Clinical Trials Including Open-Label Extension

Incidence rate in clinical trials:[1]

	OPERA (Pooled)[a]		ORATORIO[b]	
	IFN β-1a Incidence Rate[c] (95% CI)	Ocrelizumab Incidence Rate[c] (95% CI)	Placebo Incidence Rate[c] (95% CI)	Ocrelizumab Incidence Rate[c] (95% CI)
Ocrelizumab 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 interferon beta-1a (44 µg) three times weekly.[2]
[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.[3]
[c]Expressed per 100 patient-years.

- There was no increase in fatalities in ocrelizumab-treated patients compared with controls in clinical trials

Incidence rate by exposure:[4a]

	Data Cutoff Date	Patients on Ocrelizumab (N)	Patient-Years	Fatalities (#)	Incidence Rate[c]	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	10918.5	17	0.156	0.091, 0.249

[a]Data cuts are inclusive; each data cut includes the previous cut.
[b]Includes all patients exposed to ocrelizumab in the global and US MS clinical trials except ENSEMBLE; excludes patients in compassionate use program.
[c]Expressed per 100 patient-years.

- The causes of the fatalities in the all-exposure population are as follows: Cardiac arrest (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), metastatic pancreatic cancer (n=1), MS disease progression (n=1), pneumonia (n=1), pulmonary embolism (n=1), suicide (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[4]

There was no pattern observed in the causes of fatalities as reported to the FDA.

	Market Period	Patients on Ocrelizumab[b]	Patient-Years	Fatalities (#)[c]	Incidence Rate[d]
Ocrelizumab Post-Marketing[a]	APRIL 2017–MAY 2018	~ 48,780	~23,776	64	0.27
	APRIL 2017–SEP 2018	~66,662	~43,560	114	0.26

[a]Overall exposure is calculated in patient years on ocrelizumab.
[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.
[d]Expressed per 100 patient-years.

- The causes of the post-marketing fatalities are as follows: Unknown cause (n=65), symptoms reported as a cause of death (asthenia, chest pain, pyrexia and decreased appetite) (n=1), sepsis (n=5), myocardial infarction (n=5), completed suicide (n=3), urosepsis (n=2), overdose (one each of opioid and diazepam) (n=2), pulmonary embolism (n=2), cardiac disorder (n=1), pneumonia aspiration (n=1), acute kidney injury (n=1), pancreatic carcinoma (n=1), hepatic cancer metastatic (n=1), cerebral hemorrhage (n=1), influenza (n=1), brain herniation with toxic leukoencephalopathy (n=1), sudden death and metastatic neoplasm (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), pneumonia aspiration with respiratory failure (n=1), lung cancer metastatic with metastases to bone and CNS (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), pneumonia aspiration with sepsis, intestinal sepsis, and cardiac arrest (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), sepsis, liver disorder, neoplasm malignant, and general physical health deterioration (n=1), encephalopathy, asthenia, seizure, and respiratory failure (n=1), influenza-like illness (n=1), cardiorespiratory arrest (n=1), and subdural hematoma (n=1)

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

Background Rates in the MS Population

- Estimated mortality rates in the MS population ranged from 0.37 per 100 patient-years[5] to 0.9 per 100 patient-years[6]
- These estimates were based on an observational study in France (27,603 MS patients)[5] and a retrospective study in the US (30,402 MS patients from the OptumInsight Research database)[6]

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.

References:
1. Hauser SL, et al. Presented at: ECTRIMS-ACTRIMS 2017 (Poster P676); 2. Hauser SL, et al. N Engl J Med. 2017; 376:221–234; 3. Montalban X, et al. N Engl J Med. 2017; doi: 10.1056/NEJMoa1606468 [suppl]; 4. Genentech data on file; 5. Leray E, et al. PLoS One. 2015;10(7):e0132033; 6. Goodin DS, et al. PLoS One. 2014;9(8):e105207.

Information current as of September 2018. 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.

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