Good cardiac safety in patients with relapsing remitting multiple sclerosis upon first fingolimod dose

Volker Limmroth[1], Susanne Hoyer[2], Stephan Schmidt[3], Michael Lang[4], Tjalf Ziemssen[5]

[1] Neurologische Klinik, Kliniken der Stadt Köln, Cologne, Germany; [2] Novartis Pharma GmbH, Nuremberg, Germany; [3] NTD Study Group, Neurologische Gemeinschaftspraxis, Bonn, Germany; [4] NTD Study Group, Neurologische Praxis, Ulm, Germany; [5] Neurologische Klinik, Universität Dresden, Dresden, Germany

Conclusion

- 99.5 % of patients were discharged ≤ 8 hours after the first dose of fingolimod
- 99.3 % of patients had no bradycardia (< 45bpm), 100% of patients had no QTcF-interval prolongation (≥ 500 msec), 98.4 % of patients had no AV Block II^0 or higher after the first dose of fingolimod
- No patient had bradycardia, QTcF-interval prolongation and/or AV block II^0 or higher approx. 7 days after treatment initiation

Introduction

- Once daily oral fingolimod (FTY720; Gilenya®, Novartis Pharma AG), a sphingosine 1-phosphate receptor (S1PR) modulator, is approved for the treatment of relapsing multiple sclerosis and more than 91,500 patients have been treated with fingolimod in both the clinical trial and post-marketing settings; total patient exposure now exceeds 135,800 patient years.[a]
- Following treatment initiation, fingolimod activates sphingosine-1-phosphate receptors at the surface of cardiac myocytes, resulting in a transient pulse rate reduction and in rare cases in atrioventricular conduction delays.[1–4]
- The objective of this study is to obtain a more precise understanding of the nature and frequency of cardiac-associated events after treatment initiation of fingolimod.

Methods

- The START study is a prospective, 1-week, multicenter, open-label study enrolling up to 7,000 RRMS patients in more than 250 centers in Germany, according to the EU label criteria of fingolimod.
- The study consists of a screening period, a baseline visit during which the first fingolimod dose is taken, and a final visit after one week.
- The procedure at baseline is as follows: prior to the first intake of fingolimod, a 12-lead ECG is recorded. After the first dose, a continuous 6h Holter ECG is carried out, while pulse and blood pressure are measured simultaneously, every hour. A final 12-lead ECG is performed afterwards.
- The recorded data is analysed centrally by cardiologists for various conduction disorders and cardiac adverse events.

Results

- This second START interims-analysis is based on 1,230 patients for most analyses.

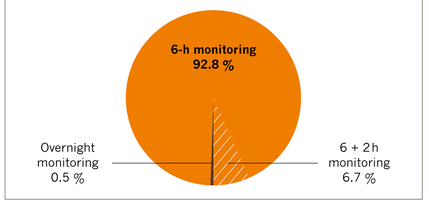
Table 1: Patient population of the START study

			Total (N = 1230)
Age [years]		Mean (± SD)	38.9 (± 10.3)
		Median (Q75)	39.0 (47.0)
		Max	73
Sex	Male	n (%)	370 (30.1 %)
	Female	n (%)	860 (69.9 %)
Race	Caucasian	n (%)	1,164 (94.6 %)
	Black	n (%)	6 (0.5 %)
	Asian	n (%)	7 (0.6 %)
	Native american	n (%)	1 (0.1 %)
	Pacific islander	n (%)	1 (0.1 %)
	Other	n (%)	51 (4.1 %)
EDSS		Mean (± SD)	2.8 ± 1.6
		Median (Q75)	2.5 (3.5)
		Max	8.0

Table 2: Duration of observation after treatment initiation

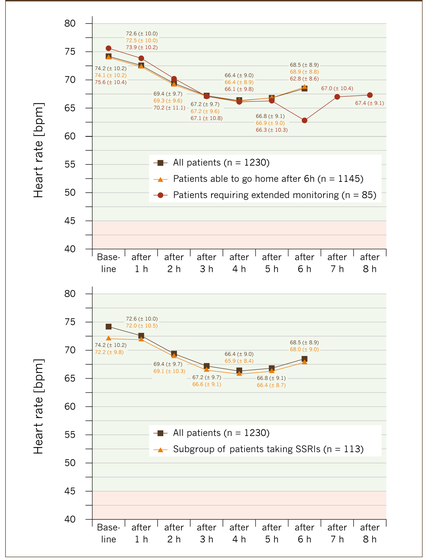
normal 6 h monitoring; n [%]	extended monitoring: 6 + 2 h monitoring; n [%]	overnight monitoring n [%]
1,142 (92.8 %)	82 (6.7 %)	6 (0.5 %)

Figure 1: Duration of observation after treatment initiation



- **99.5 %** of patients were discharged ≤ 8 h after the first dose of fingolimod (Table 2 and Figure 1)

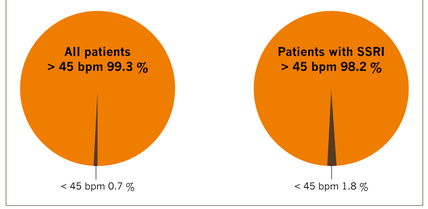
Figure 2 + 3: Heart rate on the day of treatment initiation



- The mean maximum reduction in heart rate was 11.7 (± 8.3) beats per minute (bpm) (Figure 2)
- The lowest heart rate is reached after 4.1 (± 1.3) hours (Figure 2)
- Within the first 6 hours the heart rate returned to 93 % (± 11.4 %) of the baseline level (Figure 2)

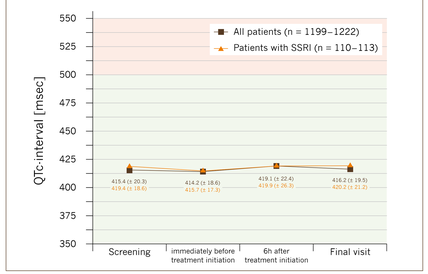
Table 3 + Figure 4: Occurrence of bradycardia after treatment initiation

n = 1230 patients	after treatment initiation	
	all patients; n = 1230	patients with SSRI; n = 113
No bradycardia	1221 (99.3 %)	111 (98.2 %)
< 45 bpm at any time during the 6h monitoring	9 (0.7 %)	2 (1.8 %)
< 40 bpm at any time during the 6h monitoring	2 (0.2 %)	0
< 45 bpm after 6 hours	3 (0.2 %)	1 (0.9 %)
< 40 bpm after 6 hours	0	0



- No patient required medication due to bradycardia
- No patients had < 45 bpm at study end, i.e. approx. 7 days after fingolimod treatment initiation

Figure 5: QTc-interval (Fridericia) over the course of the study

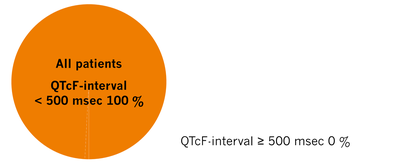


- The change in QTcF-interval 6 hours after study drug intake compared to the QTcF interval before study drug intake was
  - 5.0 (± 19.2) msec for all patients and
  - 4.5 (± 24.9) msec for patients taking SSRIs as co-medication. (Figure 5)

Table 4: QTc interval (Fridericia) 6 hours after treatment initiation

	all patients; n = 1207	patients with SSRI; n = 110
QTcF-interval < 500 msec	1207 (100 %)	110 (100 %)
QTcF-interval ≥ 500 msec	0	0

Figure 6: QTc interval (Fridericia) 6 hours after treatment initiation



- No patient had a QTcF-interval of ≥ 500 msec 7 days after treatment initiation.

AV Block I^0

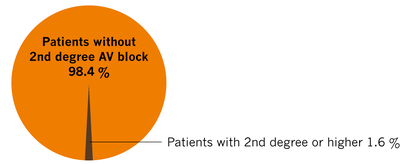
- 58 patients (4.7 %) experienced an AV block I^0 after fingolimod treatment initiation, of whom
  - 17 patients (1.4 %) already had an AV block I^0 at screening, that is, without fingolimod
  - those 41 patients (3.3 %) experiencing an AV block I^0 after fingolimod treatment initiation only had none after approx. 7 days at the final visit

AV Block II^0 type Mobitz I or higher

- Patients with AV Block II^0 type Mobitz I or higher are re-evaluated by a second cardiologist on a regular basis. Therefore, all enrolled patients are 'clean and verified' with respect to AV Block II^0 type Mobitz I or higher (enrolled patients on 14 March 2014).

Table 5 + Figure 7: Patients with AV Block II^0 or higher after treatment initiation

n = 2702 patients	after treatment initiation
No AV Block II^0 type Mobitz I or higher	2659 (98.4 %)
Patients with AV Block II^0 type Mobitz I or higher	43 (1.6 %)



- About 7 days after treatment initiation of fingolimod, no 2nd degree AV block or higher occurred in any patient

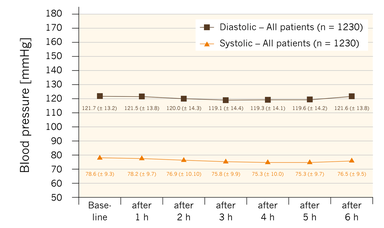
Of these 43 patients with AV Block II^0 type Mobitz I or higher

- 31 patients (72.1 %) were still on drug after approx. 7 days at study end
- 5 patients (11.6 %) took 1–2 capsules of fingolimod before stopping treatment
- 6 patients (14 %) took ≥ 3 capsules of fingolimod before stopping treatment

Table 6: Incidence of type of AV Block II^0 or higher

n = 2702 patients	after treatment initiation
AV Block II^0 – type Mobitz I	40 (1.5 %)
AV Block II^0 – 2:1 AV Block	11 (0.4 %)
AV Block II^0 – type Mobitz II	0
AV Block III^0	1 (0.04 %)

Figure 8: Blood pressure after treatment initiation



Conflicts of interest

The following authors received honoraria for lecturing or consultancy activities or the institutions for which they work received support for research projects from the following companies and establishments:

Volker Limmroth: Bayer Health Care, Biogen Idec, Merck Serono, Novartis, Sanofi Aventis and TEVA Neuroscience; **Susanne Hoyer** is employee of Novartis; **Stephan Schmidt** has received travel expenses for attending meetings and honoraria for lecturing from Novartis Pharma, Sanofi Aventis, Bayer, Biogen Idec, Genzyme, Merck Serono, and Teva Pharma. **Michael Lang:** Novartis, Biogen, Bayer, Teva, Serono and Genzyme; **Tjalf Ziemssen** has received speaking honoraria and travel expenses for scientific meetings; has been a steering committee member of clinical trials or participated on advisory boards for clinical trials in the past few years with Bayer Schering Pharma, Biogen Idec, EMD Merck Serono, Genentech, Genzyme, Novartis, Sanofi-Aventis, Teva Pharmaceuticals and Almirall

References

1. Schmouder R. et al. J Clin Pharmacol 2006; 46: 895; **2.** Schmouder R. et al. Eur J Clin Pharmacol 2012; 68: 355-62; **3.** Koyrakh L. et al. Am J Transplant 2005; 5: 529-536; **4.** Kovarik J. M. et al. Eur J Clin Pharmacol 2008; 64: 457-463

[a] The approved indication may vary from country to country. In the EU, fingolimod is approved for treatment of patients with highly active relapsing-remitting MS. In the United States, it is approved for the treatment of patients with relapsing forms of MS. Data as of February 28, 2014; Q1 Novartis Pharmaceuticals Interim Financial Report, April 24, 2014

NOVARTIS PHARMACEUTICALS