



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>

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

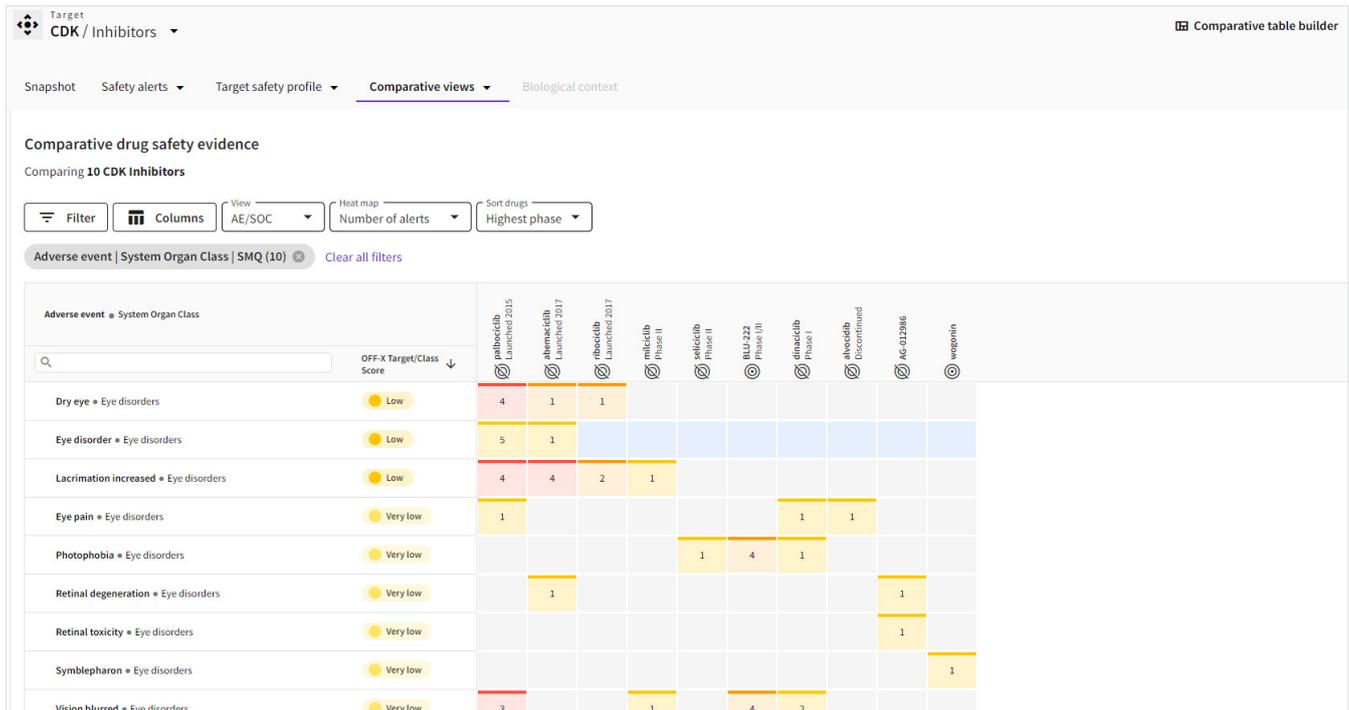
each publication (e.g., summary, severity/causality/on-target insights, alert phase, species) and which always includes a link to the original data source.

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

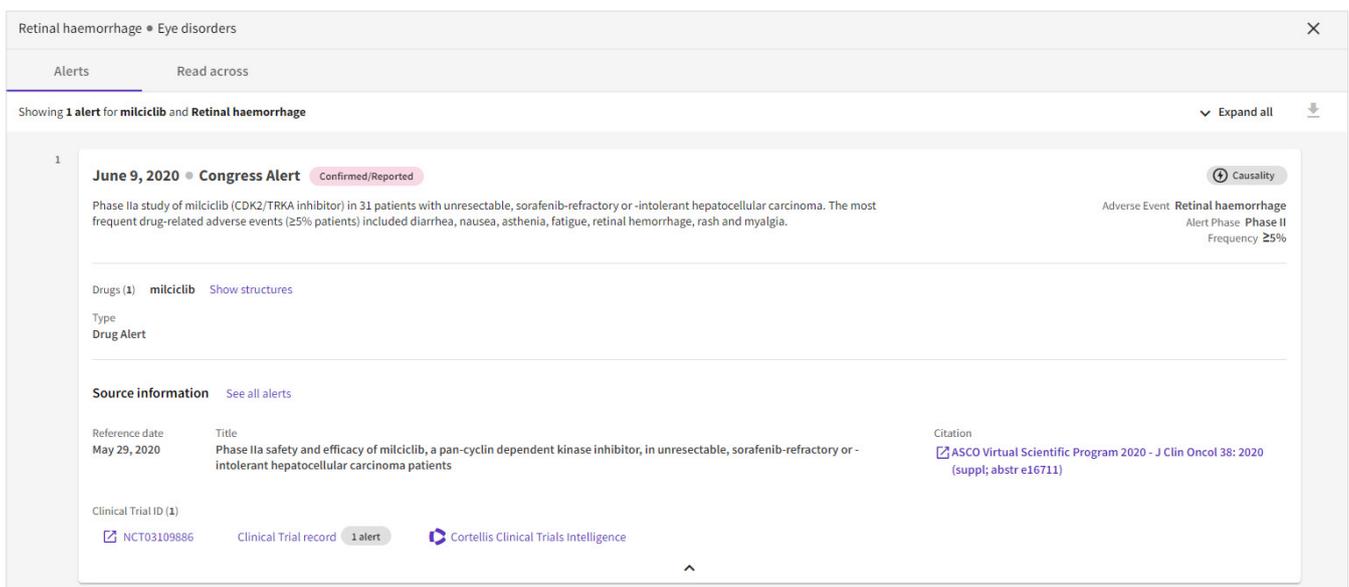
The screenshot displays the OFF-X safety alerts interface. At the top, the navigation bar includes 'Target CDK / Inhibitors' and 'Comparative table builder'. Below this, there are tabs for 'Snapshot', 'Safety alerts', 'Target safety profile', 'Comparative views', and 'Biological context'. The 'Safety alerts' tab is active, showing a list of adverse events on the left sidebar. The main content area displays 'Showing 63 safety alerts for Eye disorders'. A filter is set to 'AE/SOC'. The first alert is dated 'June 15, 2023' and is a 'Company Communication' regarding the termination of NUV-422 clinical development due to a potential safety signal of uveitis. The second alert is dated 'June 13, 2023' and is a 'Congress Alert' regarding a Phase I/II study of BLU-222 (CDK2 inhibitor) in 27 patients with advanced solid tumors. The interface also includes a 'Support' button and a 'Keep me posted' option.

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

Comparative drug safety evidence

Comparing 3 CDK Inhibitors

Filter Columns View AE/SOC Heat map Label reference Sort drugs Highest phase

Adverse event | System Organ Class | SMQ (1) | Drug type | Product category/modality | Drugs/biologics (3) | Clear all filters

Adverse event • System Organ Class	OFF-X Target/Class Score	palbociclib Launched 2015	abemaciclib Launched 2017	ribociclib Launched 2017
Dry eye • Eye disorders	Low	EMA PMDA	PMDA	EMA
Lacrimation increased • Eye disorders	Low	EMA PMDA	EMA PMDA	EMA
Cornea verticillata • Eye disorders	Very low			
Cataract • Eye disorders	Very low	FDA		
Eye disorder • Eye disorders	Low	FDA EMA		
Eye pain • Eye disorders	Very low			
Lacrimation disorder • Eye disorders	Very low			
Lens degeneration • Eye disorders	Very low	FDA		
Lens dislocation • Eye disorders	Very low			
Ocular vascular disorder • Eye disorders	Very low			
Periorbital swelling • Eye disorders	Very low			
Retinal degeneration • Eye disorders	Very low		PMDA	
Vision blurred • Eye disorders	Very low	EMA PMDA		

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

Retinal degeneration • Eye disorders

Alerts Read across

Showing 1 alert from drug labels for **abemaciclib** and **Retinal degeneration** Expand all

1 **September 21, 2018 • Regulatory Agency Communication** Suspected Causality

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**
Alert Phase: **Preclinical**
Species: **mouse • rat**

Drugs (1) **abemaciclib** Show structures

Type
Drug Alert

Source information See all alerts

Reference date	Title	Citation
September 21, 2018	Verzenio (abemaciclib)	<a>PMDA package insert. Verzenio (abemaciclib)

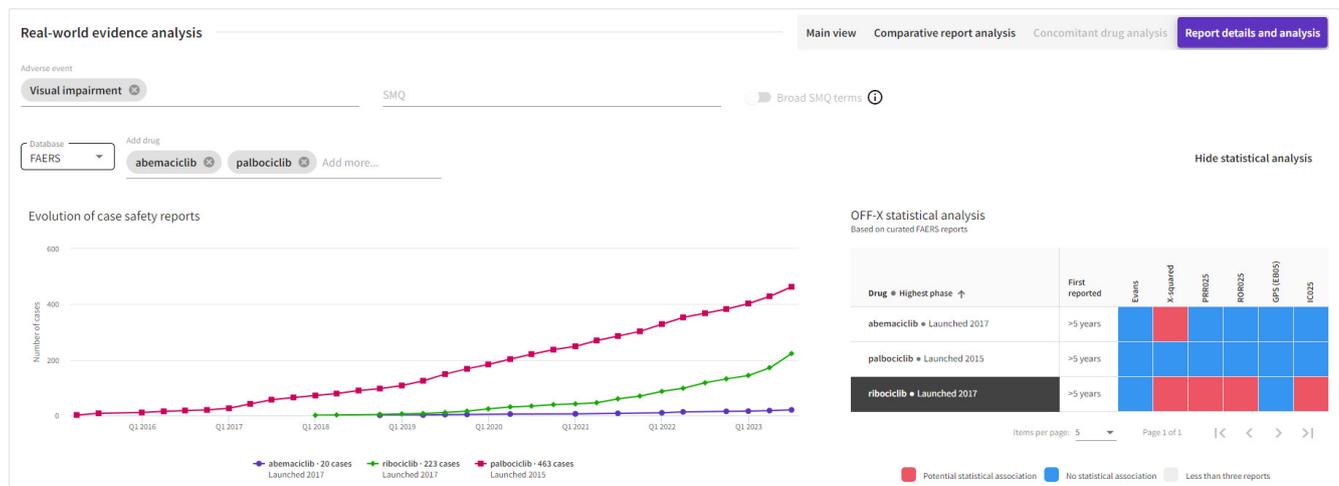
Figure 6: Comparative view of ocular toxicities reported in FAERS and approval documents

Real-world evidence analysis Main view **Comparative report analysis** Concomitant drug analysis Report details and analysis

Comparing 3 drugs (launched, sharing primary target action) AE/SOC: FAERS

Adverse event • System Organ Class	ribociclib Launched 2017		palbociclib Launched 2015		abemaciclib Launched 2017		Tools
	OFF-X Drug Score	Number of reports	% of reports	OFF-X Drug Score	Number of reports	% of reports	
Visual impairment • Eye disorders		223	0.2		463	0.2	✓
Vision blurred • Eye disorders		111	0.1		407	0.1	✓
Lacrimation increased • Eye disorders		132	0.1		389	0.1	
Dry eye • Eye disorders		125	0.1		301	0.1	
Cataract • Eye disorders		48	0.1		299	0.1	✓
Blindness DME • Eye disorders		31			141	0.1	✓
Eye disorder • Eye disorders		44			133		✓
Eye pruritus • Eye disorders		35			101		✓
Eye pain • Eye disorders		35			74		✓
Diplopia • Eye disorders		35			60		✓
Ocular hyperaemia • Eye disorders		31			52		✓
Eye irritation • Eye disorders		26			47		✓

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/HD Animal data	Preclinical	Phase I	Phase II	Phase III	Clinical Regulatory	Postmarketing	Phase not specified		
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: On/off-target
Drug Alert: 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

Comparative table builder

View:
 Heat map:

Adverse event | System Organ Class | SMQ (12)

Adverse event • System Organ Class	CDK1 inhibitors	CDK2 inhibitors	CDK4 inhibitors	CDK5 inhibitors	CDK6 inhibitors	CDK7 inhibitors	CDK8 inhibitors	CDK9 inhibitors	CDK19 inhibitors	CDK inhibitors
<input type="text" value="eye disorder"/>										
Lacrimation increased • Eye disorders		1	9		9					10
Dry eye • Eye disorders			6		6					6
Vision blurred • Eye disorders	2	7	3	2	3			2		10
Photophobia • Eye disorders	1	6		2		1		2		6
Visual impairment • Eye disorders		4		1		1		1		4
Eye pain • Eye disorders	2	2	2	1	2	1		2		3
Retinal degeneration • Eye disorders	1	1	2	1	2			1		2
Congenital eye disorder • Congenital, familial and genetic disorders							1		1	1
Periorbital swelling • Eye disorders			1		1					1
Retinal disorder • Eye disorders	1	1	1	1	1			1		1
Retinal haemorrhage • Eye disorders		1								1
Retinal toxicity • Eye disorders	1	1	1	1	1			1		1

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.

About Clarivate

Clarivate™ is a leading global provider of transformative intelligence. We offer enriched data, insights & analytics, workflow solutions and expert services in the areas of Academia & Government, Intellectual Property and Life Sciences & Healthcare. For more information, please visit clarivate.com.

Contact our experts at
lifesciences.support@clarivate.com

+1 215 386 0100 (U.S.)

+44 (0) 20 7433 4000 (Europe)

clarivate.com/products/biopharma/off-x/