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Post-marketing Experience of Vedolizumab in Inflammatory Bowel Disease: Analysis of Pneumonia and Other Respiratory Tract Infections

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Background

- The annual incidence of pneumonia has been reported as 13.8/1000 in patients with IBD compared with 7.6/1000 in healthy individuals (incidence rate ratio 1.82; 95% CI: 1.75–1.88)¹
- Vedolizumab (ENTYVIO®) is a humanised, monoclonal antibody that selectively targets the $\alpha_4\beta_7$ integrin expressed on gut-homing lymphocytes, with non-gut-homing T-lymphocytes remaining unaffected^{2,3}
- Although respiratory tract infections (RTIs) have been reported with vedolizumab,⁴ its gut selectivity may reduce the risk of RTIs compared with therapies that produce systemic immunosuppression (e.g. anti-tumour necrosis factor-alpha [TNF α] agents)⁵
- Vedolizumab is licensed in over 50 countries to treat adults with moderate to severely active ulcerative colitis (UC) or Crohn’s disease (CD),⁴ and has been incorporated into the latest ECCO guidelines for CD⁶
- Here, we describe pneumonia and other RTIs reported with vedolizumab therapy in the post-marketing setting

Methods

- A review of safety data from the vedolizumab post-marketing Global Safety Database was conducted (between launch [May 2014] and 19 May 2016)
 - Estimated vedolizumab exposure was ~46,978 patient-years (PY)
- Reports of lower respiratory tract infections (LRTIs) and upper RTIs (URTIs) were identified using the following MedDRA v19.0 High Level Terms: ‘Lower Respiratory Tract (LRT) and lung infections’, ‘LRTIs not elsewhere classified (NEC)’, ‘URTIs’ and ‘URTIs (NEC)’

Results

- Patient demographics and clinical characteristics are presented in Table 1

Table 1. Patient Demographics and Clinical Characteristics

	LRTIs (N=106 patients)	URTIs (N=300 patients)
Female sex, n/N (%)	66/105 (62.9)*	173/279 (62.0) [†]
Age, mean (SD), years	46.5 (16.5)	43.0 (14.7)
Current/former smoker, n/N (%)	6/10 (60.0) [‡]	5/20 (25.0) [§]
Prior/concomitant anti-TNF α therapy, n/N (%)	53/74 (71.6)	180/239 (75.3)
Prior/concomitant IMM use, n/N (%)	26/74 (35.1)	180/239 (75.3)
No prior/concomitant medications reported, n (%)	32 (30.2)	61 (20.3)
Surgery \leq 30 days prior to event onset reported, n (%)	2 (1.9) [¶]	1 (0.3) [¶]

Data cut-off: 19 May 2016; N = the number of patients with available information (denominator). If N is not stated, the denominator is the total number of patients overall (LRTI, N=106; URTI, N=300)
*Sex was not reported in one patient
†Sex was not reported in 21 patients
‡Smoking history was not reported in 96 patients
§Smoking history was not reported in 280 patients
¶104 and 299 patients did not report having surgery within 30 days prior to event onset, for LRTIs and URTIs respectively
IMM, immunomodulator; LRTI, lower respiratory tract infection; TNF α , tumour necrosis factor-alpha; URTI, upper respiratory tract infection

Frequency and Seriousness of LRTIs

- During ~46,978 PYs of vedolizumab therapy, a total of 108 LRTIs were reported in 106 patients (Table 2)
 - Most events were non-serious (68/108 events; 63.0%; Figure 1)
- Overall, pneumonia accounted for 54 events (n=34 serious; n=20 non-serious). This was equivalent to ~1 event/1000 PYs of therapy
 - There were 4 fatal pneumonia events (Table 3)
- The second most commonly reported LRTI was bronchitis (n=1 serious; n=26 non-serious)

Table 2. Frequency of LRTIs

Reported AE	Serious events	Non-serious events
Total LRTI events	40	68
Pneumonia	34	20
Bronchitis*	1	26
LRTIs (not specified)	2	20
Lung infection	2	2
Lung abscess	1	0

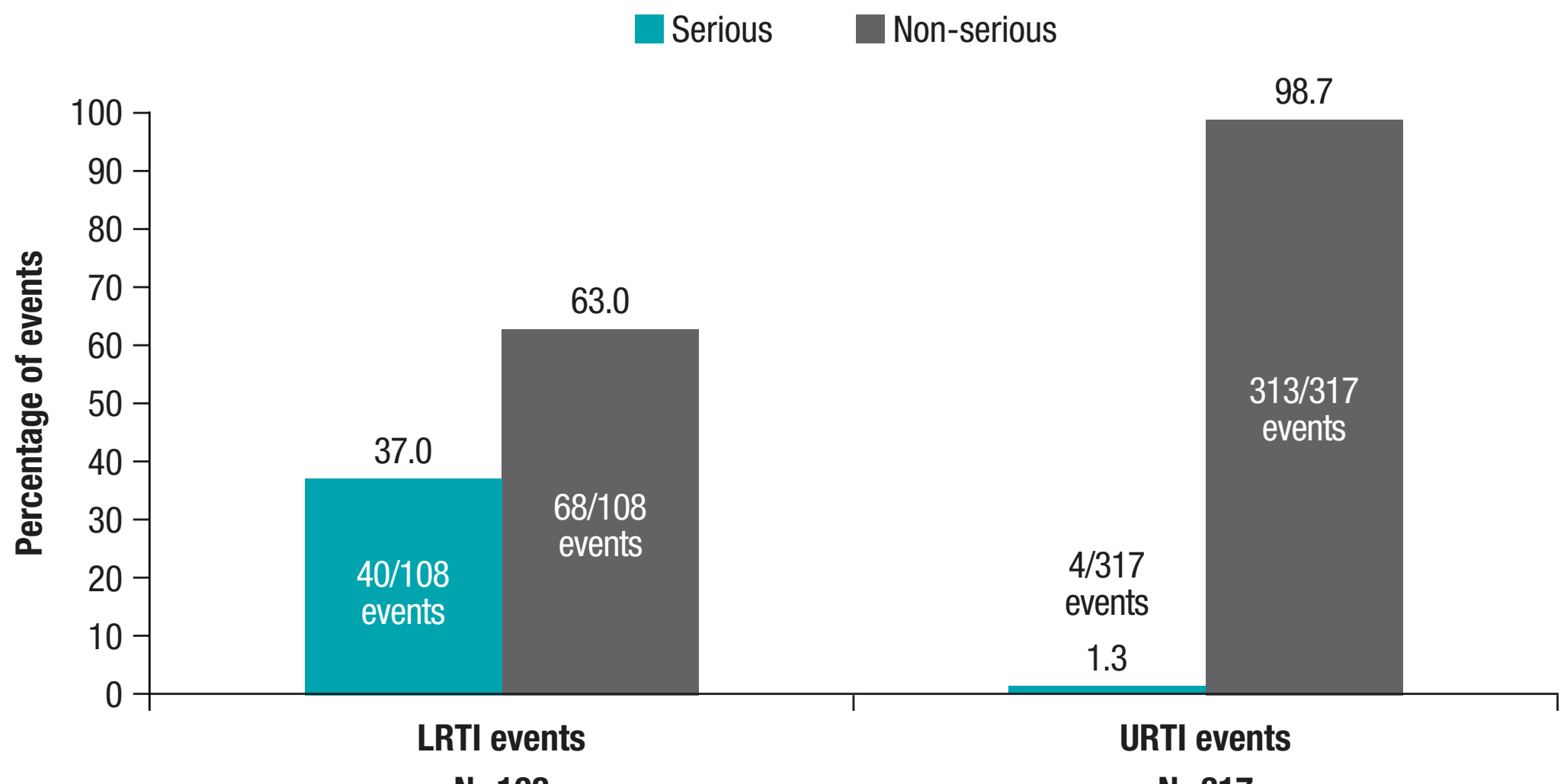
Data cut-off: 19 May 2016
*AE included in the vedolizumab summary of product characteristics⁴
AE, adverse event; LRTI, lower respiratory tract infection

Table 3. Fatal Events of Pneumonia

Patient details	Cause of death	Concomitant and prior medications	Medical history
Male, 84 years, UC	Pneumonia	NR	NR
Male, 71 years, UC	Myocardial infarction Pulmonary embolism in the context of fatal pneumonia	Concomitant: tamsulosin, prednisolone Prior: NR	Coronary heart disease Cardiovascular disorder Hypertension Past pneumonia
Male, 53 years, CD	Pneumonia	NR	COPD
Male, age NR, CD	Septicaemia Pneumonia	Concomitant: calcium carbonate/colecalfiferol (Calci Chew-D3), zinc sulfate (Solvezink), cyanocobalamin (Behapan), ferrous sulfate (Duroferon), folic acid (Folacin), betamethasone sodium phosphate (Betapred), fentanyl patches (Matrifren), parenteral nutrition (Nutrifix) Prior: NR	Generalised illness

Data cut-off: 19 May 2016
CD, Crohn’s disease; COPD, chronic obstructive pulmonary disease; NR, not reported; UC, ulcerative colitis

Figure 1. Seriousness of RTIs



Data cut-off: 19 May 2016
~46,978 patient-years of vedolizumab therapy
LRTI, lower respiratory tract infection; RTI, respiratory tract infection; URTI, upper respiratory tract infection

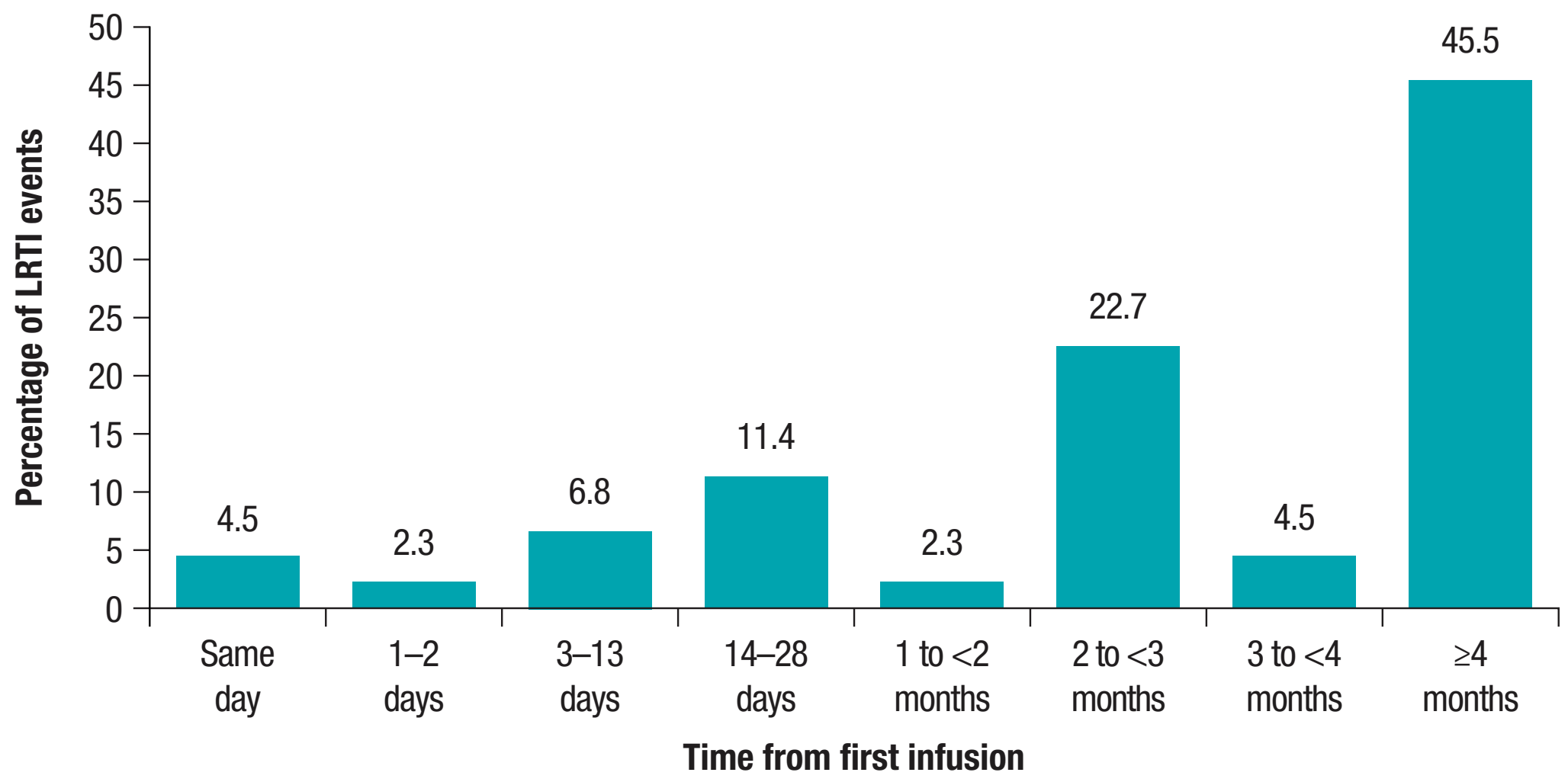
Risk Factors for LRTIs, Including Pneumonia

- Known risk factors for pneumonia include smoking, recent surgery, older age (>65 years) and comorbidities, including immunosuppressive conditions^{7,8}
- Smoking history was reported in a minority of patients with LRTIs (10/106) and URTIs (20/300) (Table 1)
- Information on prior surgery was reported for 7 patients with a pneumonia event; of these, two had undergone surgery \leq 30 days prior to reporting pneumonia
- Of those experiencing an LRTI (and who had information regarding prior medication use), 53/74 (71.6%) reported prior/concomitant use of anti-TNF α therapy and 26/74 (35.1%) reported prior/concomitant immunomodulator use
 - Information regarding prior medication was not available in 32 patients

LRTIs: Event Onset and Treatment Outcome

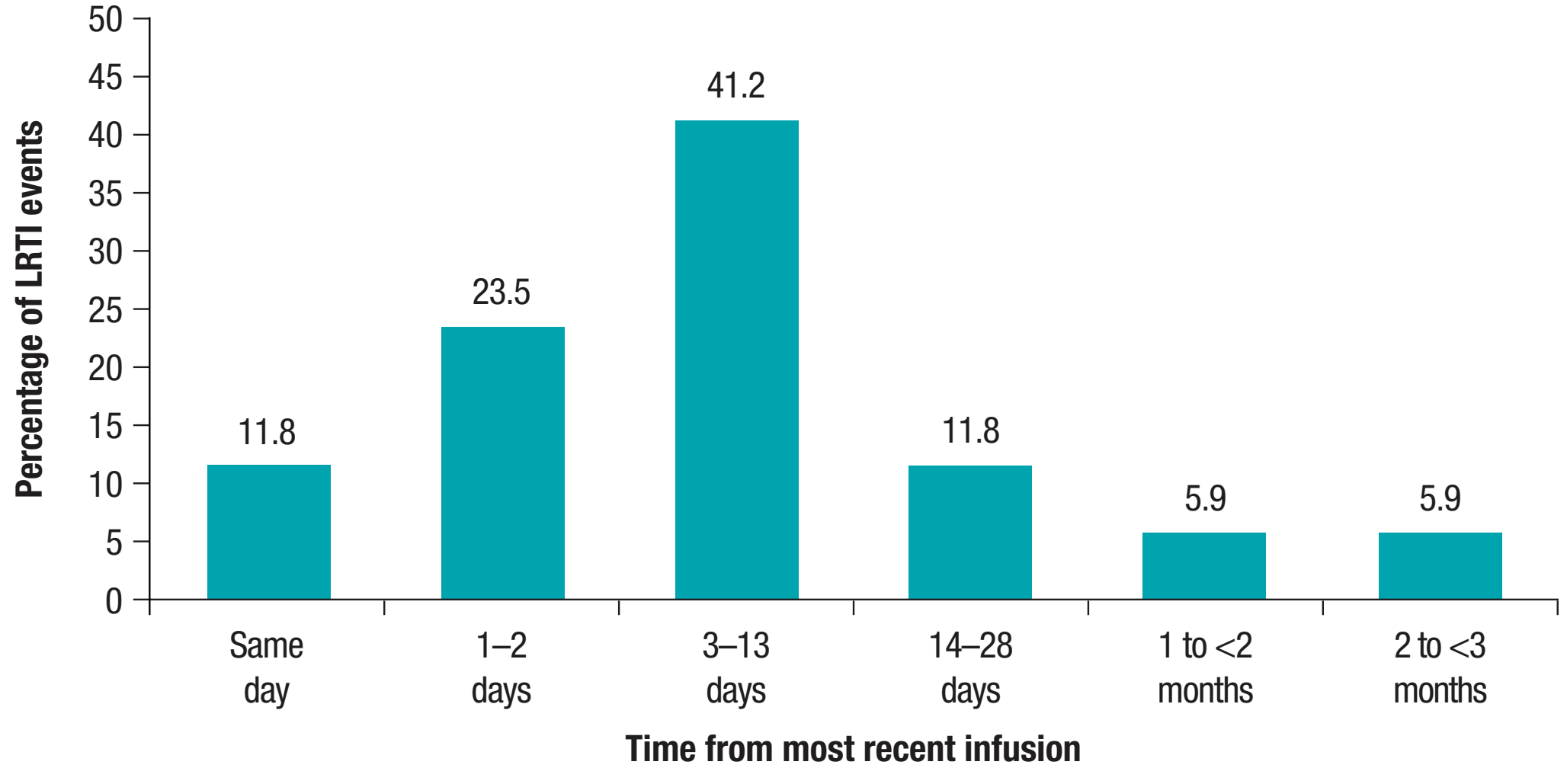
- From the 44 reports with available information, most LRTIs occurred \geq 2 months after the first vedolizumab infusion (n=32/44 events; time to onset was not reported [NR] for n=64/108 events; Figure 2)
- From the 17 reports with available information, most (n=13/17; NR n= 91/108 events) occurred \leq 13 days after the most recent infusion of vedolizumab (Figure 3)
- Vedolizumab treatment was continued in most patients (n=61/89; NR n=17/106) who experienced an LRTI (Figure 4)

Figure 2. Time to Onset of LRTI Events from the First Infusion (n=44 events)*



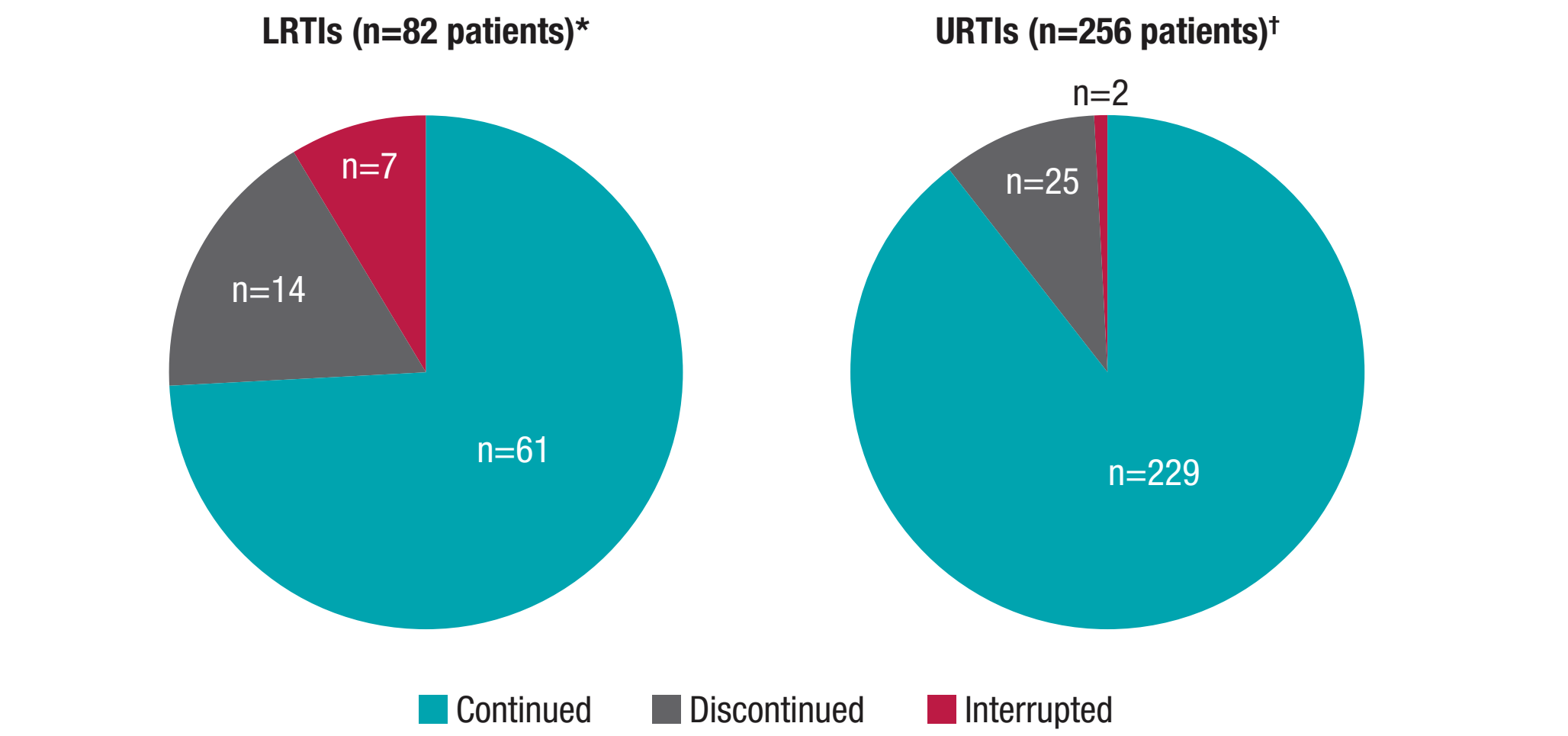
Data cut-off: 19 May 2016
*64 of 108 event reports did not have information available
LRTI, lower respiratory tract infection

Figure 3. Time to Onset of LRTI Events from the Most Recent Infusion (n=17 events)*



Data cut-off: 19 May 2016
*91 of 108 event reports did not have information available
LRTI, lower respiratory tract infection

Figure 4. Vedolizumab Treatment Status after an RTI Event



Data cut-off: 19 May 2016
*Total number of LRTI patients, N=106; vedolizumab treatment status after event NR in 17 patients; six patients died after the event (including four patients with fatal pneumonia [Table 3]) and two patients that died as a result of events other than an LRTI); treatment was discontinued in one patient prior to LRTI onset
*Total number of URTI patients, N=300; vedolizumab treatment status after event NR in 43 patients; one patient died after the event as a result of an event other than the URTI
LRTI, lower respiratory tract infection; NR, not reported; URTI, upper respiratory tract infection

Frequency and Seriousness of URTIs

- A total of 4 serious and 313 non-serious URTIs were reported in 300 patients (Table 4; Figure 1)
 - There were no fatal URTIs
- Nasopharyngitis was found to be a ‘very common’ adverse event (occurring in \geq 1/10 patients) in the vedolizumab clinical trials⁴ and, not unexpectedly, was the most frequently reported URTI (n=201/317 events reported from >46,000 PYs of therapy)
 - Sinusitis and URTIs (not specified) were the next most frequently reported events (Table 4)

Table 4. Frequency of URTIs

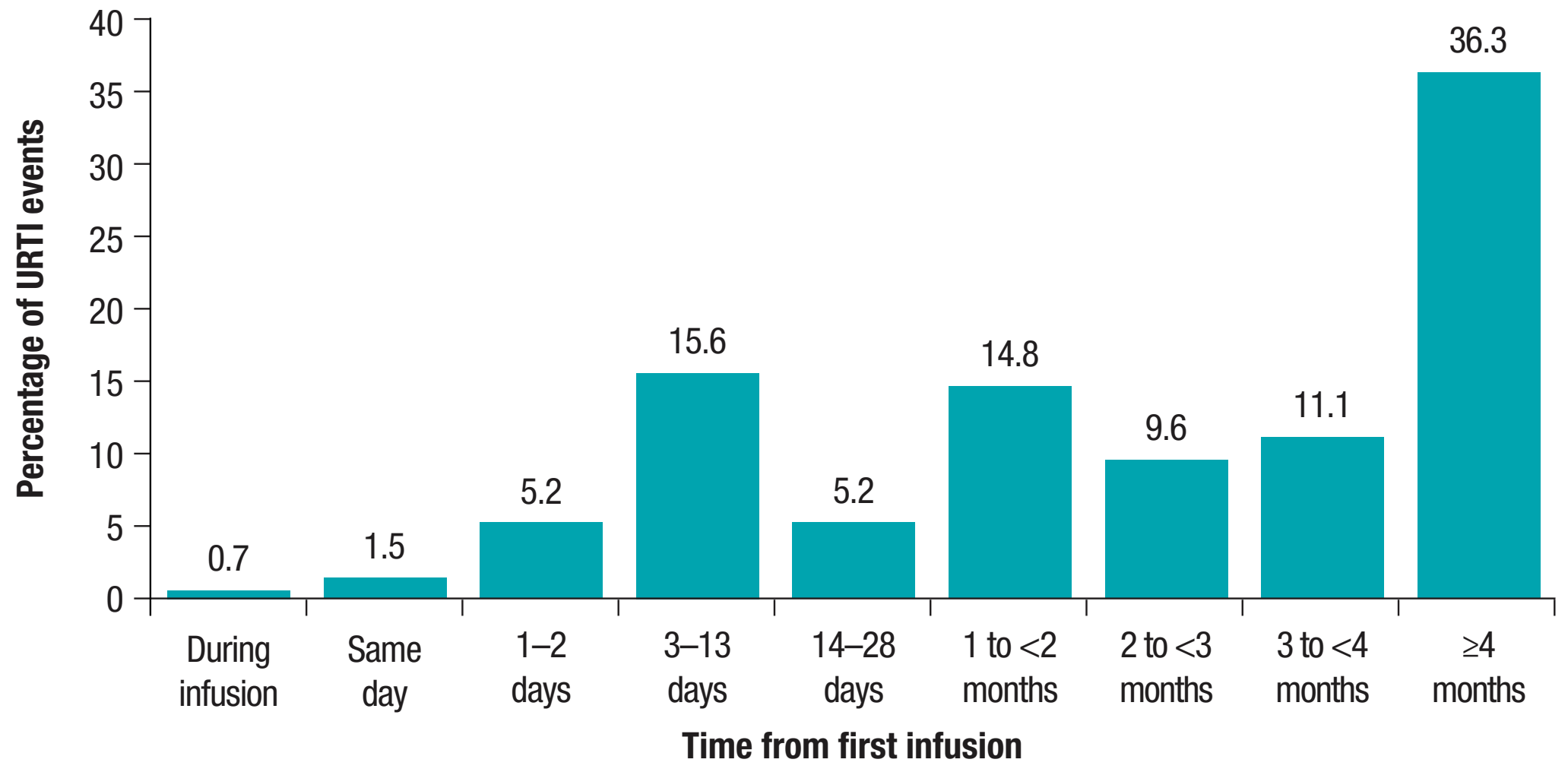
Reported AE	Serious events	Non-serious events
Total URTI events	4	313
Nasopharyngitis*	1	200
Sinusitis*	2	60
URTIs* (not specified)	0	22
Pharyngitis*	1	14
Rhinitis	0	6
Tonsillitis	0	5
Laryngitis	0	5
Croup	0	1

Data cut-off: 19 May 2016
*AEs included in the vedolizumab summary of product characteristics⁴
AE, adverse event; URTI, upper respiratory tract infection

URTIs: Event Onset and Treatment Outcome

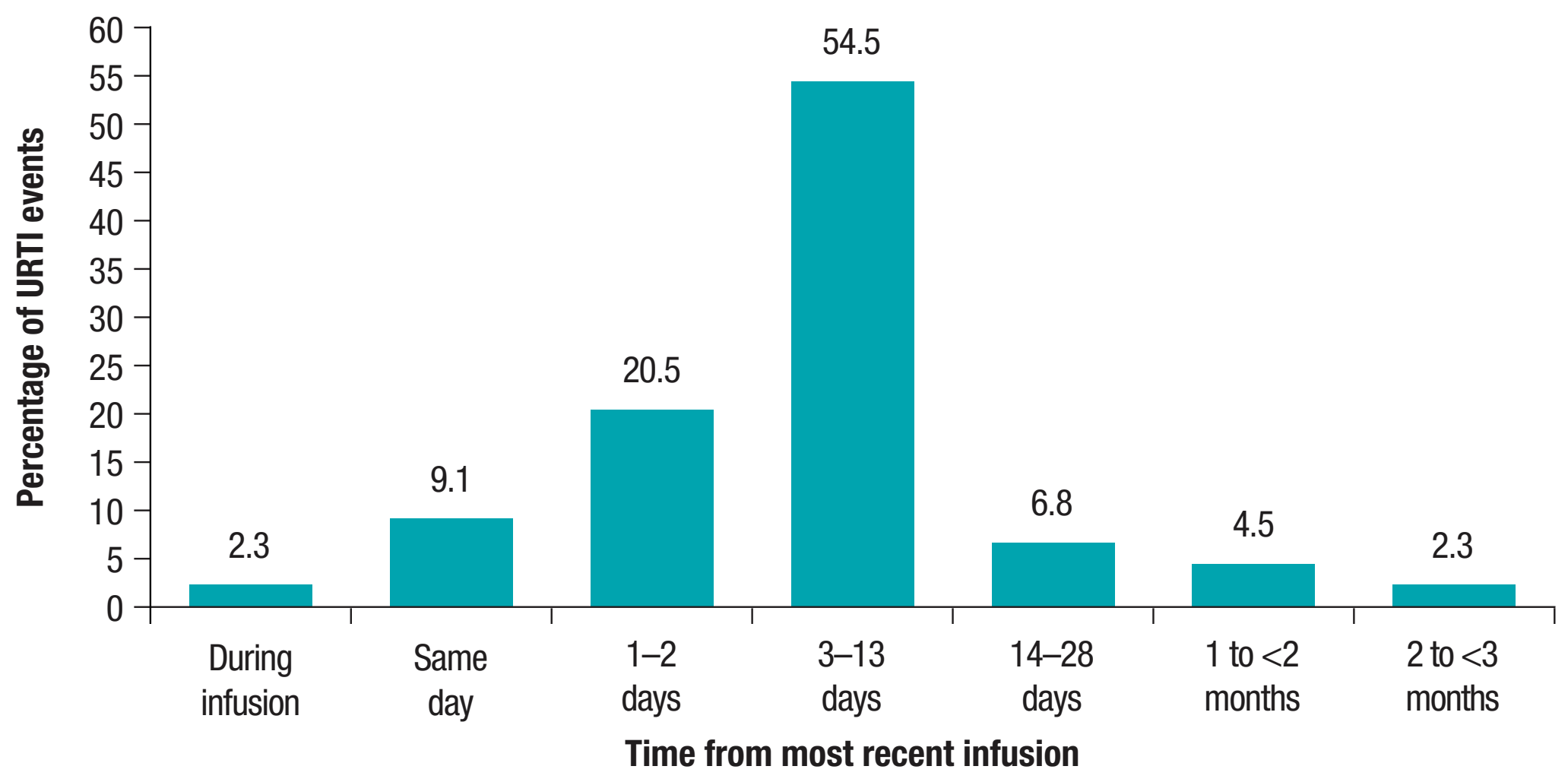
- From the 135 reports with available information, most URTIs occurred \geq 2 months after the first vedolizumab infusion (n=77/135 events; NR n=182/317 events; Figure 5) and \leq 13 days after the most recent infusion (n=38/44 events; NR n=273/317 events; Figure 6)
- Vedolizumab treatment was continued in most patients (n=229/257; NR n=43/300) who experienced a URTI (Figure 4)

Figure 5. Time to Onset of URTI Events from First Infusion (n=135 events)*



Data cut-off: 19 May 2016
*182 of 317 event reports did not have information available
URT, upper respiratory tract infection

Figure 6. Time to Onset of URTI Events from the Most Recent Infusion (n=44 events)*



Data cut-off: 19 May 2016
*273 of 317 event reports did not have information available
URT, upper respiratory tract infection

Conclusions

- LRTIs (including pneumonia) were infrequently reported in real-life clinical practice
- The most frequently reported LRTI was pneumonia, which is likely to be a reflection of reporting bias of more serious events compared with non-serious events in the post-marketing setting
- Of the 106 patients with an LRTI from ~46,978 PYs of therapy, 34 serious and 20 non-serious events of pneumonia were observed (equivalent to ~1 event/1000 PYs of therapy)
- Vedolizumab treatment was continued after the event in over half of LRTI reports (including pneumonia)
- The observation that nasopharyngitis was the most commonly reported URTI is not unexpected, and is in line with findings from vedolizumab clinical trials^{4,9}
 - Nasopharyngitis is also commonly reported with anti-TNF α treatment¹⁰ and in the general population
- No new trends were identified in the characterisation of RTIs from post-marketing experience with vedolizumab
- Limitations to consider when interpreting these data are those associated with post-marketing safety reporting, such as the voluntary nature of reporting, the inconsistent level of detail regarding patient history (including surgery and smoking), the timing of prior medication, and the resulting difficulty in establishing a causal relationship between drug and event
- Active pharmacovigilance will be maintained and, together with ongoing observational studies, will increase our understanding of RTIs with vedolizumab use

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