Ocrelizumab and Fatalities

Summary of Fatalities[1,2]

- In the ocrelizumab clinical trials and their open-label extensions, there was no increase in fatalities in ocrelizumab-treated patients compared with controls
- From the post-marketing experience, there was no pattern observed in the causes of fatalities as reported to the regulatory authorities

Background Rates in the MS Population[3,4]

- Estimated mortality rates in the overall MS population between 1968 and 2010 ranged from 0.37 per 100 PY to 0.9 per 100 PY
- These estimates were based on an observational study in France (27,603 MS patients) and a retrospective study in the US (30,402 MS patients from the OptumInsight Research database)

The incidence rates of fatalities are derived from varied sources and intended to provide context. Confounding factors that may influence mortality have not been accounted for, and therefore, no direct comparisons should be made. Such factors may include, but are not limited to, type of MS, age, gender, disease duration, geographical region, population size, drug exposure, comorbid conditions, treatment history, and duration of follow-up.

Clinical Trials (Controlled Treatment Period and Open-Label Extension)

Incidence rate in phase 3 clinical trials (controlled treatment period only)[2]

	OPERA I/OPERA II (Pooled)[a] Incidence Rate per 100 PY (95% CI)		ORATORIO[b] Incidence Rate per 100 PY (95% CI)	
	IFN β-1a	Ocrelizumab	Placebo	Ocrelizumab
Phase 3 Controlled Treatment Period	0.14 (0.02, 0.52)	0.07 (0, 0.38)	0.41 (0.08, 1.20)	0.25 (0.07, 0.64)

[a]Two identical phase 3, global, randomized, double-blind, double-dummy studies with a 96-week controlled period during which 1656 patients with relapsing forms of MS received either intravenous ocrelizumab (600 mg) every 24 weeks or subcutaneous IFN β-1a (44 µg) three times weekly.[5]
[b]A phase 3, global, randomized, double-blind study with a ≥120-week controlled period during which 732 patients with primary progressive MS received either intravenous ocrelizumab (600 mg) or placebo every 24 weeks.[6]

Incidence rate by exposure in clinical trials (controlled treatment period and open-label extension)[1a]

	Data Cutoff Date[a]	Patients on Ocrelizumab (n)	PY	Fatalities (n)	Incidence Rate per 100 PY	95% CI
Ocrelizumab All-Exposure Population[b]	JUL 2015	2147	4484.5	8	0.178	0.077, 0.352
	JAN 2016	2279	5710.7	8	0.140	0.060, 0.276
	SEP 2016	2300	6940.9	11	0.158	0.079, 0.284
	FEB 2017	2301	7747.8	13	0.168	0.089, 0.287
	SEP 2017	3778	9473.5	16	0.169	0.097, 0.274
	FEB 2018	3811	10,918.5	17	0.156	0.091, 0.249
	JUL 2018	4501	12,558.9	19	0.151	0.091, 0.236
	JAN 2019	4611	14,328.5	23	0.161	0.102, 0.241
	JAN 2020	5680	18,218.4	26	0.143	0.093, 0.209

[a]Data cuts are cumulative; each data cut includes the previous cut, and fatalities are included from both the controlled treatment period and the open-label extension.
[b]Includes all patients exposed to ocrelizumab in the global and US MS clinical trials; excludes patients in compassionate use program.

- The causes of the fatalities in the all-exposure population are as follows: Suicide (n=6), cardiac arrest (n=2), metastatic pancreatic cancer (n=2), acute coronary insufficiency (n=1), adenocarcinoma of esophagus (n=1), aspiration pneumonia (n=1), bladder cancer (n=1), bronchopneumonia (n=1), epileptic seizure (n=1), fall (n=1), injury (n=1), medically assisted suicide (n=1), MS disease progression (n=1), pneumonia (n=1), probable seronegative autoimmune encephalitis (n=1), pulmonary embolism (n=1), systemic inflammatory response syndrome of undetermined origin (n=1), unknown (n=1), and urinary infection/urosepsis (n=1).

Post-Marketing Experience, as of July 31, 2020

Incidence rate by exposure in the post-marketing setting[1*]

	Market Period[a]	Patients on Ocrelizumab (n)[b]	PY	Fatalities (n)[c]	Incidence Rate per 100 PY
Ocrelizumab Post-Marketing	APR 2017–DEC 2017	~27,678	~8899	24	0.27
	APR 2017–MAR 2018	~37,171	~15,682	45	0.29
	APR 2017–MAY 2018	~48,780	~23,776	64	0.27
	APR 2017–JUL 2018	~58,667	~33,526	87	0.26
	APR 2017–SEP 2018	~66,662	~43,560	114	0.26
	APR 2017–DEC 2018	~78,554	~60,710	149	0.25
	APR 2017–MAY 2019	~103,290	~94,964	250	0.26
	APR 2017–JUL 2019	~114,943	~111,166	293	0.26
	APR 2017–DEC 2019	~142,855	~159,317	434	0.27
	APR 2017–JUL 2020	~167,684	~235,630	666	0.28

[a]Numbers reported include only the post-marketing period and are inclusive of the whole month stated.
[b]The number of post-marketing patients exposed to ocrelizumab is based on estimated total number of vials sold, as well as US claims data.
[c]Based on reported fatalities in the Roche safety database in patients treated with ocrelizumab within the designated post-marketing period.

The Prescribing Information is the primary source of information on the known and potential risks associated with ocrelizumab.

Footnote:

*There are well-recognized limitations that should be considered when interpreting spontaneous post-marketing safety reports, including events that may not causally be related to drug exposure; in the real-world setting, events are frequently confounded by factors such as multiple drug use and the presence of pre-existing comorbidities; reporting bias may exist for more significant outcomes, which may result in an overrepresentation of the more serious outcomes; and reporting rates can be stimulated by external factors, such as press reports.

The causes of fatalities are recorded as reported to the company; while the company follows up on all reports to identify the cause, an exact diagnosis is not always possible. Some of the investigations remain ongoing and, therefore, the information may be subject to change.

Abbreviations:

CI=confidence interval; IFN=interferon; MS=multiple sclerosis; PY=patient-years; US=United States.

References:

1. Genentech data on file; 2. Hauser SL, et al. Presented at European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) 2020 (P0389); 3. Leray E, et al. *PLoS One.* 2015;10(7):e0132033; 4. Goodin DS, et al. *PLoS One.* 2014;9(8):e105207; 5. Hauser SL, et al. *N Engl J Med.* 2017;376:221–234; 6. Montalban X, et al. *N Engl J Med.* 2017;376(3):209-220. doi: 10.1056/NEJMoa1606468.

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