Risk of neoplasm with the neurokinin 3 receptor antagonist fezolinetant

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The data from the SKYLIGHT programme trial, aiming at evaluating the efficacy and safety of fezolinetant over 12–52 weeks in menopausal women, showed a numerical imbalance of neoplasms between the study groups.[1–3] In the 52-week SKYLIGHT 4 study (NCT04003389), six events of neoplasms were reported in five (0·82%) of 611 participants in the group administered fezolinetant 30 mg and ten events of neoplasms were reported in nine (1·48%) of 609 participants in the group administered fezolinetant 45 mg. Two events of neoplasms were reported in two (0·33%) of 610 participants in the placebo group, which is in line with the annual occurrence of neoplasms in this age group—namely, 335 per 100 000 people per year in the USA in people aged 50–69 years.[4]

	Placebo	Fezolinetant 30 mg once per day	Fezolinetant 45 mg once per day	Fezolinetant all
SKYLIGHT 1 (NCT04003155)				
12 weeks	0/175	0/174	3/173 (1·73%)	3/347 (0·86%)
52 week extension	NA	1/76 (1·32%)	1/76 (1·32%)	2/152 (1·32%)
SKYLIGHT 2 (NCT04003142)				
12 weeks	0/167	0/166	2/167 (1·20%)	2/333 (0·60%)
52 week extension	NA	1/76 (1·32%)	1/75 (1·33%)	2/151 (1·32%)
SKYLIGHT 4 (NCT04003389)				
52 weeks	2/610 (0·33%)	5/611 (0·82%)	9/609 (1·48%)	14/1220 (1·15%)
Fixed effect model meta-analysis without extension				
n/N (%)	2/952 (0·21%; reference)	5/951 (0·53%)	14/949 (1·48%)	19/1900 (1·00%)
Peto OR (95% CI)	NA	2·36 (0·53–10·43)	4·55 (1·70–12·15)	2·94 (1·18–7·32)
p value	NA	p=0·257	p=0·003	p=0·020
Fixed effect model meta-analysis with extension				
n/N (%)	2/952 (0·21%; reference)	7/1103 (0·64%)	16/1100 (1·46%)	23/2203 (1·04%)
Peto OR (95% CI)	NA	2·83 (0·76–10·54)	4·25 (1·67–10·80)	2·94 (1·25–6·93)
p value	NA	p=0·120	p=0·002	p=0·013

Data are n/N (%) unless otherwise specified. Cases of neoplasms were extracted from ClinicalTrials.gov and are reported in detail in the appendix (pp 13–14). For the fixed-effect model meta-analysis, pooled ORs were computed using the Peto method. n=number of participants affected by neoplasm. NA=not applicable. OR=odds ratio.

Table: **Summary of participants affected by benign, malignant, and unspecified (including cysts and polyps) neoplasm events in the fezolinetant SKYLIGHT programme**

In the 12-week SKYLIGHT 1 (NCT04003155) and SKYLIGHT 2 (NCT04003142) studies, three neoplasm events in three (1·73%) of 173 participants and two neoplasm events in two (1·20%) of 167 participants, respectively, were reported, both in the fezolinetant 45 mg group. These two studies were extended over 52 weeks and participants in the placebo group were switched to fezolinetant 30 mg or 45 mg from week 13 to week 52. During this period, four additional cases of neoplasms were reported in four participants, one in each of the two fezolinetant group in the two studies.

Three (12·00%) of the 25 cases retrieved across the trials were considered benign. Details about these cases, data collection, and statistical methods are provided in the appendix (pp 1, 14). The Peto odds ratio (OR) from a meta-analysis of the SKYLIGHT programme revealed that the OR of risk of neoplasms was significantly higher in the fezolinetant groups compared with placebo, when not including extension trials (Peto OR 2·94, 95% CI 1·18–7·32, p=0·020). Stratification by dose shows that the risk was higher with fezolinetant 45 mg, which might suggest a dose-dependent effect (table).

In the phase 2b dose-ranging study of fezolinetant (NCT03192176), one case of neoplasm was also observed in the fezolinetant 60 mg group (one [2·22%] of 45 participants). Notably, over the 26 neoplasm events reported in 24 participants in the fezolinetant groups—namely, 25 events in the SKYLIGHT programme plus one event in the phase 2b study—13 (50·00%) of these events concerned neoplasms from the skin or the mucosa.

The higher incidence of neoplasms with fezolinetant requires an in-depth evaluation of all cases observed to further assess associated baseline risk factors and propose risk minimisation strategies. According to the US Food and Drug Administration clinical review, no underlying mechanism or potential risk was identified during the non-clinical development of fezolinetant.[5] Fezolinetant acts as an antagonist of the neurokinin B receptor 3 in kisspeptin, neurokinin B, and dynorphin neurons, possibly affecting kisspeptin signalling, but this adverse event could also result from other off-target effects.

JD conceived the study. JD and CB performed the extraction of the data and the analyses. J-MD supervised the content and provided expert testimony and revised the data. JD reports personal fees from Daiichi-Sankyo, Diagnostica Stago, Gedeon Richter, GyneBio Pharma, Mithra Pharmaceuticals, Norgine, Roche, Roche Diagnostics, Technoclone, Werfen, and YHLO, outside the submitted work. All other authors declare no competing interests. All data are available on request from the corresponding author.

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See Online for appendix

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1 Johnson KA, Martin N, Nappi RE, et al. Efficacy and safety of fezolinetant in moderate-to-severe vasomotor symptoms associated with menopause: a phase 3 RCT. *J Clin Endocrinol Metab* 2023; **108:** 1981–97.

2 Neal-Perry G, Cano A, Lederman S, et al. Safety of fezolinetant for vasomotor symptoms associated with menopause: a randomized controlled trial. *Obstet Gynecol* 2023; **141:** 737–47.

3 Lederman S, Ottery FD, Cano A, et al. Fezolinetant for treatment of moderate-to-severe vasomotor symptoms associated with menopause (SKYLIGHT 1): a phase 3 randomised controlled study. *Lancet* 2023; **401:** 1091–102.

4 Roser M, Ritchie H. Cancer. July, 2015. https://ourworldindata.org/cancer (accessed April 19, 2023).

5 Centre for Drug Evaluation and Research. Clinical review(s). Jan 23, 2023. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/216578Orig1s000MedR.pdf (accessed July, 6, 2023).