Assessment of ocular toxicity of CDK inhibitors

This case study outlines how OFF-X™ can be leveraged to assess the potential risk of ocular toxicity associated with Cyclin-dependent kinase (CDK) inhibitors.

The recent findings of eye disorders reported during clinical studies with different CDK inhibitors leading to clinical holds[1,2] have raised various questions:

- Is ocular toxicity a class effect of CDK inhibitors?
- Have ocular disorders been reported with already marketed CDK inhibitors?
- Were these toxicities anticipated in preclinical studies performed with different CDK inhibitors?
- Is the inhibition of all CDK subtypes associated with this safety liability or does evidence suggest a particular member(s) of the family to be the culprit?

[1] https://investors.nuvationbio.com/news/news-details/2022/Nuvation-Bio-Announces-FDA-Partial-Clinical-Hold-for-Phase-1-Study-of-NUV-422-in-Solid-Tumors/default.aspx

[2] https://ir.blueprintmedicines.com/news-releases/news-release-details/blueprint-medicines-announces-partial-clinical-hold-phase-12

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The unique combination of expertly curated data from multiple data sources (journal articles, congress proceedings, company communications, clinical trial registries and regulatory agency documents) and analytic tools offered by OFF-X saves time compiling the different preclinical and clinical evidence available in the public domain when we seek to address the questions above.

Is ocular toxicity a class effect of CDK inhibitors?

OFF-X facilitates the assessment of the overall safety profile of CDK inhibitors based on the **OFF-X Target/Class Score**, a measure of the evidence for each target-action and adverse event association based on the available information in the portal. This rule-based algorithm, applied to the daily updated OFF-X content, considers not only the publications describing class effects, but also the degree of evidence for each individual drug in the class (OFF-X Drug Score) as well as the percentage of drugs in the class linked with the same adverse event.

We can easily browse the different ocular findings, coded as **MedDRA** Preferred Terms and grouped by System Organ Class. This allows us to identify our OFF-X safety alerts of interest i.e. the details manually extracted from each publication (e.g., summary, severity/causality/on-target insights, alert phase, species) and which always includes a link to the original data source.

Using the comparative drug safety evidence tool we can easily benchmark the evidence linking each CDK inhibitor with eye disorders, covering approved, discontinued or drugs in development. The granularity of the data and the multiple filters available in OFF-X allows us to identify causal and/or serious/severity grade ≥3 events. Despite overall evidence linking the whole class of CDK inhibitors with ocular disorders is not as high as with hematologic or gastrointestinal issues, we can easily identify relevant similarities (and differences) among the different members of the class.

Figure 1: OFF-X safety alerts covering eye disorders associated with CDK inhibitors

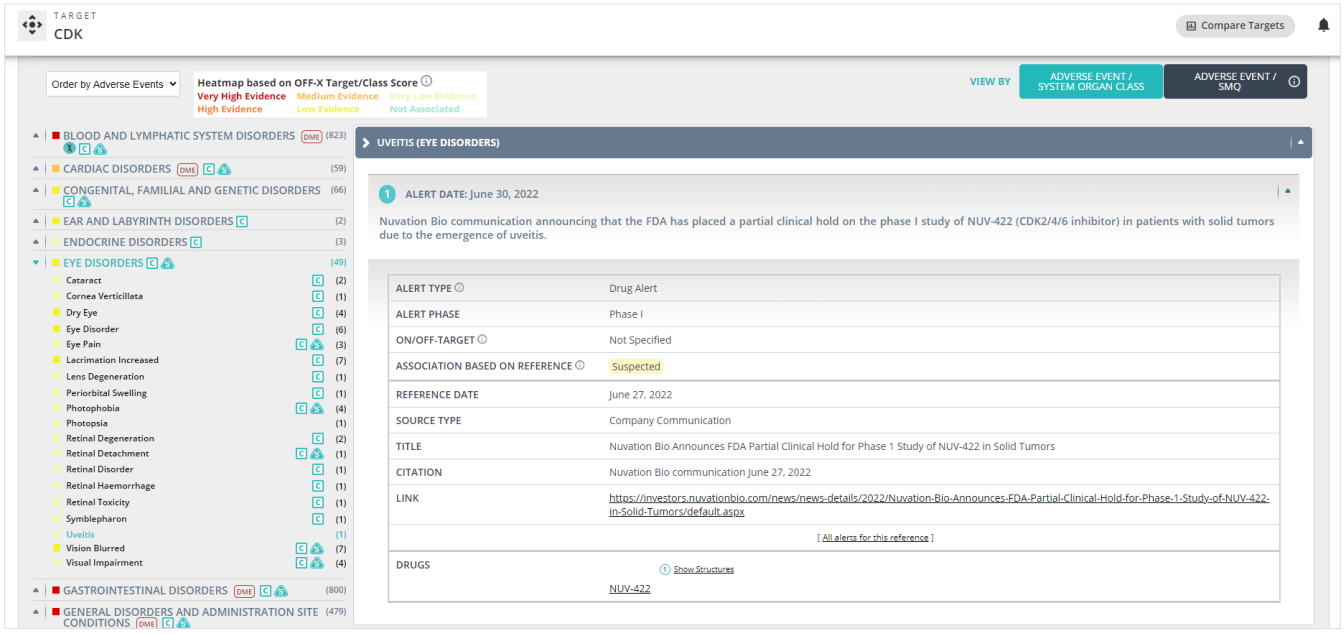
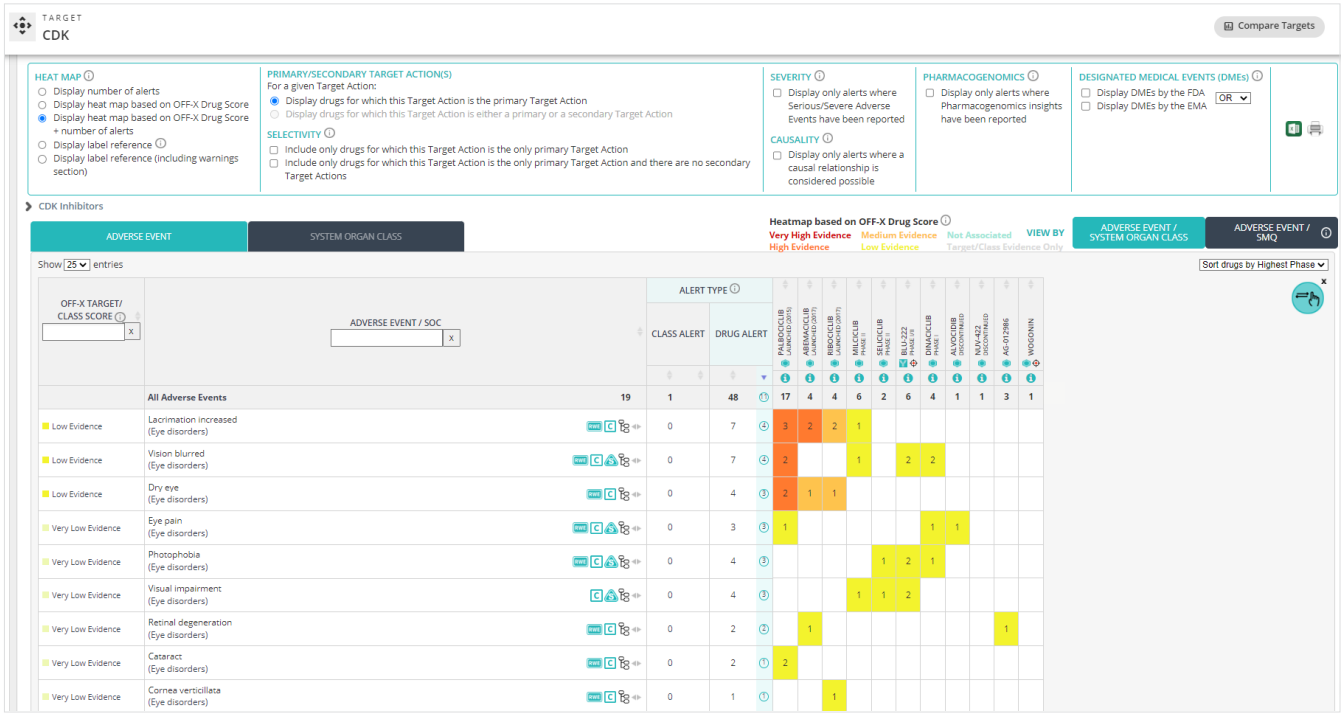
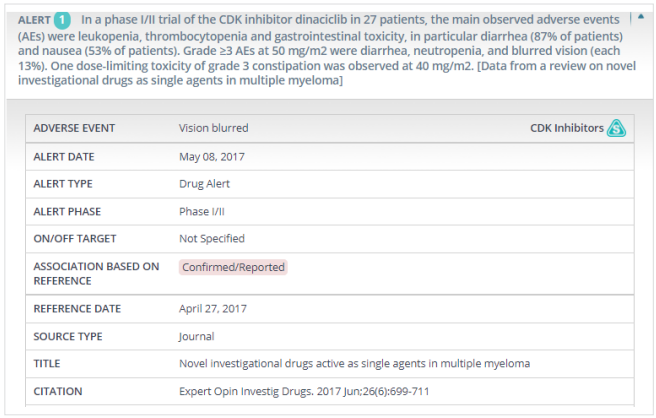


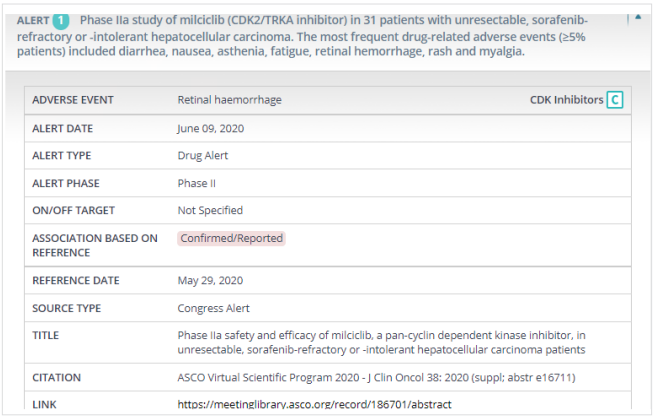
Figure 2: Comparative view of ocular toxicities of CDK inhibitors



From the table above we can access the details behind the associations between different CDK inhibitors and ocular adverse events extracted from multiple data sources.

Figure 3: Examples of OFF-X Safety Alerts from journals and congresses





Have ocular disorders been reported with already marketed CDK inhibitors?

OFF-X allows us to assess the ocular safety of the CDK4/CDK6 inhibitors that have been approved such as palbociclib, abemaciclib and ribociclib, including insights from their approval documents and real-world data.

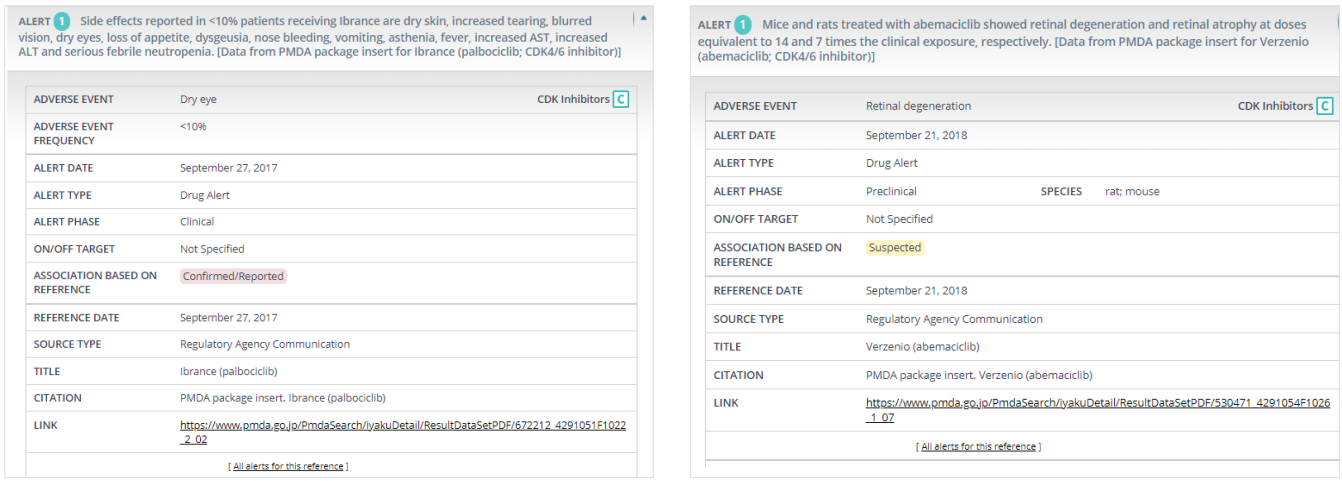
Focusing on the safety intelligence extracted from regulatory approval documents, we can identify and compare mentions of ocular toxicities included in the labels by the **EMA, FDA and PMDA** of these 3 drugs, including the frequency of the adverse event in clinical studies and preclinical toxicity data.

Additionally, the **real-world evidence dashboard** allows us to analyze and compare reports of ocular toxicities in FDA Adverse Event Reporting System (**FAERS**) and Japanese Adverse Drug Event Report (**JADER**) database. Both the OFF-X Drug Score and those adverse events included in each drug's label are shown for reference when analyzing the individual case safety reports, and their statistical significance, in FAERS and JADER. This OFF-X data facilitates the identification and assessment of potential new signals, such as visual impairment, which is not included in any of the 3 labels for any of the 3 approved drugs. According to 4 out of the 6 well-established statistical methods included in OFF-X, visual impairment is significantly associated with ribociclib but not with abemaciclib (1 of 6 methods) or palbociclib (0 of 6 methods).

Figure 4: Comparative view of ocular toxicities included in regulatory approval documents

OFF-X TARGET/ CLASS SCORE	ADVERSE EVENT / SOC	ALERT TYPE: CLASS ALERT	ALERT TYPE: DRUG ALERT	PALBOCICLIB LAUNCHED (2015)	ABEMACICLIB LAUNCHED (2017)	RIBOCICLIB LAUNCHED (2017)
	All Adverse Events 10	**0**	**24**	**17**	**4**	**4**
Low Evidence	Eye disorder (Eye disorders)	0	5	L FDA EMA		
Low Evidence	Lacrimation increased (Eye disorders)	0	6	L EMA PMDA	L EMA PMDA	L EMA
Low Evidence	Dry eye (Eye disorders)	0	4	L EMA PMDA	L PMDA	L EMA
Low Evidence	Vision blurred (Eye disorders)	0	2	L EMA PMDA		
Very Low Evidence	Cataract (Eye disorders)	0	2	L FDA		
Very Low Evidence	Eye pain (Eye disorders)	0	1			
Very Low Evidence	Retinal degeneration (Eye disorders)	0	1		L PMDA	
Very Low Evidence	Lens degeneration (Eye disorders)	0	1	L FDA		
Very Low Evidence	Cornea verticillata (Eye disorders)	0	1			
Very Low Evidence	Periorbital swelling (Eye disorders)	0	1			

Figure 5: Examples of OFF-X Safety Alerts from approval documents



ALERT 1 Side effects reported in <10% patients receiving Ibrance are dry skin, increased tearing, blurred vision, dry eyes, loss of appetite, dysgeusia, nose bleeding, vomiting, asthenia, fever, increased AST, increased ALT and serious febrile neutropenia. [Data from PMDA package insert for Ibrance (palbociclib; CDK4/6 inhibitor)]

ADVERSE EVENT	Dry eye	CDK Inhibitors C
ADVERSE EVENT FREQUENCY	<10%	
ALERT DATE	September 27, 2017	
ALERT TYPE	Drug Alert	
ALERT PHASE	Clinical	
ON/OFF TARGET	Not Specified	
ASSOCIATION BASED ON REFERENCE	Confirmed/Reported	
REFERENCE DATE	September 27, 2017	
SOURCE TYPE	Regulatory Agency Communication	
TITLE	Ibrance (palbociclib)	
CITATION	PMDA package insert. Ibrance (palbociclib)	
LINK	https://www.pmda.go.jp/PmdaSearch/iyakuDetail/ResultDataSetPDF/672212_4291051F1022_2_02	

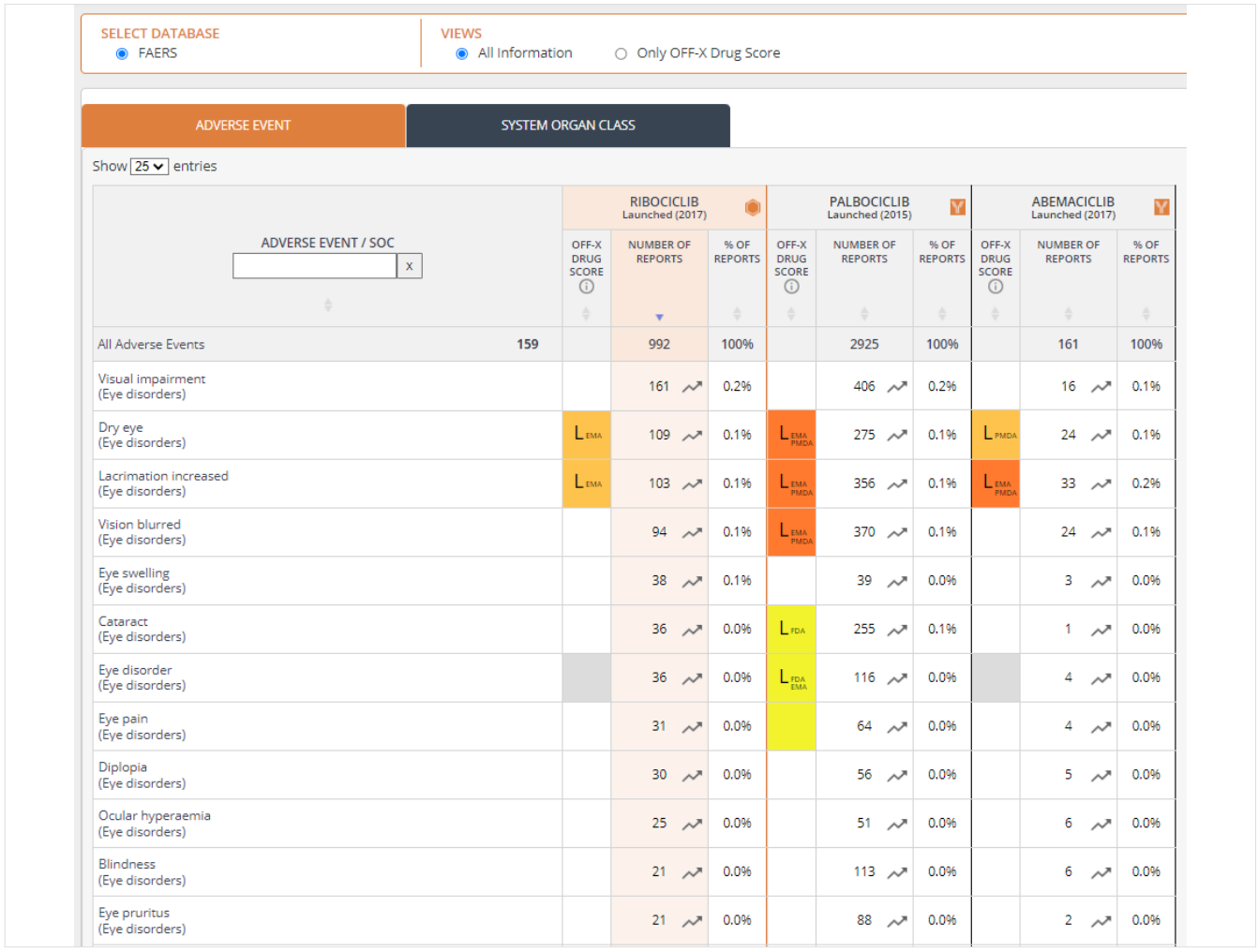
[All alerts for this reference]

ALERT 1 Mice and rats treated with abemaciclib showed retinal degeneration and retinal atrophy at doses equivalent to 14 and 7 times the clinical exposure, respectively. [Data from PMDA package insert for Verzenio (abemaciclib; CDK4/6 inhibitor)]

ADVERSE EVENT	Retinal degeneration		CDK Inhibitors C
ALERT DATE	September 21, 2018		
ALERT TYPE	Drug Alert		
ALERT PHASE	Preclinical	SPECIES	rat; mouse
ON/OFF TARGET	Not Specified		
ASSOCIATION BASED ON REFERENCE	Suspected		
REFERENCE DATE	September 21, 2018		
SOURCE TYPE	Regulatory Agency Communication		
TITLE	Verzenio (abemaciclib)		
CITATION	PMDA package insert. Verzenio (abemaciclib)		
LINK	https://www.pmda.go.jp/PmdaSearch/iyakuDetail/ResultDataSetPDF/530471_4291054F1026_1_07		

[All alerts for this reference]

Figure 6: Comparative view of ocular toxicities reported in FAERS and approval documents



SELECT DATABASE: FAERS | VIEWS: All Information / Only OFF-X Drug Score

ADVERSE EVENT | SYSTEM ORGAN CLASS

Show 25 entries

ADVERSE EVENT / SOC		RIBOCICLIB Launched (2017)			PALBOCICLIB Launched (2015)			ABEMACICLIB Launched (2017)		
		OFF-X DRUG SCORE	NUMBER OF REPORTS	% OF REPORTS	OFF-X DRUG SCORE	NUMBER OF REPORTS	% OF REPORTS	OFF-X DRUG SCORE	NUMBER OF REPORTS	% OF REPORTS
All Adverse Events	159		992	100%		2925	100%		161	100%
Visual impairment (Eye disorders)			161	0.2%		406	0.2%		16	0.1%
Dry eye (Eye disorders)		L EMA	109	0.1%	L EMA PMDA	275	0.1%	L PMDA	24	0.1%
Lacrimation increased (Eye disorders)		L EMA	103	0.1%	L EMA PMDA	356	0.1%	L EMA PMDA	33	0.2%
Vision blurred (Eye disorders)			94	0.1%	L EMA PMDA	370	0.1%		24	0.1%
Eye swelling (Eye disorders)			38	0.1%		39	0.0%		3	0.0%
Cataract (Eye disorders)			36	0.0%	L FDA	255	0.1%		1	0.0%
Eye disorder (Eye disorders)			36	0.0%	L FDA EMA	116	0.0%		4	0.0%
Eye pain (Eye disorders)			31	0.0%		64	0.0%		4	0.0%
Diplopia (Eye disorders)			30	0.0%		56	0.0%		5	0.0%
Ocular hyperaemia (Eye disorders)			25	0.0%		51	0.0%		6	0.0%
Blindness (Eye disorders)			21	0.0%		113	0.0%		6	0.0%
Eye pruritus (Eye disorders)			21	0.0%		88	0.0%		2	0.0%

Figure 7: Case report analysis and statistical significance of FAERS data

Has ocular toxicity been reported during preclinical development of CDK inhibitors?

Early detection of safety liabilities using preclinical animal models is key to reducing risk during the first stages of clinical development. And access to preclinical toxicity information can be used to determine the best model to anticipate issues of new drug candidates.

OFF-X's unique translational safety approach allows us to identify ocular toxicities reported with CDK inhibitors in preclinical studies, including conflicting results observed in different species, and assess their translation into clinical findings. This information is critical to anticipate and monitor potential issues with novel members of the class but also to better understand the mechanism of adverse events observed in later stages of development.

Figure 8: Translational approach to eye disorders reported with CDK inhibitors

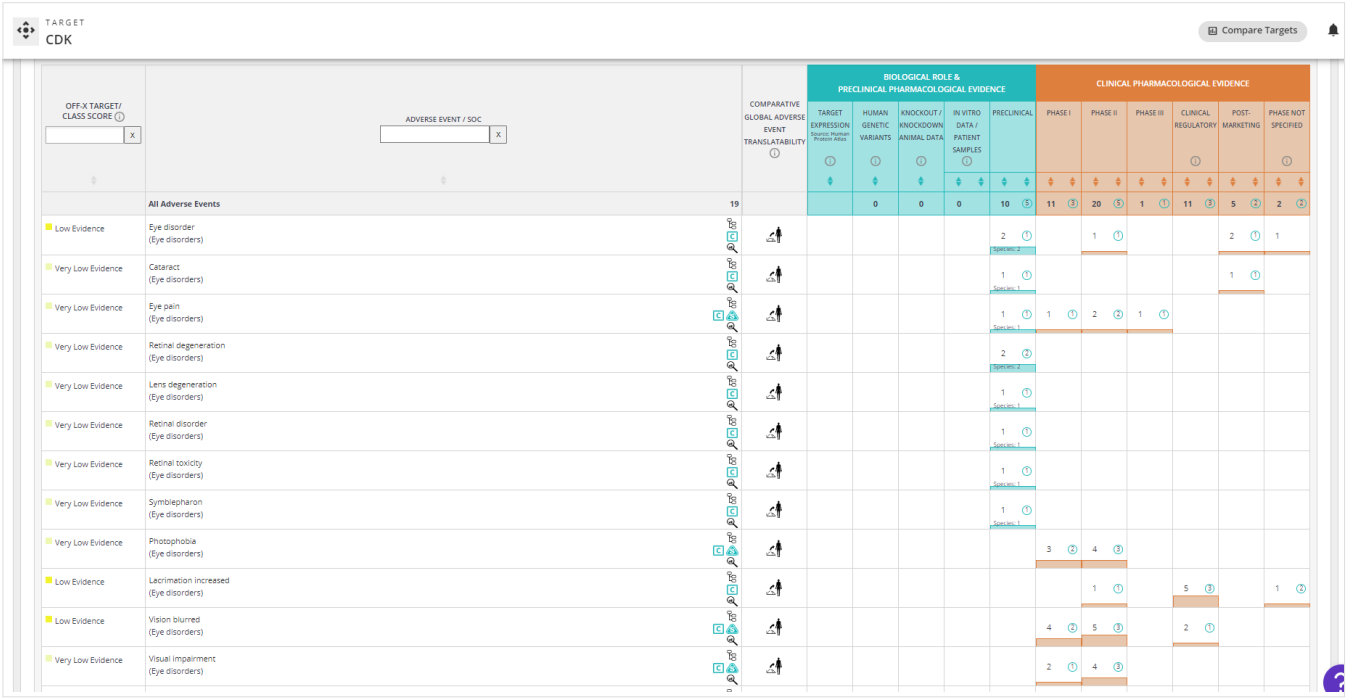
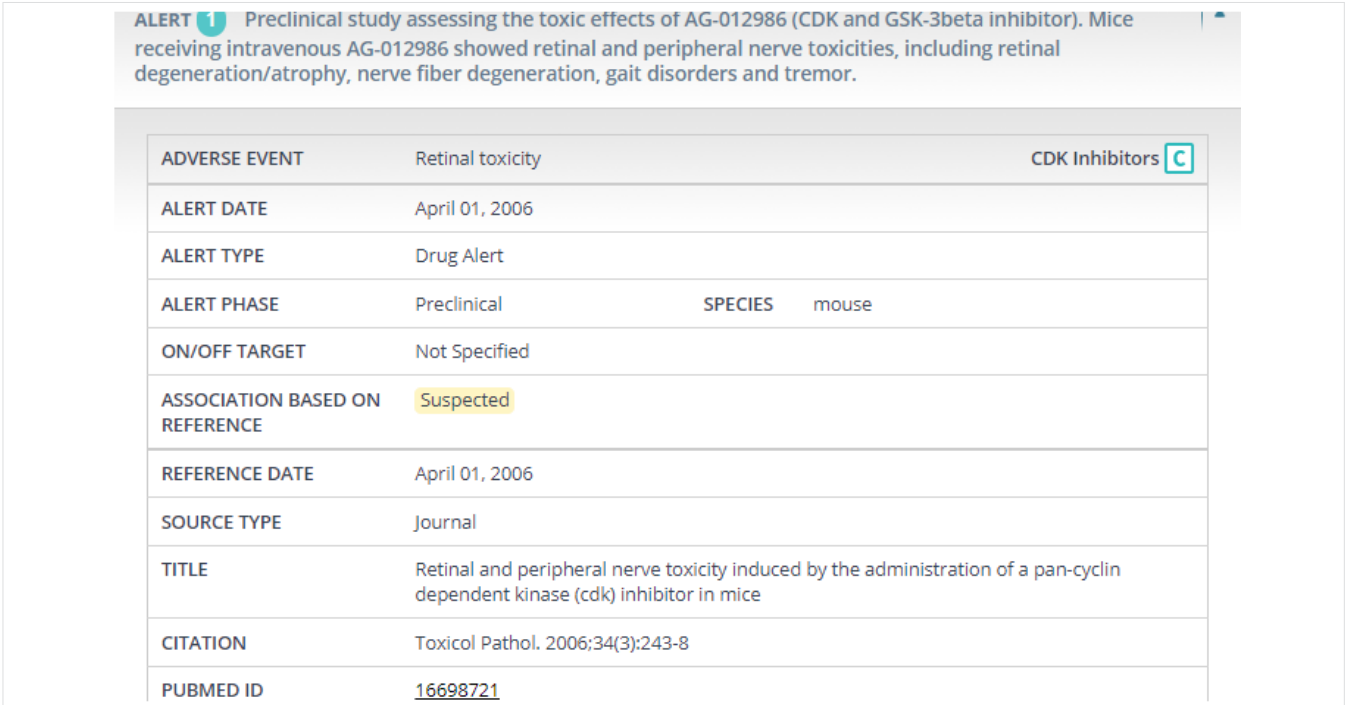


Figure 9: Example of preclinical OFF-X Safety Alert

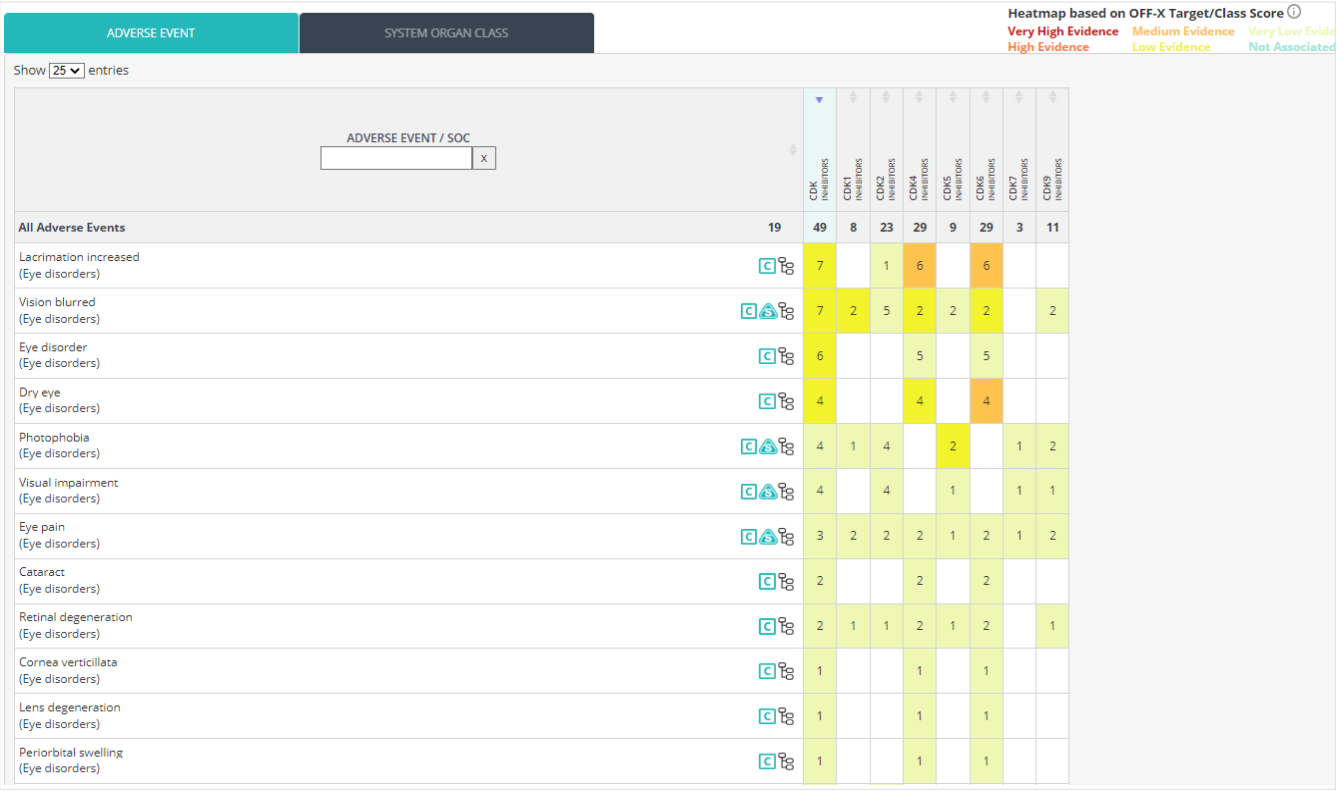


Is ocular toxicity equally associated with all members of the CDK family?

Once we have been able to assess the amount of information available in OFF-X supporting the association between CDK inhibitors and the development of eye disorders, we can further analyze if there are insights linking specific members of the CDK family with such toxicities.

To do so, we can easily compare the safety profile of the CDK class with that of each family member using the OFF-X Target/Class Analytics. This approach allows us to identify significant differences between CDK4/CDK6 and other subtypes, such as CDK2 or CDK5. Thus, whilst CDK4/CDK6 inhibitors, including those on the market, have been mainly associated with lacrimation disorders and blurred vision, the inhibition of CDK2 and CDK5 seems to be associated with visual impairment and photophobia. These findings suggest different roles for different members of the CDK family in the development of ocular toxicities. Thus, the relative selectivity profile of CDK inhibitors with respect to each family member may determine their risk of causing concerning ocular toxicities.

Figure 10: Comparative view of the ocular safety profile of different members of the CDK family



This case study highlights how OFF-X's combination of curated data and analytic tools can be leveraged to save time and provide insights when assessing the amount of evidence behind potential new class effects.

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