**Phase of development of the study:** III

Objectives:

The primary objective was to study, using fluorescein retinal angiography, the effect of trimetazidine MR 35 mg on the emergence of, and time to emergence of, choroidal neovascularisation vessels in the studied eye, compared to baseline.

The secondary objectives were to determine by using fluorescein retinal angiography the effect of trimetazidine MR 35 mg on the occurrence of, and time to occurrence of, atrophy exceeding 1/3 of the papillary diameter in the studied eye, the evolution of the drusen and pigment epithelium lesions, the characterisation of the choroidal neovascularisation, and to evaluate the clinical acceptability of trimetazidine MR 35 mg.

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Methodology:

This multicenter, international, phase III study with randomised, double-blind, comparative design was implemented in 2 parallel groups, one receiving trimetazidine MR 35 mg and the other placebo (2 tabs/day).
1100 patients, aged 55 to 83 years, of Caucasian origin, and presenting with AMD characterised by neovascularisation lesions in one eye (the first eye) and serous drusen or lesions of the pigment epithelium in the contralateral eye (which was the only eye studied) were to be included.
After a treatment-free screening period of, at most, 3 months, during which a fluorescein retinal angiography was conducted and validated by the Reading Committee for enabling the patient's inclusion, the study treatment was allocated by randomisation with minimisation on 3 criteria: age, gender and type of AMD lesions in the studied eye.
The patients included in the study were to be followed up and treated for 3 to 5 years (i.e. until the end of the third year of follow-up for the last patient included) or until emergence of neovascularisation in the studied eye (validated by the Reading Committee). Follow-up visits were scheduled every 6 months and a contact by phone in the 2 months preceding each visit. Every year or in the event of exacerbation of the symptoms or in case of withdrawal, a fluorescein retinal angiography had to be conducted as per the angiography protocol defined and forwarded to the Reading Committee.

Number of participants:

Planned: 1100 (550 by treatment group)
Enrolled: 1618 – Selected: 1607
Included: 1192 (TMZ 35mg: 594; placebo: 598)
Safety Set: 1189 (TMZ 35mg: 593; placebo: 596)
FAS: 1086 (TMZ 35mg: 546; placebo: 540)

Diagnosis and main criteria for inclusion:

Selection criteria:

- male or female of Caucasian origin, aged 55 to 83 years (amendment No. 2),
- presenting with ocular media that are sufficiently clear to enable implementation of good quality angiography, and AMD characterized by:
  - for the first eye, neovascularisation lesions preferably discovered less than 12 months previously
  - and, in the contralateral eye, which was the eye under study:
    - either isolated serous drusen or drusen associated with other types of drusen or lesions of the pigment epithelium,
    - or isolated lesions of the pigment epithelium
      (for patients already having undergone laser phototherapy or radiotherapy on the first eye, the previous angiographic images were to be forwarded to the angiography Reading Committee in order to enable identification of the previous neovascularisation),
- after having been informed, to give informed consent in writing.

Angiographic criteria for patient inclusion: (double reading by Reading Committee using a predefined grading system)

- a good quality angiography with the required number of images,
- unilateral neovascularisation lesion of the first eye: neovascularisation vessels defined and/or occult or any other neovascular form as per the grading system defined,
- and on the eye under study:
  - at least 5 isolated serous drusen ($\varnothing > 63\ \mu$),
  - or at least 5 serous drusen ($\varnothing > 63\ \mu$) associated with other types of drusen or lesions of the PE,
  - or isolated lesions of the PE.

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Diagnosis and main criteria for inclusion: (cont'd)

Non selection criteria:

- Ophthalmologic criteria:
  - Allergic reaction during a previous fluorescein angiography;
  - Form of AMD not complying with the inclusion criteria, i.e. a study eye presenting with:
    - choroidal neovascularisation irrespective of type,
    - chorioretinal atrophy (of a dimension ˜ 1/3 of the papillary diameter),
    - detachment of the pigment epithelium (DPE),
    - subretinal material deposits suggesting the presence of pseudo-vitelliform dystrophy;
  - Dense cataract, corneal or vitreous opacity, etc.;
  - Inadequate pupil dilatation interfering with angiography;
  - Myopia of the eye under study greater than -6 diopters (measured with far-sight correction);
  - Diabetic retinopathy (irrespective of stage);
  - Optical neuropathy: recognized glaucomatous neuropathy, toxic or inflammatory neuropathy or other macular disease (clarified by amendment No. 2).
- Treatment-related criteria
  - Patient already treated with t rimetazidine 20 mg (Vastarel 20 m g) and whose treatment cannot be discontinued (a wash-out period of 15 days was required to enable patient inclusion in the study);
  - Patient receiving long-term treatment with potential retinal toxicity (clarified by amendment No. 2):
    - synthetic antimalarial,
    - tiliquinol, tilbroquinol (Intetrix®),
    - thioridazine (Melleril®) at a dose superior to 800 mg/day,
    - tamoxifen (Nolvadex®),
    - indometacin (Indocid®) at a dose superior to 150 mg/day.
  - Patient having undergone laser macular treatment on the eye under study.
- General criteria
  - Patient presenting with a serious life-threatening disease or disease liable to compromise follow-up to the end of the study;
  - Patient unlikely to be able to complete the study (moving house scheduled, etc.);
  - Serious heart, kidney or liver failure, serious respiratory insufficiency;
  - Patient presenting with vitamin A deficiency (malabsorption, etc.);
  - Patient unable to attend the various controls scheduled for the study;
  - Patient taking part in another study or having taken part in a clinical study in the month preceding the study;
  - Patient not having signed the informed consent form.

Study drug:

Trimetazidine MR 35 mg, 2 tablets daily
Batch No. (see appendix 16.1.6.1)

Reference product:

Placebo, 2 tablets daily
Batch No. (see appendix 16.1.6.1)

Duration of treatment:

Screening period: 3 months at most
Active treatment period: 3 to 5 years (*i.e.* 3 years after the last patient inclusion)

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Criteria for evaluation:

Primary efficacy criterion:
Incidence and time to occurrence of choroidal neovascularisation in the studied eye.

Secondary efficacy criteria:
- Occurrence and time to occurrence of an atrophy above 1/3 of the papillary diameter.
- Evolution of the serous drusen:
  - Changes between baseline and last follow-up in appearance of the serous drusen (highest grade present within the external circle and grade most frequently observed inside the external circle).
  - Changes between baseline and last follow-up in the maximum size of the serous drusen in the eye as a whole.
  - Changes between baseline and follow-up in the mean over all subfields of the number, size and density of serous drusen.
- Evolution of the area covered by the serous drusen in their main location.
- Evolution of the area of hypo- and hyperpigmentation.

Safety assessment criteria:
- Adverse events.
- Evolution of the optimal acuity with correction far and near in both eyes.
- Evolution of the intraocular pressure in both eyes.
- Occurrence of cataract or cataract extraction during the study period.

Statistical methods:

Analysis was a final analysis. Objectives were to demonstrate a difference between trimetazidine MR 35 mg and placebo. Tests were bilateral, the type I error α was set at 5% for all analyses.

Primary efficacy criterion: time to occurrence of choroidal neovascularisation was analysed on the FAS, as main analysis, and the Per Protocol Set 1 Year (PPS 1 Year), as sensitivity analysis.
The following tests were performed in both sets:
- as main analysis: a Cox semi-parametric regression model without adjustment for covariates;
- as sensitivity analyses: a Cox regression with adjustment on age classes and non-parametric comparisons using the non-stratified log-rank test and the log-rank test stratified on age classes.

Secondary efficacy criterion: were analysed on the FAS, as main analysis, and the Per Protocol Set 3 Years (PPS 3 Years) as sensitivity analysis.
Qualitative changes (occurrence, emergence) were analysed using a Chi-square test on the patients at risk and quantitative changes using the t-test as main analysis and the Wilcoxon's rank sum test as sensitivity analysis.
For time to occurrence of atrophy, the same tests as for the primary criterion were used

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SUMMARY – CONCLUSIONS

STUDY POPULATION AND OUTCOME

Disposition of patients and analysis sets

	Trimetazidine MR 35mg	**Placebo**	**Whole population**
Enrolled			**1618**
Selected			**1607**
Included (randomised)	**594**	**598**	**1192**
Lost to follow-up	**0**	**0**	**0**
Withdrawn	**135**	**164**	**299**
Due to adverse event	59	68	127
Due to lack of efficacy	2	1	3
Due to non medical reason	74	95	169
Completed with neovascularisation	**181**	**178**	**359**
Completed without neovascularisation	**278**	**256**	**534**
Safety Set	593 (99.8 %)	596 (99.7 %)	1189 (99.7 %)
Full Analysis Set	546 (91.9 %)	540 (90.3 %)	1086 (91.1 %)
PPS 1 Year	429 (72.2 %)	418 (69.9 %)	847 (71.1 %)
PPS 3 Years	268 (45.1 %)	246 (41.1 %)	514 (43.1 %)

%: % of Included Set

Main baseline characteristics in the FAS

		TMZ MR 35 mg (N = 546)	***Placebo (N = 540)***	***All FAS (N =1086)***
Age (years)	N	546	540	1086
	Mean ± SD	73.35 ± 5.66	73.73 ± 5.59	73.54 ± 5.63
	Median	74	74	74
	Min ; Max	54 ; 90	53 ; 84	53 ; 90
≤ 70 years	n (%)	147 (26.9 %)	144 (26.7 %)	291 (26.8 %)
>70 years	n (%)	399 (73.1 %)	396 (73.3 %)	795 (73.2 %)
≤ 75 years	n (%)	333 (61.0 %)	304 (56.3 %)	637 (58.7 %)
>75 years	n (%)	213 (39.0 %)	236 (43.7 %)	449 (41.3 %)
Sex	N	546	540	1086
Male	n (%)	210 (38.5 %)	206 (38.1 %)	416 (38.3 %)
Female	n (%)	336 (61.5 %)	334 (61.9 %)	670 (61.7 %)
Family history of AMD	N	546	540	1086
Yes	n (%)	64 (11.7 %)	63 (11.7 %)	127 (11.7 %)
Time since onset of neovascular complications in the first eye (months)	N	540	536	1076
	Mean ± SD	23.1 ± 29.0	22.8 ± 29.6	22.9 ± 29.3
	Min ; Max	2.2 ; 276.6	2.0 ; 323.7	2.0 ; 323.7
< 12 months	n (%)	264 (48.9 %)	262 (48.9 %)	526 (48.9 %)
[12 ; 36] months	n (%)	175 (32.4 %)	181 (33.8 %)	356 (33.1 %)
> 36 months	n (%)	101 (18.7 %)	93 (17.4 %)	194 (18.0 %)
OPHTHALMOLOGIC EXAMINATION: STUDIED EYE				
Optimal acuity with correction far	N	544	540	1084
[0/10 ; 2/10 [	n (%)	5 (0.9 %)	0 (0.0 %)	5 (0.5 %)
[2/10 ; 5/10 [	n (%)	41 (7.5 %)	38 (7.0 %)	79 (7.3 %)
≥ 5/10	n (%)	498 (91.5 %)	502 (93.0 %)	1000 (92.3 %)
Optimal acuity with correction near (Parinaud scale – French patients)	N	460	438	898
P1 to P3	n (%)	435 (94.6 %)	421 (96.1 %)	856 (95.3 %)
P4 to P9	n (%)	24 (5.2 %)	17 (3.9 %)	41 (4.6 %)
P10 to P20	n (%)	1 (0.2 %)	0 (0.0 %)	1 (0.1 %)

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STUDY POPULATION AND OUTCOME (CONT'D)

Risks factors at inclusion in the FAS

		TMZ MR 35 mg (N = 546)	***Placebo (N = 540)***	***All FAS (N =1086)***
At least one risk factor (“smoker” and/or “frequent exposure to the sun” and/or “at least one cardiovascular risk factor”)	n (%)	428 (78.4 %)	418 (77.4 %)	846 (77.9 %)
Smoker	n (%)	70 (12.8 %)	52 (9.6 %)	122 (11.2 %)
Frequent exposure to the sun	n (%)	122 (22.3 %)	126 (23.3 %)	248 (22.8 %)
At least one cardiovascular risk factor	n (%)	318 (58.2 %)	319 (59.1 %)	637 (58.7 %)
Diabetes	n (%)	47 (8.6 %)	43 (8.0 %)	90 (8.3 %)
Hypertension	n (%)	283 (51.8 %)	270 (50.0 %)	553 (50.9 %)
Angina pectoris	n (%)	58 (10.6 %)	56 (10.4 %)	114 (10.5 %)
Myocardial infarction	n (%)	29 (5.3 %)	29 (5.4 %)	58 (5.3 %)
Cerebrovascular accident	n (%)	22 (4.0 %)	19 (3.5 %)	41 (3.8 %)

Retinal lesions in the studied eye on inclusion angiography in the FAS

		TMZ MR 35 mg	***Placebo***	***All FAS***
Area covered by serous drusen in their main location	N	546	539	1085
Serous drusen absent	n (%)	35 (6.4 %)	33 (6.1 %)	68 (6.3 %)
Less than 10%	n (%)	118 (21.6 %)	96 (17.8 %)	214 (19.7 %)
Between 10 and 25%	n (%)	146 (26.7 %)	170 (31.5 %)	316 (29.1 %)
Between 25 and 50%	n (%)	146 (26.7 %)	137 (25.4 %)	283 (26.1 %)
More than 50%	n (%)	101 (18.5 %)	103 (19.1 %)	204 (18.8 %)
Highest grade of drusen within the external circle	N	544	540	1084
Moderate dimensions	n (%)	46 (8.5 %)	50 (9.3 %)	96 (8.9 %)
Large dimensions	n (%)	463 (85.1 %)	457 (84.6 %)	920 (84.9 %)
Grade of drusen most frequent inside external circle	N	544	540	1084
Moderate dimensions	n (%)	170 (31.3 %)	179 (33.1 %)	349 (32.2 %)
Large dimensions with blurred margins	n (%)	339 (62.3 %)	328 (60.7 %)	667 (61.5 %)
Mean number of drusen in the eye as a whole	N	535	532	1067
	Mean ± SD	5.94 ± 3.94	6.07 ± 3.93	6.01 ± 3.93
	Min ; Max	0.0 ; 22.8	0.0 ; 19.4	0.0 ; 22.8
Mean size of drusen in the eye as a whole	N	500	499	999
Eyes without drusen excluded	Mean ± SD	113.16 ± 56.81	113.01 ± 56.19	113.09 ± 56.47
	Min ; Max	14.0 ; 251.0	7.0 ; 251.0	7.0 ; 251.0
Maximum size of drusen in the eye as a whole	N	535	532	1067
> 250 microns	n (%)	243 (45.4 %)	242 (45.5 %)	485 (45.5 %)
Mean score of density of the serous drusen	N	535	532	1067
	Mean ± SD	1.935 ± 1.169	1.950 ± 1.158	1.942 ± 1.163
	Min ; Max	0.00 ; 5.00	0.00 ; 5.00	0.00 ; 5.00
Hyperpigmentation	N	539	535	1074
Area greater than 63 microns	n (%)	286 (53.1 %)	293 (54.8 %)	579 (53.9 %)
Hypopigmentation	N	537	528	1065
Area greater than 63 microns	n (%)	237 (44.1 %)	229 (43.4 %)	466 (43.8 %)
Hyperpigmentation AND Hypopigmentation	N	534	527	1061
Yes	n (%)	226 (42.3 %)	221 (41.9 %)	447 (42.1 %)
Hyperpigmentation OR Hypopigmentation	N	542	536	1078
Yes	n (%)	302 (55.7 %)	305 (56.9 %)	607 (56.3 %)
Main hypo/hyperpigmentation sites	N	302	305	607
In the intermediate field	n (%)	255 (84.4 %)	253 (83.0 %)	508 (83.7 %)
In the central field	n (%)	38 (12.6 %)	42 (13.8 %)	80 (13.2 %)
TYPE OF LESIONS ON THE STUDIED EYE	N	546	540	1086
≥ 5 isolated serous drusen	n (%)	241 (44.1 %)	232 (43.0 %)	473 (43.6 %)
≥ 5 serous drusen with other drusen or PE lesions	n (%)	270 (49.5 %)	275 (50.9 %)	545 (50.2 %)
Isolated lesions of the PE	n (%)	35 (6.4 %)	33 (6.1 %)	68 (6.3 %)

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STUDY POPULATION AND OUTCOME (CONT'D)

Comparability of both treatment groups

No clinically relevant between-group difference was observed:

- for demographic data and main baseline characteristics, in particular for risk factors and retinal lesions in the studied eye, in the Included Set, FAS, PPS 1 Year and PPS 3 Years.
- for the mean treatment duration in the Included Set (trimetazidine MR 35 mg: 36 ± 18 months; placebo: 34 ± 18 months), FAS (trimetazidine MR 35 mg: 38 ± 16 months; placebo: 37 ± 16 months), PPS 1 Year (trimetazidine MR 35 mg: 42 ± 14 months; placebo: 40 ± 14 months) and PPS 3 Years (trimetazidine MR 35 mg: 50 ± 9 months; placebo: 49 ± 9 months).

The treatment compliance was similar in both groups in these four analysis sets. More than 90% of the patients were compliant (compliance between 70% and 130%) in the Included Set (trimetazidine MR 35 mg: 95.4% of the patients; placebo: 94.0%) and in the FAS (trimetazidine MR 35 mg: 97.8 % of the patients; placebo: 96.3 %).
The two groups were considered comparable for baseline characteristics and study participation.

EFFICACY RESULTS

Primary assessment criterion

Incidence of choroidal neovascularisation in the FAS - Comparison between groups

		TMZ MR 35 mg (N = 546)	***Placebo (N = 540)***
Exposed patients	N	546	540
Events	N (%)	181 (33.2%)	177 (32.8%)
Exposed patient-years	N	1666.7	1590.1
Incidence per 100 patient-years	N	10.86	11.13
Cox's prop. Hazard model	E (SE) (1) 95% CI (2) p-value (3)	0.971 (0.103) [0.789 ; 1.195] p = 0.781	
Logrank test	p-value	p = 0.781	
Cox's prop. Hazard model adjusted on age classes (≤ 70y/>70y)	E (SE) (1) 95% CI (2) p-value (3)	0.970 (0.103) [0.789 ; 1.194] p = 0.775	
Logrank test stratified by age classes (≥ 70 years/>70 years)	p-value	p = 0.782	

(1) Estimate (standard error) of the hazard ratio between groups : TMZ MR 35 mg / Placebo
(2) 95 % confidence interval of the hazard ratio estimate
(3) p-value of the likelihood ratio test

No between-group difference in the time to occurrence of choroidal neovascularisation was evidenced, whatever the model and the test used, in the FAS (Table above) and PPS 1 Year (without adjustment: Cox's model: p=0.526 and Logrank test: p=0.525; with adjustment on age classes: Cox's model: p=0.521 and Logrank test: p=0.521). Similar results were obtained for visible neovascularisation and occult neovascularisation in the FAS and PPS 1 Year.

Secondary assessment criterion: atrophy above 1/3 of the papillary diameter

Occurrence of atrophy above one third of the papillary diameter was observed less often in the trimetazidine MR 35 mg-treated patients than in the placebo group in the FAS (trimetazidine MR 35 mg: 14.7% of the patients; placebo: 17.5%) and the PPS 3 Years (trimetazidine MR 35 mg: 17.8%; placebo: 21.5%), but the between-group differences were not statistically significant (FAS: p=0.210; PPS 3 Years: p=0.297).
Analysis of the time to occurrence of atrophy in the FAS by a survival analysis evidenced a between group difference close to the significance whatever the model and the test used (Table below) in favour of an incidence of atrophy during the whole study period lower in the trimetazidine MR 35 mg group than in the placebo group with a hazard ratio between groups of 0.756.

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EFFICACY RESULTS (CONT'D)

Incidence of atrophy above 1/3 of the papillary diameter in the FAS - Comparison between groups

		TMZ MR 35 mg (N = 546)	***Placebo (N = 540)***
Exposed patients	N	530	530
Events	N (%)	78 (14.7%)	93 (17.5%)
Exposed patient-years	N	1527.6	1442.8
Incidence per 100 patient-years	N	5.11	6.45
Cox's prop. Hazard model	E (SE) (1)	0.756 (0.116)	
	95% CI (2)	[0.559 ; 1.022]	
	p-value (3)	0.069	
Logrank test	p-value	0.068	
Cox's prop. Hazard model adjusted on age classes (≤ 70y/>70y)	E (SE) (1)	0.756 (0.116)	
	95% CI (2)	[0.559 ; 1.022]	
	p-value (3)	0.069	
Logrank test stratified by age classes (≥ 70 years/>70 years)	p-value	0.069	

(1) Estimate (standard error) of the hazard ratio between groups : TMZ MR 35 mg / Placebo
(2) 95 % confidence interval of the hazard ratio estimate
(3) p-value of the likelihood ratio test

Similar results in favour of an effect of trimetazidine MR 35 mg on atrophy were showed in the FAS for the age class "≤ 75 years", the male patients, the subgroup of patients with isolated PE lesions at baseline, the subgroup of patients whose duration of neovascularisation in the first eye was between 12 and 36 months at baseline, and for the subgroups of patients with risk factors of atrophy (Table below).

Incidence of atrophy in the FAS subgroups of patients with risk factors of atrophy

		TMZ MR 35 mg (N = 546)	***Placebo (N = 540)***	***p-value***
Hypopigmentation > 63µ at baseline	N	231	223	
% of occurrence		24.2%	34.1%	**p=0.020**
Incidence per 100 patient-years		9.73	14.86	
Hazard ratio [95% CI]		0.636 [0.450 ; 0.898]		**p=0.010**
Hyperpigmentation > 63µ at baseline	N	277	286	
% of occurrence		23.5%	30.1%	p=0.077
Incidence per 100 patient-years		9.18	12.56	
Hazard ratio [95% CI]		0.719 [0.521 ; 0.993]		**p=0.044**
Hypopigmentation or hyperpigmentation > 63µ at baseline	N	293	298	
% of occurrence		22.9%	28.9%	p=0.096
Incidence per 100 patient-years		8.96	11.96	
Hazard ratio [95% CI]		0.732 [0.532 ; 1.008]		p=0.055
Serous drusen associated with PE lesions or other drusen and area covered by serous drusen > 25%	N	137	130	
% of occurrence		20.4%	30.8%	p=0.053
Incidence per 100 patient-years		8.23	13.71	
Hazard ratio [95% CI]		0.598 [0.368 ; 0.970]		**p=0.035**
Hypopigmentation > 63µ at baseline and area covered by serous drusen > 25%	N	101	88	
% of occurrence		20.8%	39.8%	**p=0.004**
Incidence per 100 patient-years		8.52	18.91	
Hazard ratio [95% CI]		0.450 [0.261 ; 0.776]		**p=0.003**
Hyperpigmentation > 63µ at baseline and area covered by serous drusen > 25%	N	129	126	
% of occurrence		21.7%	31.7%	p=0.070
Incidence per 100 patient-years		8.71	14.06	
Hazard ratio [95% CI]		0.633 [0.389 ; 1.029]		p=0.063

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SAFETY RESULTS

Adverse events

Clinical safety results are summarised in the table below.

		TMZ MR 35 mg (N = 593)	***Placebo (N = 596)***
Participants having reported			
at least one adverse event	n (%)	466 (78.6%)	482 (80.9%)
at least one emergent adverse event	n (%)	447 (75.4%)	471 (79.0%)
at least one treatment-related emergent adverse event	n (%)	18 (3.0%)	24 (4.0%)
Participants having experienced			
at least one SAE (including death) during study period	n (%)	211 (35.6%)	204 (34.2%)
at least one emergent SAE (including death)	n (%)	204 (34.4%)	199 (33.4%)
at least one treatment-related SAE	n (%)	1 (0.2%)	2 (0.3%)
Participants withdrawn due to an emergent adverse event	n (%)	47 (7.9%)	56 (9.4%)
Participants who died			
during the study period	n (%)	31 (5.2%)	32 (5.4%)
during the treatment period (fatal emergent SAE)	n (%)	31 (5.2%)	28 (4.7%)
Treatment-related death	n (%)	0 (0.0%)	1 (0.2%)

The most frequently system organ class affected by emergent adverse e vents was "Eye dis orders" (trimetazidine MR 35 mg: 24.6%, placebo: 23.2%). They were mainly composed of adverse events related either to the t reated disease and its com plications or with ocular diseases that were frequent in t he target population (cataract: trimetazidine MR 35 mg: 4.7%, placebo: 3.0%). Analysis of cases of cataract and cataract extraction showed that the appearance of cataract, requiring or not its extraction, as well as cataract extractions in patients with cataract before inclusion, were as f requent in the trimetazidine MR 35 mg group as i n the placebo group.

The most common treatm ent-related emergent adverse events were gastrointestinal disorders. They were observed in 1.3% of the trimetazidine MR 35 mg-treated patients (8 patients having reported 8 adverse events: 4 cases of dyspepsia, 2 cases of gastrointestinal disorder, 1 case of gastrointestinal pain and 1 case of oesophagitis, which required an hospitalisation) and 2.0% of the patients in the placebo group (12 patients having reported 13 adverse events: 4 cases of gastrointestinal disorder, 2 cases of abdominal pain upper, 2 cases of gastric disorder, 2 cases of nausea, 2 cases of diarrhoea and 1 case of dyspepsia).

Serious adverse events were mainly surgical pr ocedures (7.4% in each group), cardiac disorders (trimetazidine MR 3 mg: 5.6%, placebo: 6.4%) a nd malignant diseases (trimetazidine MR 35 mg: 5.6%, placebo: 5.4%) and the first two ca uses of death, cardiac disorders (trimetazidine MR 35 mg: 1.3%, placebo: 1.5%) and malignant diseases (trimetazidine MR 35 mg: 1.3%, placebo: 1.2%).

Only 3 serious adverse events were related to study medication by investigators: 1 case of oesophagitis, which required an hospitalisation in the trimetazidine MR 35 mg group, and in the placebo group, 1 case of epistaxis, who was hospitalised, and 1 case of unexplained death.

After the occurrence of cardiovascular accidents or malignant diseases, the most common cause of treatment withdrawals for adverse events was gastrointestinal disorders (5 trimetazidine MR 35 mg-treated patients: 0.8%, and 12 patients under placebo: 2.0%).

Parkinson's disease occurred in 2 patients under trimetazidine MR 35 mg (0.3%) and 8 patients in the placebo group (1.3%). None of these events was considered as treatment- related by investigator.

No relevant difference between both groups was observed for frequency, nature, intensity, causality, outcome and seriousness of adverse events, except for arterial hypertension and cardiac disorders that were less frequent in the trimetazidine MR 35 mg group than in the placebo group.

Name of Company: **I.R.I.S.** **6 place des Pléiades** **92415 Courbevoie – France**	**Individual Study Table Referring to Part of the Dossier**	*(For National Authority Use only)*
Name of Finished Product: **VASTAREL® 35 mg -**	**Volume:**	
Name of Active Ingredient: ***Trimetazidine MR 35mg***	**Page:**	

SAFETY RESULTS (CONT'D)

Other safety evaluations

Evolution of visual acuity with correction far or near in the studied eye and in the first eye was not clinically different between both groups. The mean intra-ocular pressure remained stable between baseline and last follow-up in both groups.

CONCLUSION

Under the conditions of this study in which the effects of trimetazidine MR 35 mg on the progression of the AMD lesions were evaluated under double-blind versus placebo in 1192 patients presenting with AMD, characterised by neovascularisation lesions in one eye and serous drusen or lesions of the pigment epithelium in the contralateral eye, an effect of trimetazidine MR 35 mg was demonstrated on the occurrence of atrophy above one third of the papillary diameter. This effect was particularly marked for patients having risk factors of atrophy (hypopigmentation, hyperpigmentation, area covered by serous drusen greater than 25% at baseline).

No significant between group difference was showed for the time to occurrence of choroidal neovascularisation or for the evolution of serous drusen and pigment lesions.

The excellent acceptability of trimetazidine MR 35 mg in elderly was confirmed in this long term study. No relevant difference between both groups was observed for frequency, nature, intensity and causality of the reported adverse events, except for arterial hypertension and cardiac disorders that were less frequent under trimetazidine MR 35 mg than in the placebo group.

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