Ocrelizumab and Fatalities

Summary of Fatalities

- In the ocrelizumab clinical trials and their open-label extensions, there was no increase in fatalities in ocrelizumab-treated patients compared with controls[1,2]
- From the post-marketing experience there was no pattern observed in the causes of fatalities as reported to the regulatory authorities.[1] Causes of fatalities in the post-marketing setting are outlined below

Background Rates in the MS Population

- Estimated mortality rates in the overall MS population between 1968 and 2015 ranged from 0.37 per 100 patient-years[3] to 0.9 per 100 patient-years[4]
- These estimates were based on an observational study in France (27,603 MS patients)[3] and a retrospective study in the US (30,402 MS patients from the OptumInsight Research database)[4]

The incidence rates of fatalities are derived from varied sources, and intended to provide context. Confounding factors which 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 (Pooled)[a] Incidence Rate per 100 Patient-Years (95% CI)		ORATORIO[b] Incidence Rate per 100 Patient-Years (95% CI)	
	IFN β-1a	Ocrelizumab	Placebo	Ocrelizumab
Phase 3Controlled 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 interferon beta-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):[1,a]

	Data Cutoff Date[a]	Patients on Ocrelizumab (N)	Patient-Years	Fatalities (n)	Incidence Rate per 100 Patient-Years	95% CIs
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

[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=5), cardiac arrest (n=2), metastatic pancreatic cancer (n=2), pneumonia (n=2), acute coronary insufficiency (n=1), adenocarcinoma of esophagus (n=1), aspiration pneumonia (n=1), bladder cancer (n=1), epileptic seizure (n=1), injury (n=1), MS disease progression (n=1), pulmonary embolism (n=1), systemic inflammatory response syndrome of undetermined origin (n=1), unknown (n=1), urinary infection/urosepsis (n=1), and fall (n=1)

Post-Marketing Experience, as of July 31 2019

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

	Market Period[a]	Patients on Ocrelizumab[b]	Patient-Years	Fatalities (n)[c]	Incidence Rate per 100 Patient-Years
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

[a]Numbers reported for the marketing period 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 with patients suffering from relapsing or progressive multiple sclerosis treated with ocrelizumab reported within the designated post-marketing period.

- The causes of the post-marketing fatalities are as follows: Unknown cause (n=155), myocardial infarction (n=13), completed suicide (n=9), pneumonia (n=9), pulmonary embolism (n=8), sepsis (n=7), pancreatic carcinoma (n=4), fall (n=3), infection (n=3), multiple sclerosis (n=3), sudden death (n=3), cerebral hemorrhage (n=2), urosepsis (n=2), cardiac disorder (n=2), cardiac arrest (n=2), urinary tract infection (n=2), subdural hematoma (n=2), victim of homicide (n=2), symptoms reported as a cause of death (asthenia, chest pain, pyrexia and decreased appetite) (n=1), multiple sclerosis relapse with infection (n=1), tumefactive multiple sclerosis (n=1), opioid overdose (n=1), aspiration pneumonia (n=1), acute kidney injury (n=1), influenza (n=1), influenza-like illness (n=1), brain herniation with toxic leukoencephalopathy (n=1), cardiogenic shock with circulatory collapse and urinary tract infection (n=1), epilepsy with status epilepticus (n=1), cellulitis with pneumonia, sepsis and urinary tract infection (n=1), aspiration pneumonia with respiratory failure (n=1), lung cancer with metastases to bone and CNS (n=1), metastatic lung adenocarcinoma (n=1), acute respiratory failure with urosepsis (n=1), dyspnea, hyperhidrosis, and circulatory collapse (n=1), cardiopulmonary arrest with pulmonary embolism and deep vein thrombosis (n=1), sepsis with aspiration pneumonia, intestinal sepsis, cardiac arrest, and intestinal obstruction (n=1), lung infection with osteomyelitis (n=1), urinary tract infection with sepsis (n=1), choking (n=1), stroke (n=1), cardiac failure congestive (n=1), respiratory failure (n=1), encephalopathy, asthenia, seizure, and respiratory failure (n=1), cardiorespiratory arrest (n=1), adenocarcinoma (n=1), renal failure (n=1), aspiration and septic shock (n=1), lung infection (n=1), cardiac failure (n=1), lung disorder (n=1), fracture (n=1), peritonitis (n=1), aortic aneurysm (n=1), acute myocardial infarction with nasopharyngitis, cardiac failure, and cardiac disorder (n=1), cardiac arrest with pulmonary embolism (n=1), hemorrhage (n=1), hepatic and renal failure (n=1), kidney infection (n=1), metastatic neoplasm (n=1), colon cancer (n=1), metastatic liver cancer (n=1), metastatic renal cell carcinoma (n=1), breast cancer with metastasis to lung (n=1), malignant lung neoplasm (n=1), sudden death and metastatic neoplasm (n=1), respiratory disorder (n=1), respiratory failure, multiple organ dysfunction syndrome, and circulatory collapse (n=1), generalized edema (n=1), thrombosis (n=1), sarcoma (n=1), angiosarcoma (n=1), septic shock (n=1), intentional product use issue, off label use (n=1), acute promyelocytic leukaemia (n=1), dyspnea (n=1), adult failure to thrive (n=1), cardiac failure, multiple sclerosis and hypotension (n=1), metastatic colon cancer (n=1), and multiple sclerosis with influenza-like illness (n=1)

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

References:
1. Genentech data on file; 2. Hauser SL, et al. Presented at: ECTRIMS-ACTRIMS 2017 (Poster P676); 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; doi: 10.1056/NEJMoa1606468 [suppl].

Existence of a safety report does not establish causation. By regulation, all cases where causality is unknown or not captured are reported as related to ocrelizumab. 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.

Information current as of July 31, 2019.

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