Ocrelizumab and Fatalities

Summary of Fatalities[1,2]

- In 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. Causes of fatalities in the post-marketing setting are outlined below

Background Rates in the MS Population[3,4]

- Estimated mortality rates in the overall MS population between 1968 and 2015 ranged from 0.37 per 100 patient-years to 0.9 per 100 patient-years
- 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 which may influence mortality have not been accounted for; 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 III 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 III 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 III, global, randomised, double-blind, double-dummy studies with a 96-week controlled period during which 1,656 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 III, global, randomised, 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 Cut-off Date[a]	Patients on Ocrelizumab (n)	PY	Fatalities (n)	Incidence Rate per 100 PY	95% CI
Ocrelizumab All-Exposure Population[b]	JUL 2015	2,147	4,484.5	8	0.178	0.077–0.352
	JAN 2016	2,279	5,710.7	8	0.140	0.060–0.276
	SEP 2016	2,300	6,940.9	11	0.158	0.079–0.284
	FEB 2017	2,301	7,747.8	13	0.168	0.089–0.287
	SEP 2017	3,778	9,473.5	16	0.169	0.097–0.274
	FEB 2018	3,811	10,918.5	17	0.156	0.091–0.249
	JUL 2018	4,501	12,558.9	19	0.151	0.091–0.236
	JAN 2019	4,611	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 open-label extension.
[b]Includes all patients exposed to ocrelizumab in the global and US MS clinical trials; excludes patients in compassionate use programme.

- 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 oesophagus (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 31 December 2019

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	~8,889	24	0.27
	APR 2017 – MAR 2018	~37,171	~15,682	45	0.29
	APR 2017 – MAY 2019	~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	~78,544	~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	433	0.27

[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 in patients treated with ocrelizumab within the designated post-marketing period.

- The causes of the post-marketing fatalities are as follows: Unknown cause (n=247), myocardial infarction (n=15), completed suicide (n=13), pneumonia (n=10), sepsis (n=10), pulmonary embolism (n=6), pancreatic cancer (n=4), fall (n=4), lung cancer (n=3), infection (n=3), MS (n=3), sudden death (n=3), urosepsis (n=3), aspiration pneumonia (n=3), cardiac arrest (n=3), cardiac disorder (n=2), urinary tract infection (n=2), subdural hematoma (n=2), victim of homicide (n=2), renal failure (n=2), colon cancer (n=2), metastatic renal cell carcinoma (n=2), urinary tract infection with sepsis (n=2), head injury (n=2), septic shock (n=2), symptoms reported as a cause of death (pyrexia, chest pain, and decreased appetite) (n=1), tumefactive MS (n=1), MS relapse (n=1), MS relapse with infection (n=1), MS relapse with influenza-like illness (n=1), cerebral hemorrhage (n=1), cerebral hemorrhage and subdural hemorrhage (n=1), opioid overdose (n=1), bacterial pneumonia with lactic acidosis and sepsis (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), metastatic lung cancer (n=1), acute respiratory failure with urosepsis (n=1), acute respiratory failure with pneumonia (n=1), dyspnea (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 (n=1), lung infection with osteomyelitis (n=1), choking (n=1), stroke (n=1), cardiac failure congestive (n=1), cardiac failure with nephropathy (n=1), respiratory failure (n=1), encephalopathy, seizure, and respiratory failure (n=1), cardiorespiratory arrest (n=1), adenocarcinoma (n=1), aspiration and septic shock (n=1), cardiac failure (n=1), lung disorder (n=1), fracture (n=1), peritonitis (n=1), aortic aneurysm (n=1), myocardial infarction with 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), liver cancer (n=1), breast cancer (n=1), sudden death and metastatic neoplasm (n=1), respiratory disorder (n=1), respiratory distress (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), acute promyelocytic leukemia (n=1), adult failure to thrive (n=1), cardiac failure, MS, and hypotension (n=1), acute kidney injury, hepatic cirrhosis, ascites, and hepatorenal syndrome (n=1), amyotrophic lateral sclerosis (n=1), anaphylactic shock (n=1) arteriovenous fistula site hemorrhage (n=1), cerebrovascular accident (n=1), circulatory collapse (n=1), glioblastoma (n=1), glioblastoma multiforme (n=1), intestinal dilatation with sepsis (n=1), lip and/or oral cavity cancer and throat cancer (n=1), malignant melanoma (n=1), multiple organ dysfunction syndrome with sepsis (n=1), myelodysplastic syndrome (n=1), metastatic non-small cell lung cancer (n=1), pancreatic cancer with cardiopulmonary arrest and pleural effusion (n=1), post-procedural pulmonary embolism (n=1), procedural complication (n=1), pulmonary mass (n=1), pulmonary edema and pulmonary hemorrhage (n=1), road traffic accident (n=1), ruptured cerebral aneurysm (n=1), seizure (n=1), septic shock with atrial fibrillation and brain injury (n=1), accident (n=1), and sleep apnea syndrome (n=1)

Prescribing Information

Indications vary in different countries. The local prescribing information from your country is the primary source of information on the known and potential risks associated with ocrelizumab.

Footnotes: *There are well-recognised limitations that should be considered when interpreting spontaneous post-marketing safety reports, including events may not be causally 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

References: 1. Roche data on file 2. Hauser SL, et al. Presented at: ECTRIMS 2019, P648; 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]

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