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

Clarivate™

The unique combination of expertly curated data from multiple data sources (journal articles, congress proceedings, company communications, clinical trial registries and regulatory agency documents), RWD (FAERS, JADER) and analytic tools 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 (SOC) or Standardized MedDRA Query (SMQ). 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

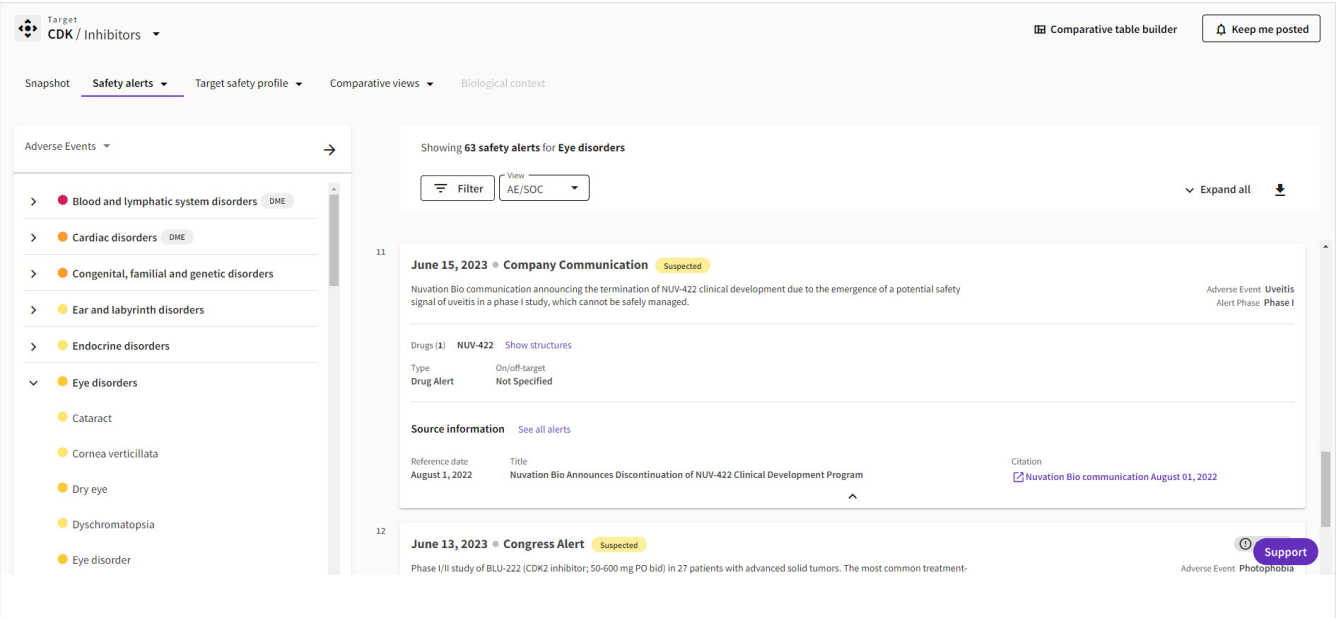
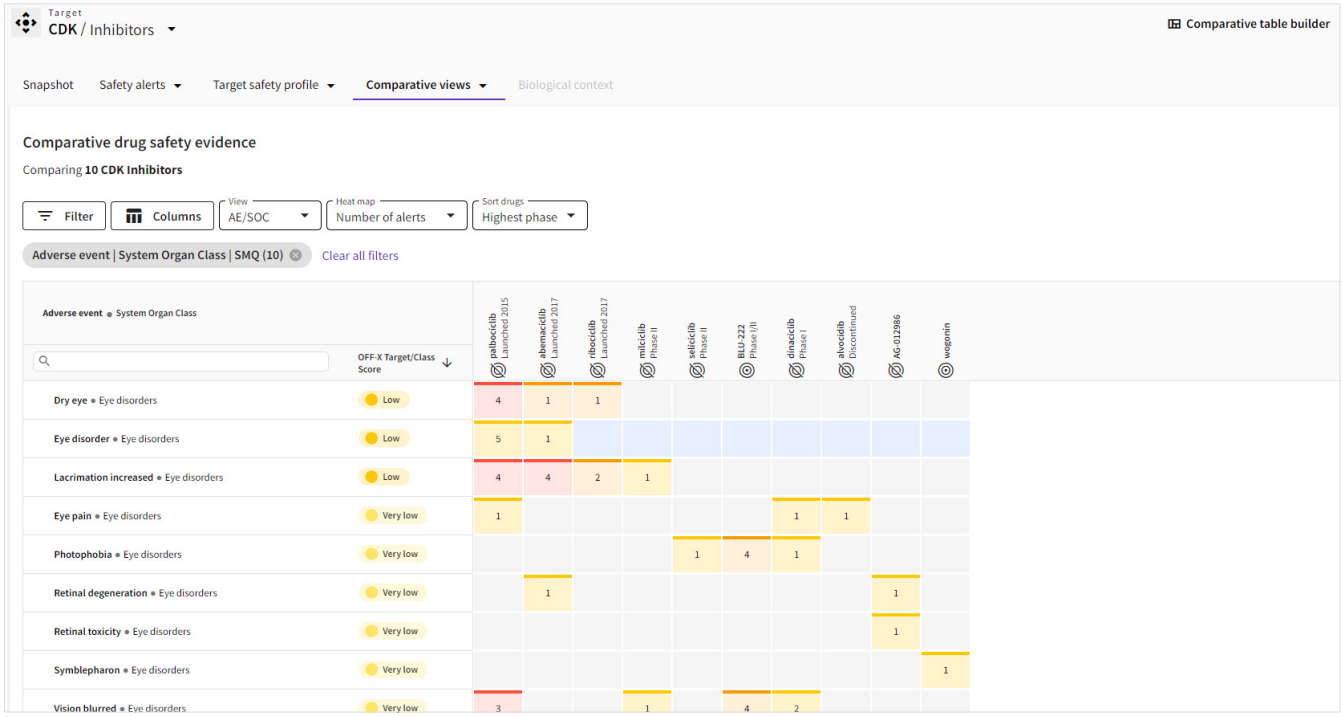
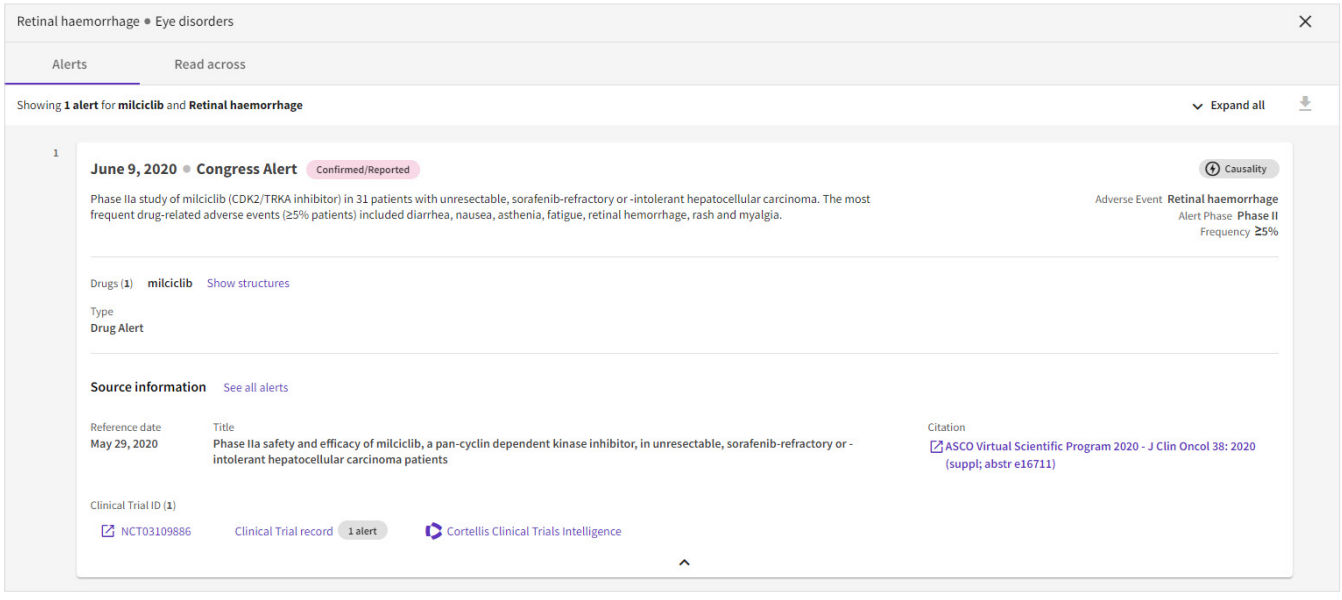


Figure 2: Comparative view of ocular toxicities of CDK inhibitors



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: Example of OFF-X Safety Alert from 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 associated with ribociclib in FAERS 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

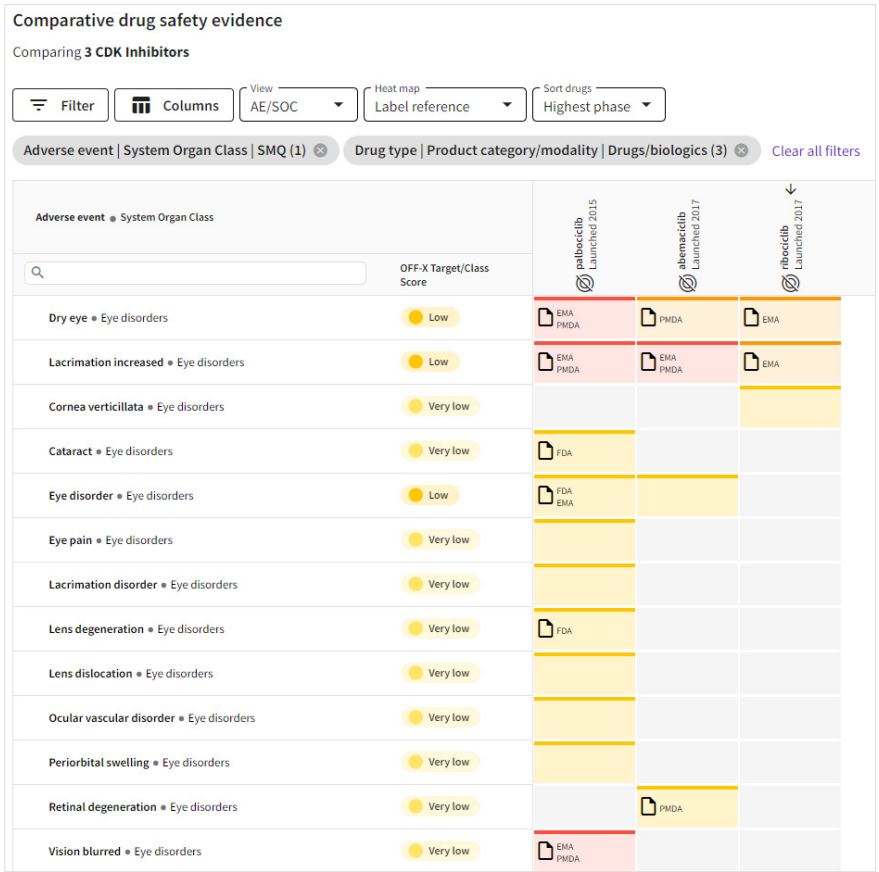


Figure 5: Example of OFF-X Safety Alert from approval documents

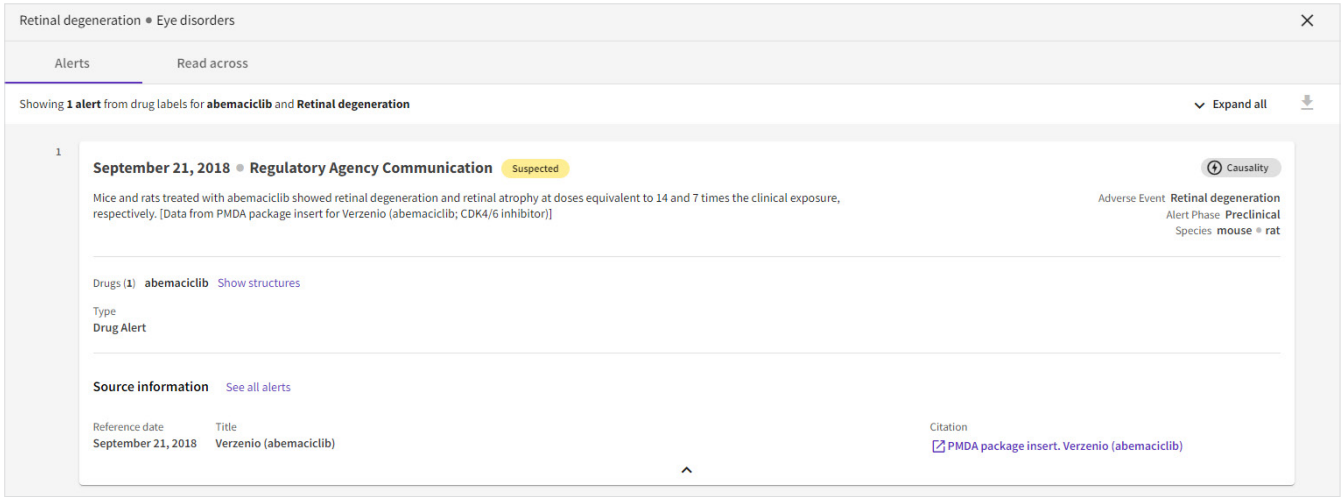


Figure 6: Comparative view of ocular toxicities reported in FAERS and approval documents

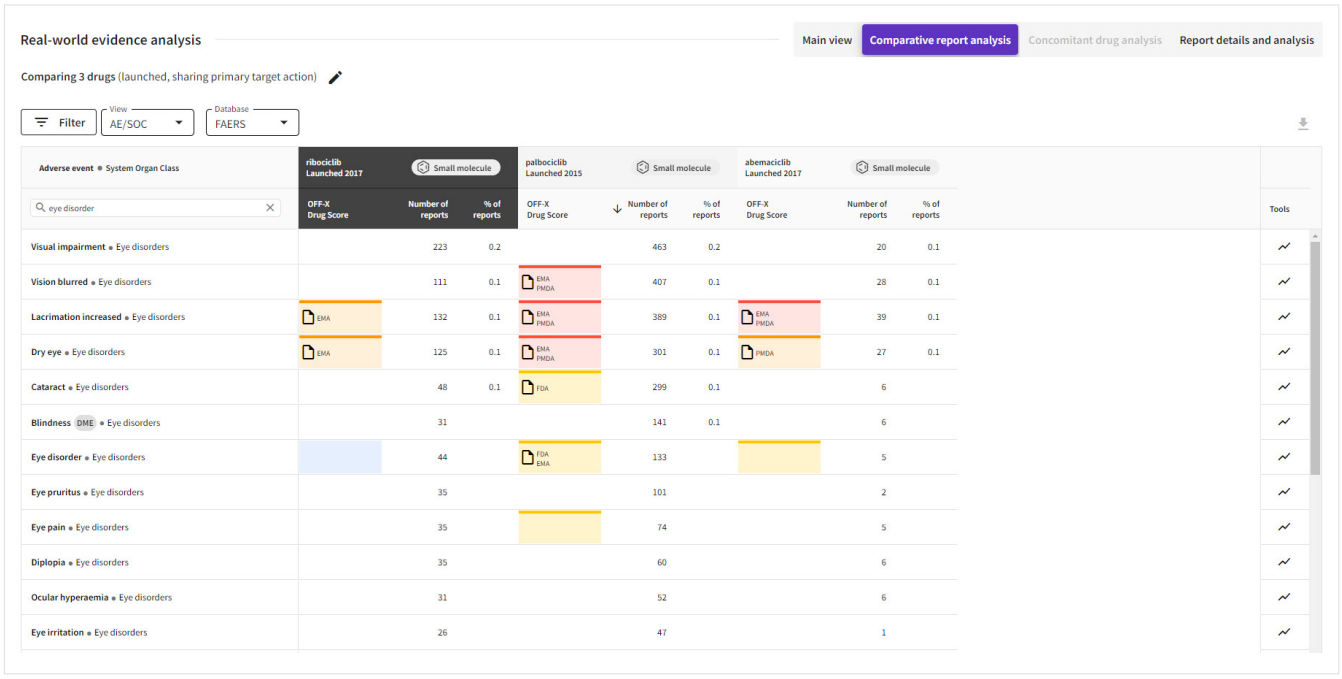
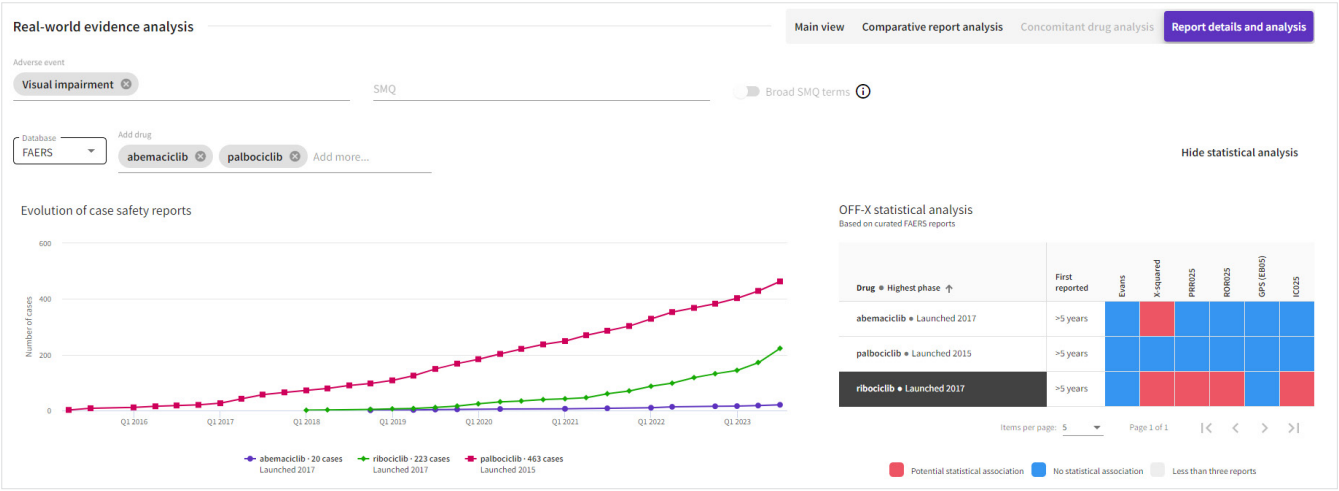


Figure 7: Case report analysis and statistical significance of FAERS data

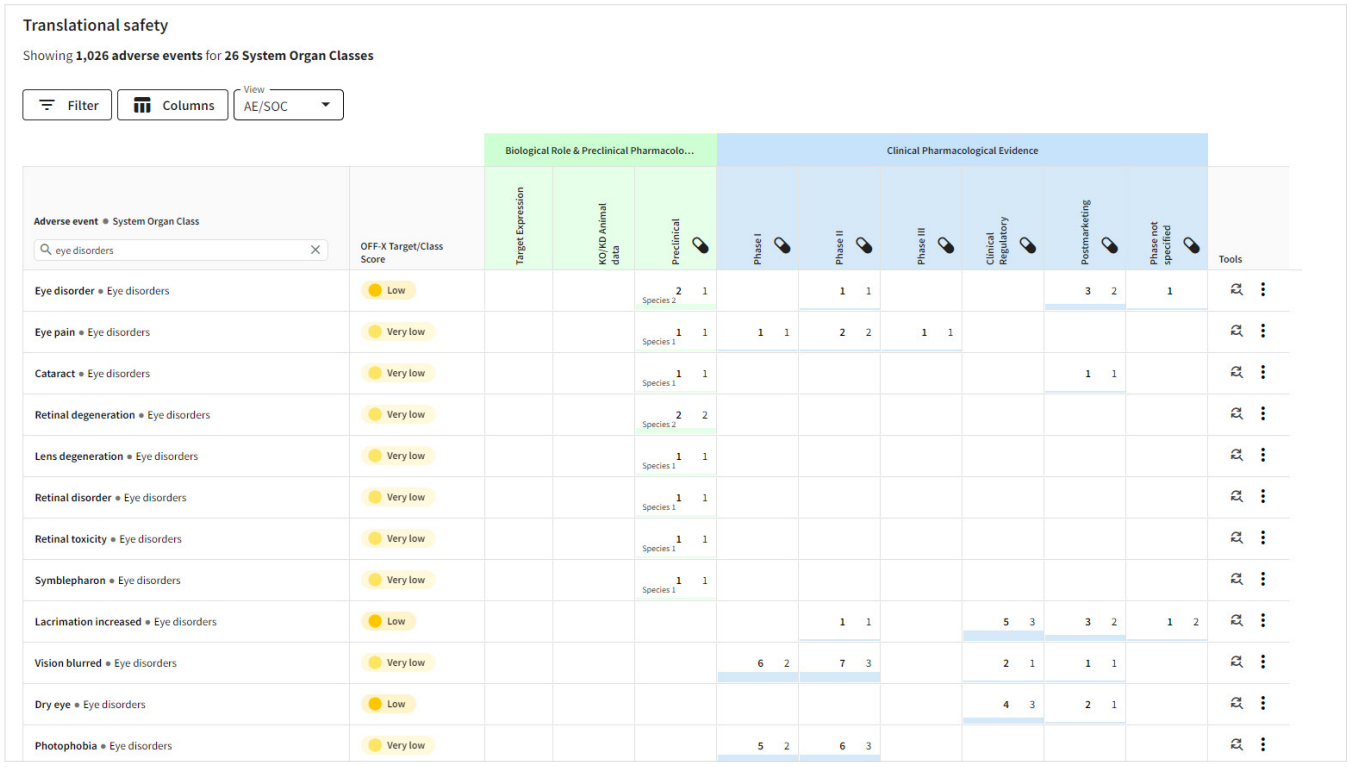


Has ocular toxicity been reported during preclinical development of CDK inhibitors?

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



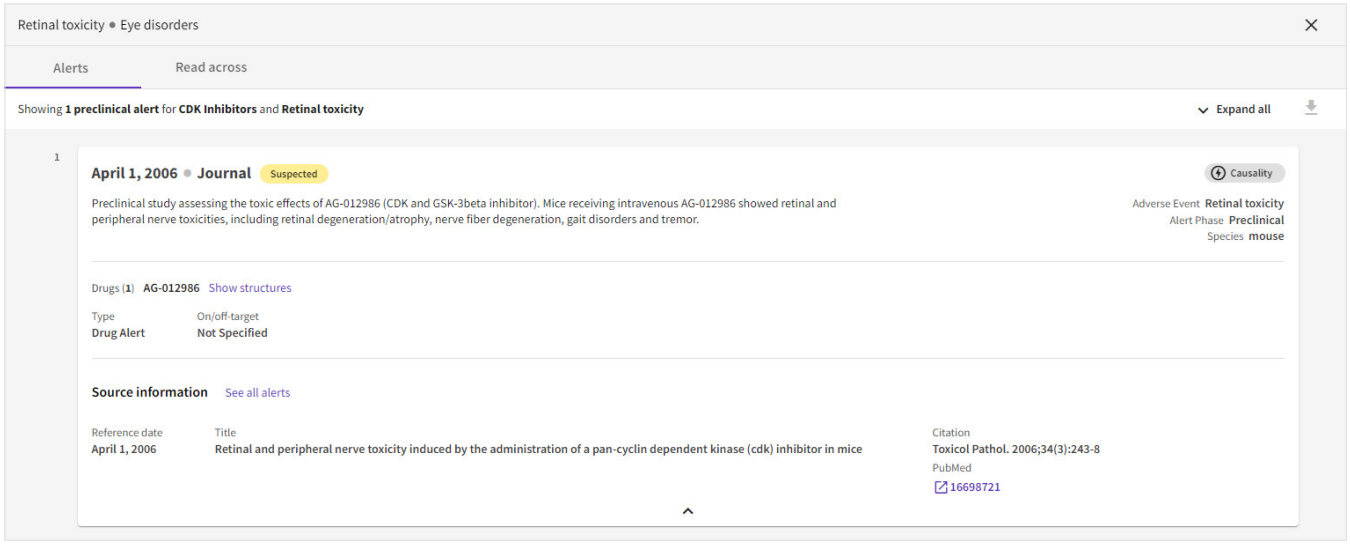
Translational safety

Showing **1,026 adverse events** for **26 System Organ Classes**

Filter | Columns | View: AE/SOC

Adverse event • System Organ Class	OFF-X Target/Class Score	Biological Role & Preclinical Pharmacolo…			Clinical Pharmacological Evidence						Tools
		Target Expression	KO/KD Animal data	Preclinical	Phase I	Phase II	Phase III	Clinical Regulatory	Postmarketing	Phase not specified	
eye disorders											
Eye disorder • Eye disorders	Low			2 1 Species 2		1 1			3 2	1	
Eye pain • Eye disorders	Very low			1 1 Species 1	1 1	2 2	1 1				
Cataract • Eye disorders	Very low			1 1 Species 1					1 1		
Retinal degeneration • Eye disorders	Very low			2 2 Species 2							
Lens degeneration • Eye disorders	Very low			1 1 Species 1							
Retinal disorder • Eye disorders	Very low			1 1 Species 1							
Retinal toxicity • Eye disorders	Very low			1 1 Species 1							
Symblepharon • Eye disorders	Very low			1 1 Species 1							
Lacrimation increased • Eye disorders	Low					1 1		5 3	3 2	1 2	
Vision blurred • Eye disorders	Very low				6 2	7 3		2 1	1 1		
Dry eye • Eye disorders	Low							4 3	2 1		
Photophobia • Eye disorders	Very low				5 2	6 3					

Figure 9: Example of preclinical OFF-X Safety Alert



Retinal toxicity • Eye disorders

Alerts | Read across

Showing **1 preclinical alert** for **CDK Inhibitors** and **Retinal toxicity**

Expand all

1

April 1, 2006 • **Journal** Suspected

Causality

Preclinical study assessing the toxic effects of AG-012986 (CDK and GSK-3beta inhibitor). Mice receiving intravenous AG-012986 showed retinal and peripheral nerve toxicities, including retinal degeneration/atrophy, nerve fiber degeneration, gait disorders and tremor.

Adverse Event **Retinal toxicity**
Alert Phase **Preclinical**
Species **mouse**

Drugs (1) **AG-012986** Show structures

Type: **Drug Alert**
On/off-target: **Not Specified**

Source information See all alerts

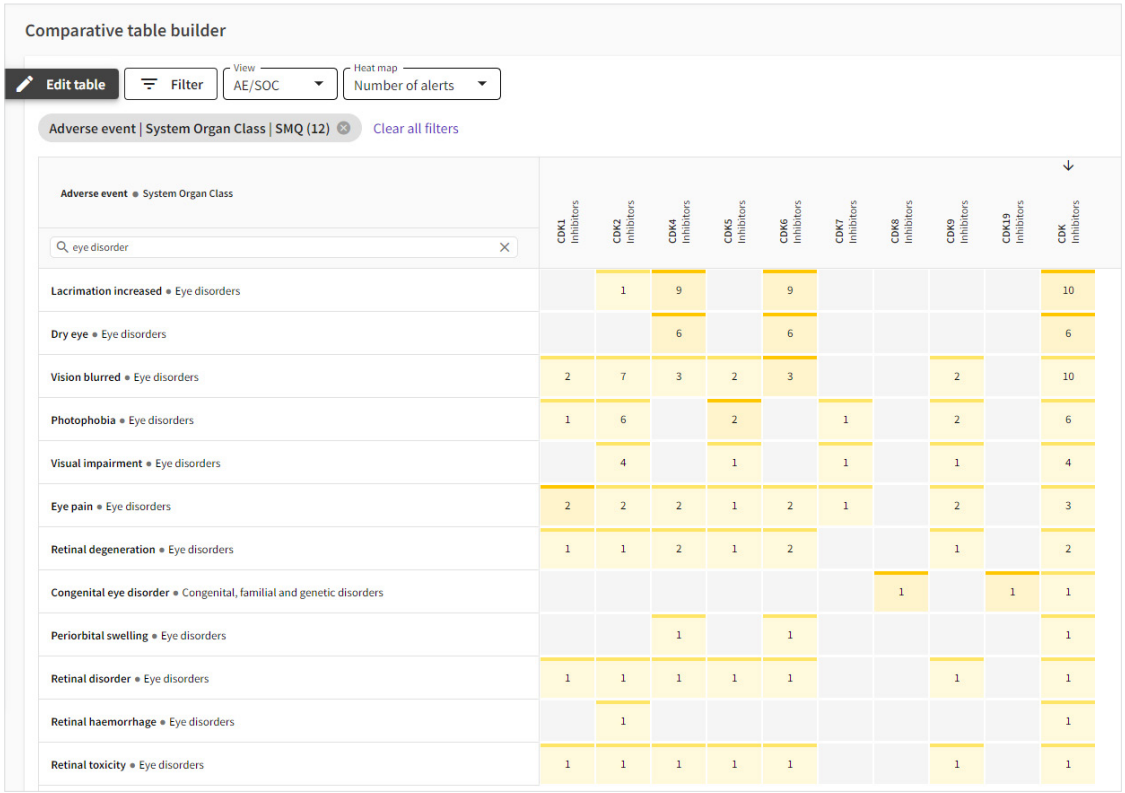
Reference date: **April 1, 2006**
Title: **Retinal and peripheral nerve toxicity induced by the administration of a pan-cyclin dependent kinase (cdk) inhibitor in mice**
Citation: **Toxicol Pathol. 2006;34(3):243-8**
PubMed: **16698721**

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 Comparative Table Builder. 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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About Clarivate

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