

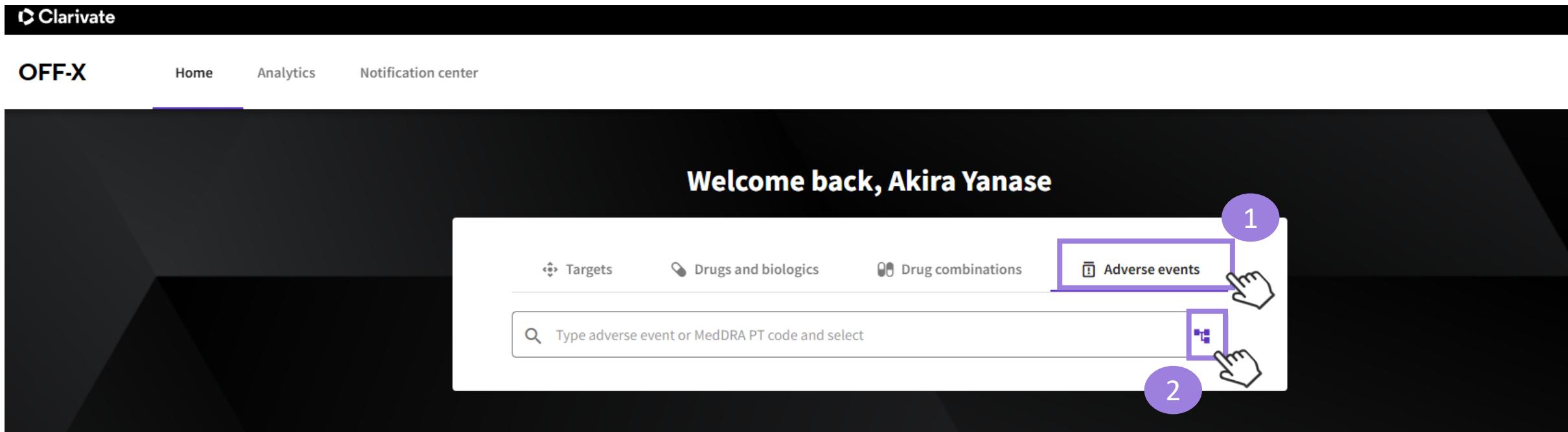
# OFF-X

**Translational safety/Mounting evidence chart/Real-world  
evidence analysisを活用した毒性・安全性情報の調査活用事例**

本事例では肝毒性を例に、  
ドラッグ・ターゲット毎にどのくらいの安全性情報が報告されているのか、  
またその安全性情報の概要を収集し、その上でトレンドの分析や  
FDA approval package上の記載確認から注目すべきAEとなるのか、  
を検討する事例をご紹介します。

# 1-1. 肝毒性(Hepatotoxicity)と関連して報告のあるターゲットやドラッグを検索する

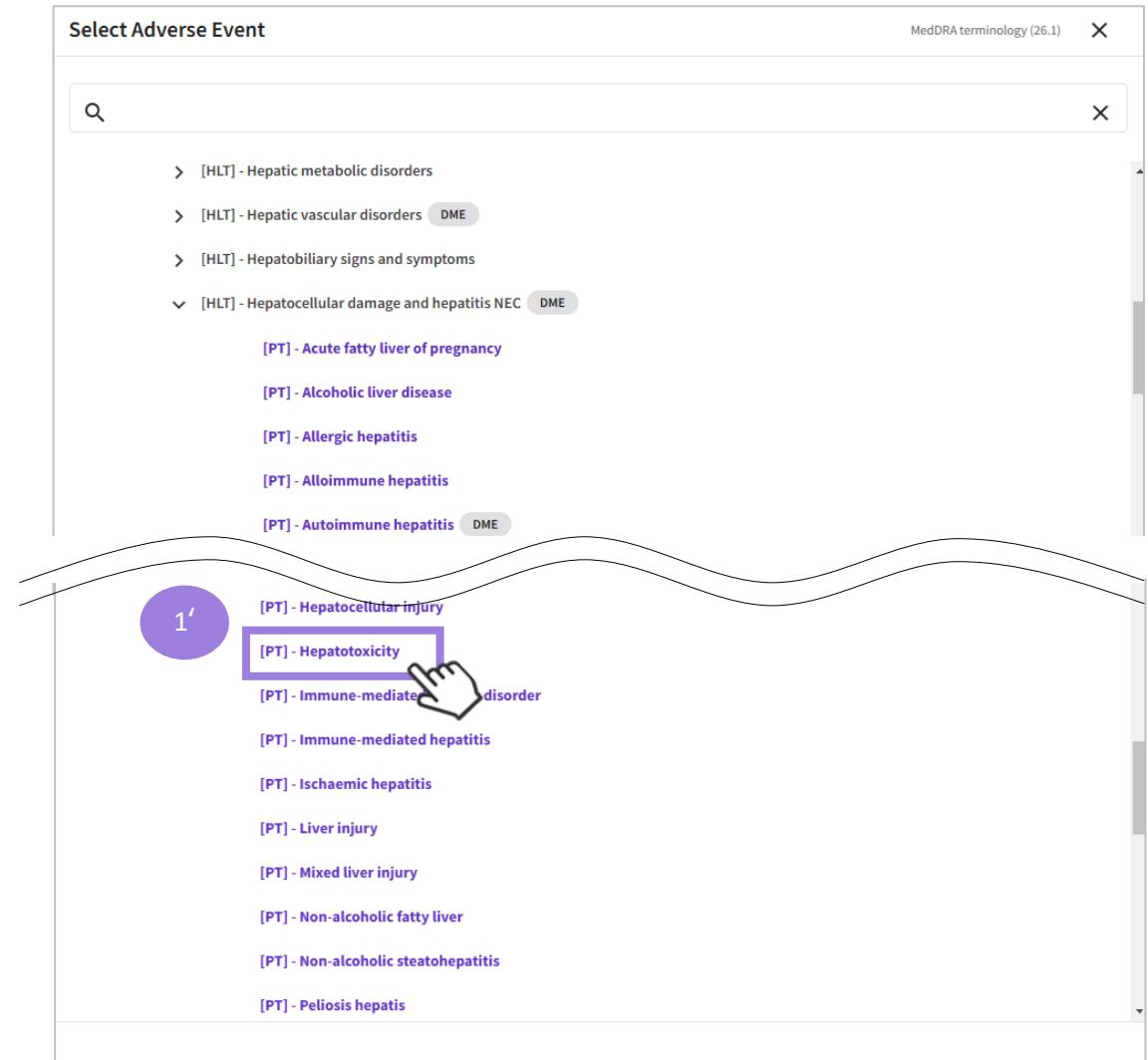
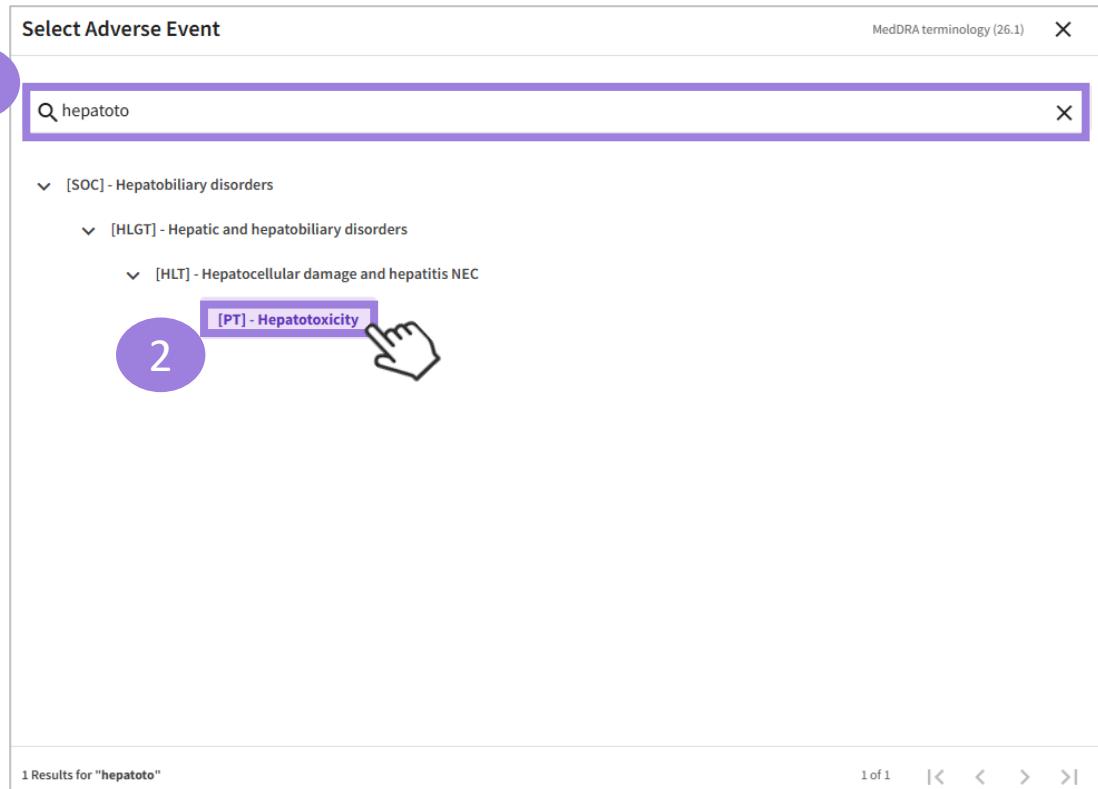
- ① TOP画面の「Adverse events」をクリック
- ② 「MedDRA hierarchy search」をクリック



## 1-2. AEとして肝毒性(Hepatotoxicity)を選択

- ① 検索ボックスに「Hepatotoxicity」を入力
- ② 「Hepatotoxicity」をクリック

or ①' 階層※からSOC> HLT>PTと降りていき、「Hepatotoxicity」をクリック



※MedDRAに加えてOFF-X独自のAE用語を「non-MedDRA terms」として用意。

# 1-3. 肝毒性(Hepatotoxicity)と関連して報告のあるドラッグ情報を収集する

① Drugs & Biologicsの「Master view」をクリックすることでHepatotoxicityが報告されているドラッグ情報の収集が可能

1

Adverse event  
Hepatotoxicity

Targets ▾ Drugs and biologics ▾ Master view Showing 1,99 Translational safety Filter Columns

Safety alertsに Causality, Severity, Pharmacogenomicsに関連するものが含まれていることを意味

Safety alertsの総数と、内訳として Class毎、Drug毎の件数を表示。

FDA approval package内のどこに記載があるのかをテキストマイニングで確認が可能

市販後安全性報告を FARES、JADER毎に確認が可能

Drug/combination	Highest phase	OFF-X Drug Score	Classifier tags	Frequency in clinical trials	Number of alerts	Alert type	Alert phase	Text mining FDA SBA	Label Reference
asparaginase	Biologic Launched	Very high	+ Causality + Severity + Pharmacogenomics	≥ 10%	20	1 0 0 20 1	2 1 18 1	0	FDA EMA PMDA Tools
fasiglifam	Small molecule Discontinued	Very high	+ Causality + Severity	≥ 0.01 - < 0.1%	16	1 0 0 16 1	5 1 11 1	0	
gemtuzumab ozogamicin	Biologic Launched	Very high	+ Causality + Severity	≥ 0.01 - < 0.1%	23	1 0 0 23 1	2 1 21 1	5	
ketoconazole	Small molecule Launched	Very high	+ Causality + Severity	< 1%	28	1 6 0 22 1	8 1 20 1	0	
lapatinib	Small molecule Launched	Very high	+ Causality + Severity + Pharmacogenomics	< 1%	32	1 11 1 21 1	5 1 27 1	0	
mercaptopurine	Small molecule Launched	Very high	+ Causality + Severity + Pharmacogenomics	≥ 1 - < 10%	32	1 6 1 26 1	1 1 31 1	0	
methotrexate	Small molecule Launched	Very high	+ Causality + Severity + Pharmacogenomics	≥ 0.01 - < 0.1%	109	1 0 0 109 1	11 1 98 1	0	
nevirapine	Small molecule Launched	Very high	+ Causality + Severity + Pharmacogenomics	≥ 1 - < 10%	33	1 4 1 29 1	3 1 30 1	1	
pazopanib	Small molecule Launched	Very high	+ Causality + Severity + Pharmacogenomics	≥ 1 - < 10%	59	1 16 1 43 1	8 1 51 1	3	
pegaspargase	Biologic Launched	Very high	+ Causality + Severity	≥ 1 - < 10%	19	1 0 0 19 1	1 1 18 1	0	
pekidartinib	Small molecule Launched	Very high	+ Causality + Severity	4%	37	1 17 1 20 1	2 1 35 1	4	

Hepatotoxicityが報告されているドラッグの一覧

Very high～Not associatedでタグ付け

臨床試験で報告された頻度を表示

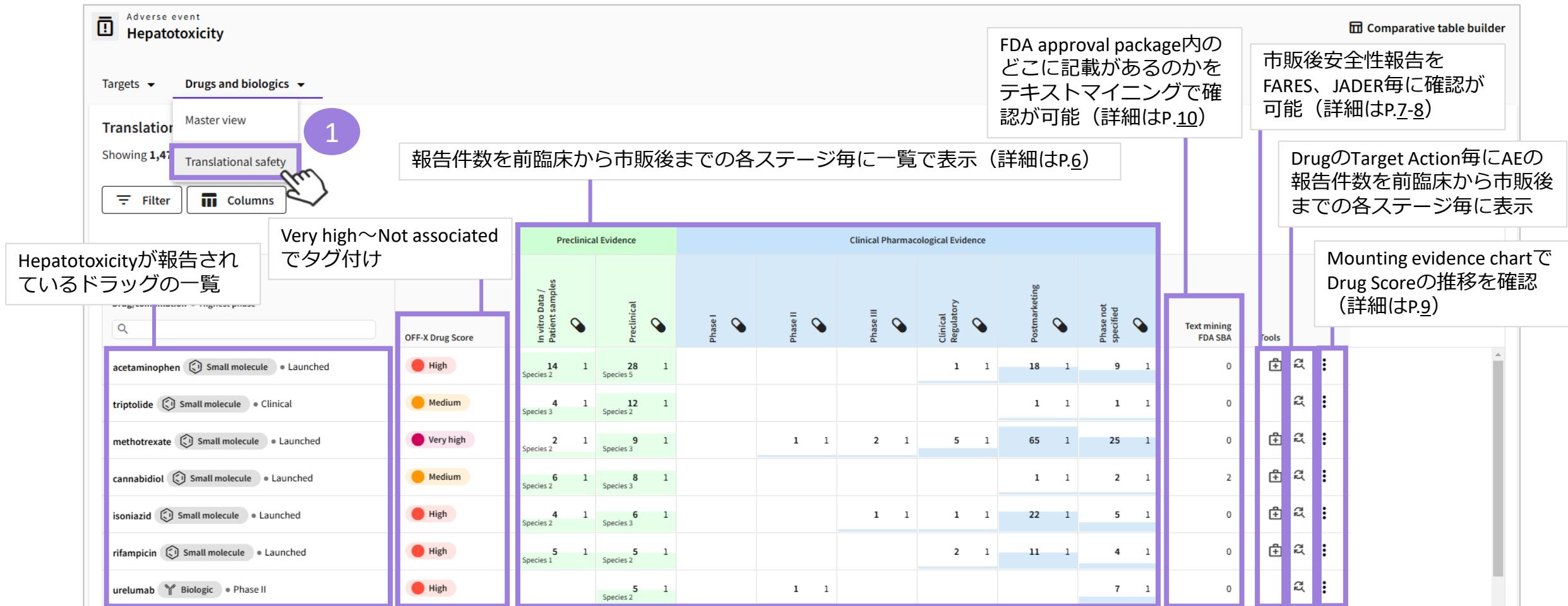
Preclinical毎、Clinical毎の件数を表示

主要当局毎に添付文書を基にしたSafety alertsの確認や添付文書へのアクセスが可能

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# 1-4. 肝毒性が各ドラッグ毎に、各ステージ毎にどのくらい報告されているのかを確認

## ① Translational safetyでは報告件数を前臨床から市販後までの各ステージ毎に一覧で確認が可能



前臨床情報を基にした臨床への外挿性考察の一助として、また競合医薬品における安全性情報の収集等に活用

# 1-5. 注目するドラッグ、ステージに応じて安全性情報の詳細を確認

- ① 各ステージに表示されている報告件数をクリック
- ② Safety alertで安全性報告の詳細を確認
- ③ 必要に応じて情報源となった文献情報へアクセス

Adverse event  
Hepatotoxicity

Targets ▾ Drugs and biologics ▾

Translation  
Master view  
Showing 1,47 Translational safety

Filter Columns

Drug/combination	Highest phase	OFF-X Drug Score	Preclinical Evidence		Phase I	Phase II
			In vitro Data / Patient samples	Preclinical		
acetaminophen	Small molecule Launched	High	14 Species 2	1 Species 5	28 Species 1	1 Species 1
triprolide	Small molecule Clinical	Medium	4 Species 3	1 Species 2	12 Species 1	1 Species 1
methotrexate	Small molecule Launched	Very high	1 Species 3	9 Species 3	1 Species 1	1 Species 1
cannabidiol	Small molecule Launched	Medium	6 Species 2	1 Species 3	8 Species 3	1 Species 1
isoniazid	Small molecule Launched	High	4 Species 2	1 Species 3	6 Species 1	1 Species 1
rifampicin	Small molecule Launched	High	5 Species 1	1 Species 2	5 Species 1	1 Species 1
urelumab	Biologic Phase II	High			5 Species 2	1 Species 1

2

cannabidiol

Alerts Read across

Showing 8 preclinical alerts for Hepatotoxicity and cannabidiol

October 11, 2024 • Journal Suspected

Study in zebrafish evaluating the toxicological mechanism of cannabidiol (CB1 receptor negative allosteric modulator) on embryonic development. Cannabidiol exposure caused pericardial edema, decrease in eye area, liver degeneration and delayed yolk sac absorption in zebrafish embryos. Other safety issues are listed.

Drugs (1) cannabidiol Show structures

Type Drug Alert

Source information See all alerts

Reference date August 10, 2024 Title Toxicological mechanism of cannabidiol (CBD) exposure on zebrafish embryonic development

Citation Food Chem Toxicol. 2024 Aug 10:193:114929 PubMed 39134136

3

PubMed

Search User Guide Advanced Save Email Send to Display options

Food Chem Toxicol. 2024 Nov;193:114929. doi: 10.1016/j.fct.2024.114929. Epub 2024 Aug 10. FULL TEXT LINKS ELSEVIER FULL-TEXT ARTICLE

Toxicological mechanism of cannabidiol (CBD) exposure on zebrafish embryonic development

Ying Wei <sup>1</sup>, Xiqi Chen <sup>2</sup>, Yue Li <sup>1</sup>, Yingxue Guo <sup>2</sup>, Sida Zhang <sup>3</sup>, Jiazheng Jin <sup>3</sup>, Jinlian Li <sup>4</sup>, Dongmei Wu <sup>5</sup>

Affiliations + expand PMID: 39134136 DOI: 10.1016/j.fct.2024.114929

Abstract

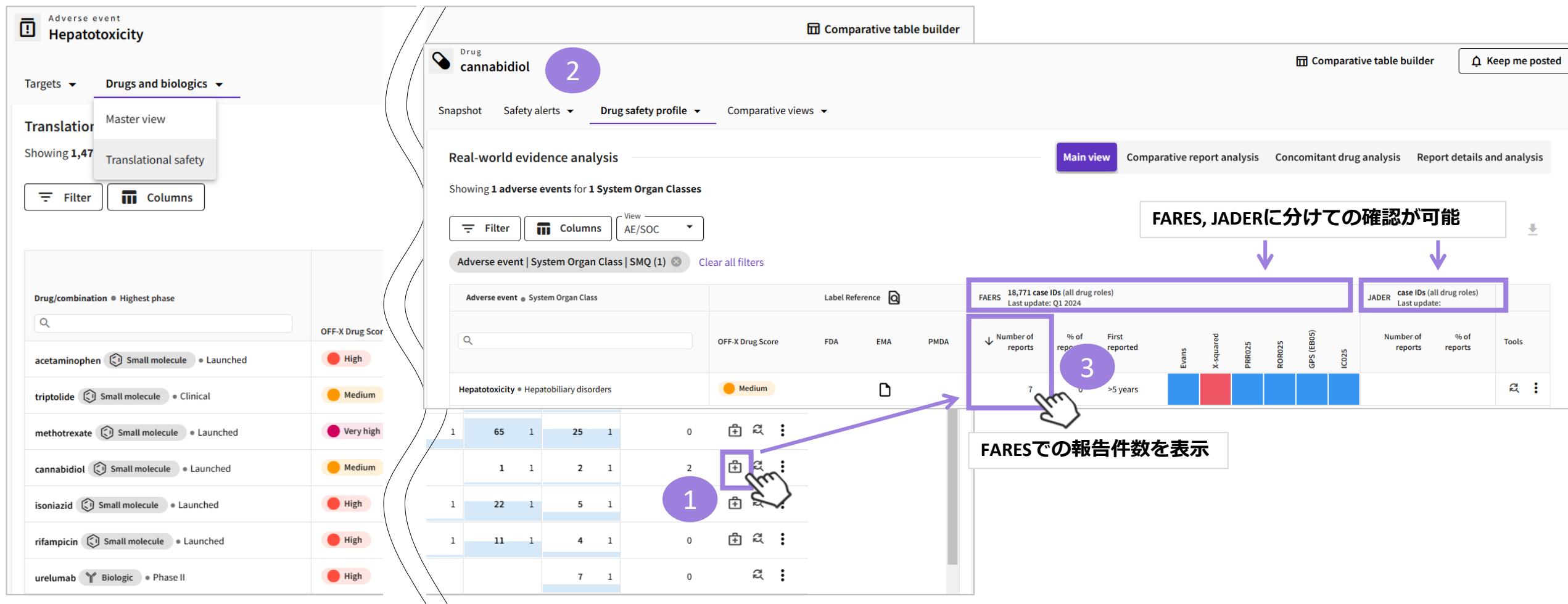
Cannabidiol (CBD) is the main component of plant Cannabis (*Cannabis sativa*), which exhibits strong antioxidant and anti-inflammatory activities. With the legalization of CBD in the United States, it is an

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# 1-6. 市販後（FARES, JADER）の報告件数を確認

- ①  をクリック
- ② Drug safety profileのReal-world evidence analysisが開き、FARES, JADERの報告件数が表示される
- ③ 報告件数をクリック



Adverse event  
Hepatotoxicity

Targets **Drugs and biologics** ▾

Translation Master view

Showing 1,47 Translational safety

Filter Columns

Drug/combination • Highest phase

Drug/combination	Phase	OFF-X Drug Score	
acetaminophen	Small molecule	Launched	High
triprolide	Small molecule	Clinical	Medium
methotrexate	Small molecule	Launched	Very high
cannabidiol	Small molecule	Launched	Medium
isoniazid	Small molecule	Launched	High
rifampicin	Small molecule	Launched	High
urelumab	Biologic	Phase II	High

Drug cannabidiol **2**

Snapshot Safety alerts **Drug safety profile** Comparative views

Real-world evidence analysis

Showing 1 adverse events for 1 System Organ Classes

Adverse event | System Organ Class | SMQ (1) **Clear all filters**

Adverse event	System Organ Class	Label Reference
Hepatotoxicity	Hepatobiliary disorders	Medium

FAERS 18,771 case IDs (all drug roles)  
Last update: Q1 2024

Number of reports	% of reports	First reported
7	0	>5 years

JADER case IDs (all drug roles)  
Last update:

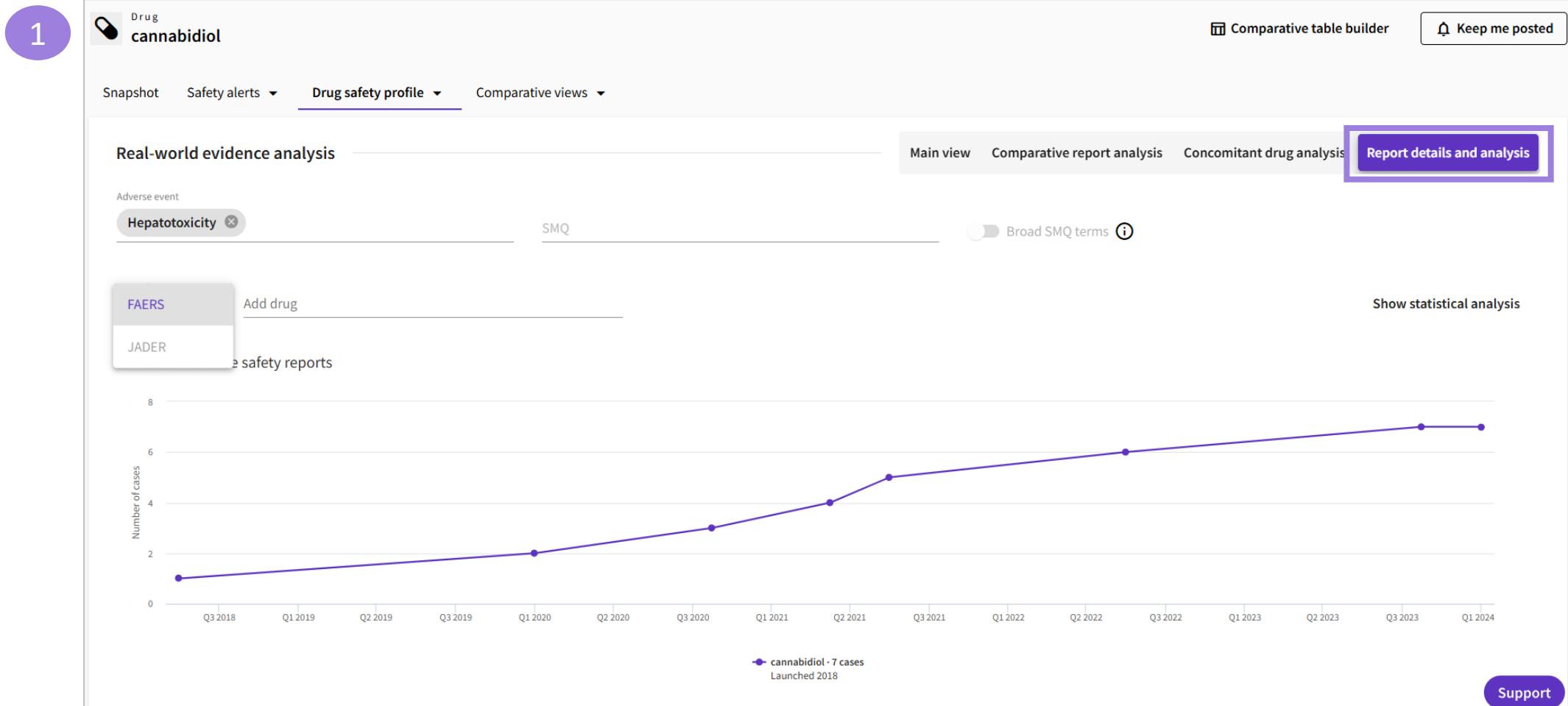
Number of reports	% of reports	Tools			
Evans	X-squared	PBR025	ROR025	GPS (E005)	IC025

**FARES, JADERに分けての確認が可能**

**FARESでの報告件数を表示**

# 1-6. 市販後（FARES, JADER）の報告件数を確認

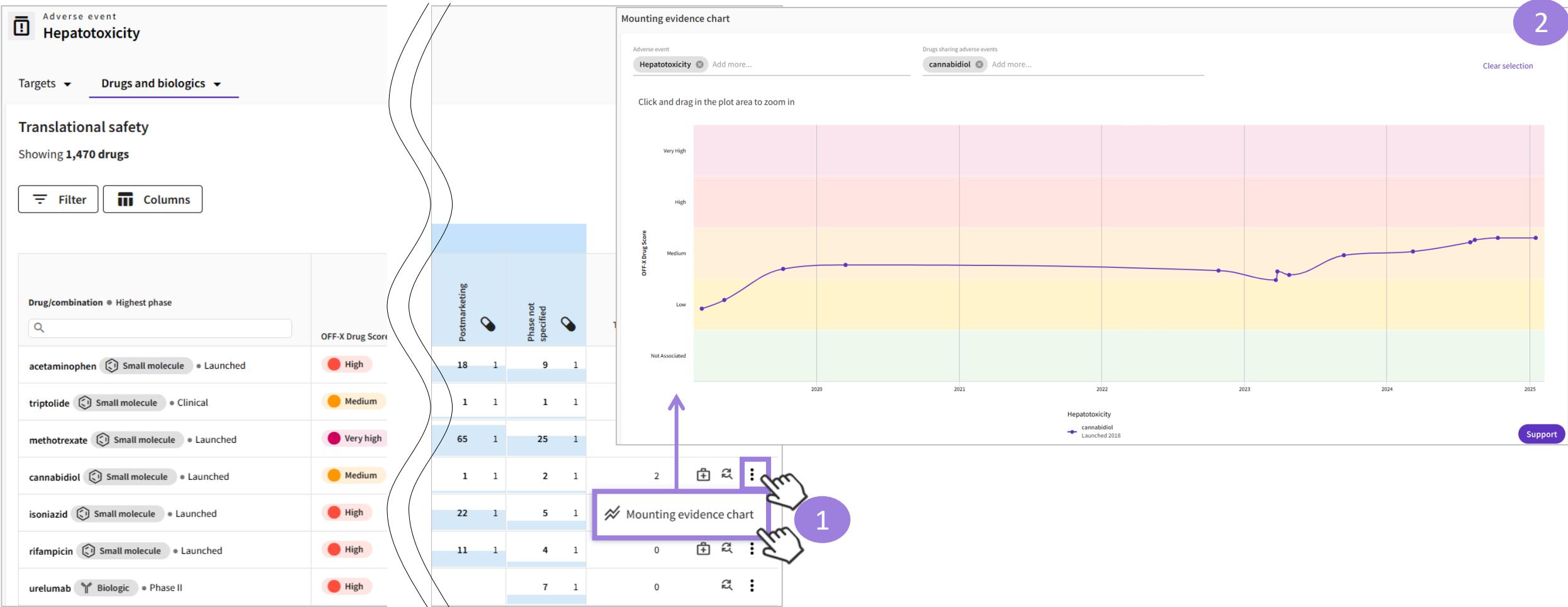
- ① Real-world evidence analysis>Report details and analysisでは  
FARES(JADER)における報告件数の経時的推移を視覚的に確認が可能



経時的推移を視覚的に確認することで今後注目すべきAEであるのか、またそのようなトレンドがあるのかを確認

# 1-7. Mounting evidence chartのDrug Scoreの経時的推移を確認

- ① P.5のTranslational safetyに戻り、:をクリックし、Mounting evidence chartをクリック
- ② OFF-X Drug Scoreの経時的推移からドラッグとAEのエビデンスの関連を支持するエビデンスの強さを確認



注目すべきAEであるかの追加判断要素に

# 1-8. FDA approval package内の記載を確認

- ① P.5のTranslational safetyに戻り、Text mining FDA SBAをクリック
- ② FDA approval package内の記載を確認

The screenshot shows the OFF-X platform interface. On the left, there is a search bar for 'Drug/combination' and a table of drugs with their Off-Label Drug Scores (e.g., acetaminophen, triptolidine, methotrexate, cannabidiol, isoniazid, rifampicin, urelumab). In the center, there is a grid showing the number of occurrences for various adverse events across different phases (Postmarketing, Phase not specified) and document types (Text mining FDA SBA). A purple circle labeled '1' highlights a cell in the grid. A purple box labeled '2' highlights the 'Source' column in the 'Text mining FDA SBA' table. A purple arrow points from the grid to the table.

Adverse event  
Hepatotoxicity

Targets ▼ Drugs and biologics ▼

Translations ▼

Showing 1,477 results

Master view Translational safety

Filter Columns

Drug/combination • Highest phase

OFF-X Drug Score

Drug/combination	Small molecule	Biologic	Phase	Off-Label Drug Score
acetaminophen	Small molecule		Launched	High
tripolidine	Small molecule		Clinical	Medium
methotrexate	Small molecule		Launched	Very high
cannabidiol	Small molecule		Launched	Medium
isoniazid	Small molecule		Launched	High
rifampicin	Small molecule		Launched	High
urelumab	Biologic		Phase II	High

Adverse event

Hepatotoxicity

Document type

Term

Number of occurrences

Source

hepatotoxicity 7

Risk Assessment and Risk Mitigation Review 1

cannabidiol

Text mining FDA SBA

Search by

Adverse event Document type

Associated term hepatotoxicity (7)

Reference ID: 4276052

Clinical Safety Review, NDA 210365, Cannabidiol; Ellis F. Unger, M.D.

aminotransferase increased,' aspartate aminotransferase increased,' gamma-glutamyltransferase increased,' hepatic enzyme increased,' hepatotoxicity,' liver function test abnormal,' and 'transaminases increased' were combined into a single hepatotoxicity grouping. 'Somnolence,' 'sedation,' and 'lethargy' were combined in a grouping. 'Candida infection,' 'fungal infection,' 'oral candidiasis,' and 'tinea cruris' were combined in a fungal infection grouping. Frequencies of adverse events were based on this grouping scheme.

FDA approval package内の記載を併せて確認し、注目すべきAEであるかの追加判断要素に

## 2-1. 肝毒性(Hepatotoxicity)と関連して報告のあるターゲット情報を収集する

- ① Targetsの「Master view」をクリックすることでHepatotoxicityが報告されているターゲット情報の収集が可能

Adverse event  
Hepatotoxicity

Targets Drugs and biologics

Master view

Translational safety

Filter Columns

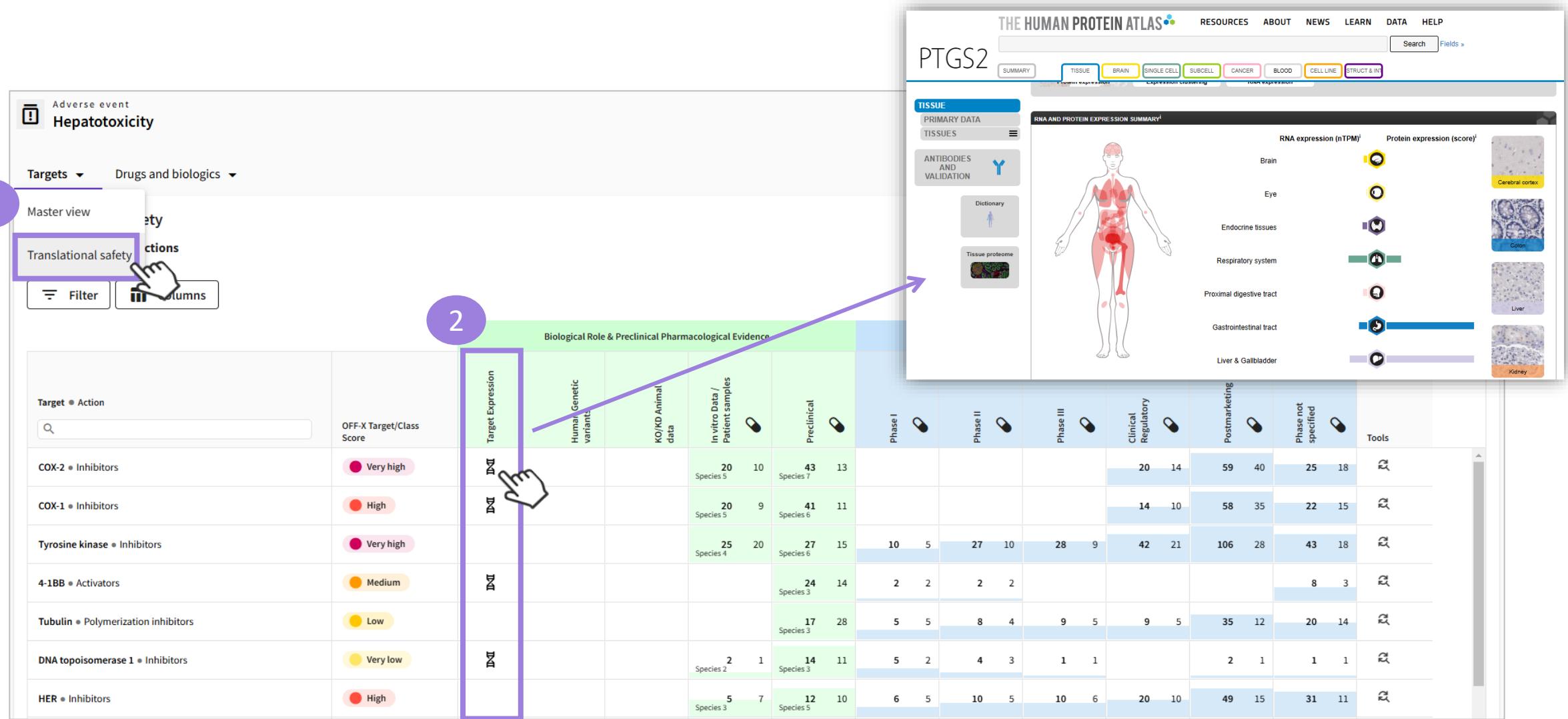
Hepatotoxicityが報告されているターゲットをMoA毎に表示

Target • Action	OFF-X Target/Class Score	Classifier tags	Number of alerts	Class alerts	Drug alerts	Preclinical	Clinical					
30S ribosomal protein • Inhibitors	Very high	Causality Severity	33	14	6	4	27	12	4	4	29	11
Amidophosphoribosyltransferase • Inhibitors	Very high	Causality Severity Pharmacogenomics	65	2	6	1	59	2	3	2	62	2
COX-2 • Inhibitors	Very high	Causality Severity Pharmacogenomics	165	53	10	14	155	53	61	20	104	46
PI3Kgamma • Inhibitors	Very high	On-Target Causality Severity	16	3	3	1	13	3	2	1	14	3
PPARgamma • Modulators	Very high	On-Target Causality Severity Pharmacogenomics	53	10	5	0	48	10	19	4	34	9
Tyrosine kinase • Inhibitors	Very high	On-Target Causality Severity Pharmacogenomics	294	37	16	12	278	37	43	25	251	34
ABL1 • Inhibitors	High	Causality Severity Pharmacogenomics	89	8	2	3	87	8	8	5	81	8
ALK • Inhibitors	High	Causality Severity Pharmacogenomics	80	9	4	5	76	9	13	6	67	9

例えば、どのMoAに多く報告があるのかを確認しつつ、AEの機序解析の一助としても活用

## 2-2. 肝毒性が各ターゲット毎に、各ステージ毎にどのくらい報告されているのかを確認

- ① Translational safetyでは報告件数を前臨床から市販後までの各ステージ毎に一覧で確認が可能
- ② Target Expression内の をクリックすることで外部データベースへ移行し組織別の発現情報も確認



# 参考 Translational safety/Mounting evidence chart/ Real-world evidence analysisはTOP画面> Analyticsからのアクセスも可能

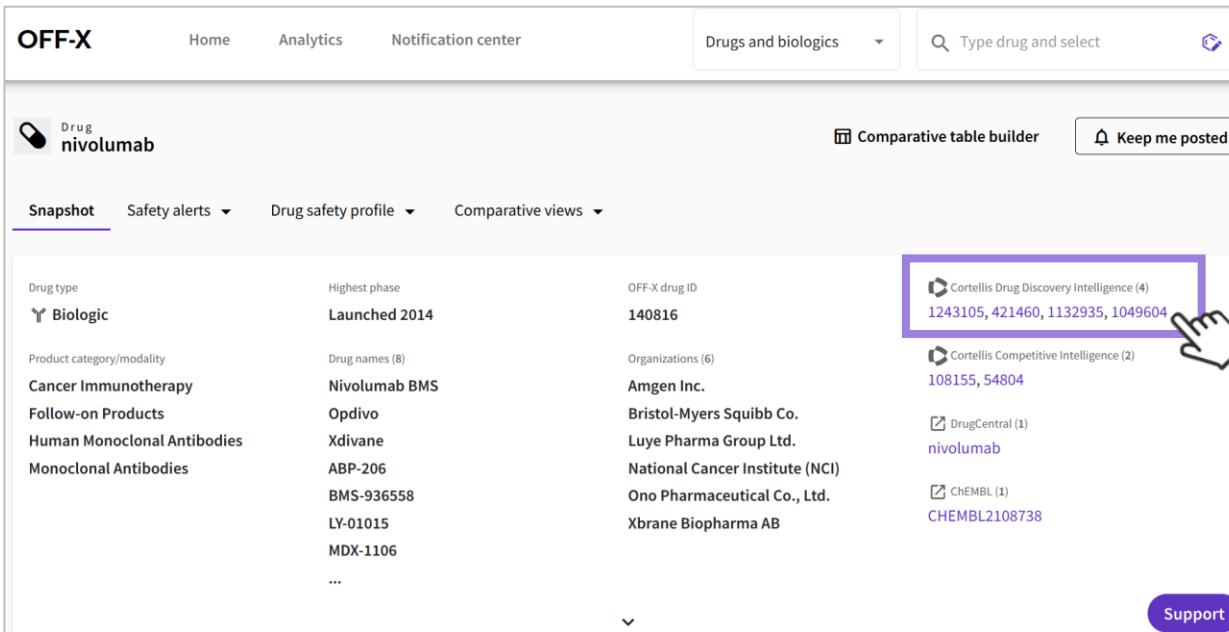
The screenshot shows the OFF-X platform interface. At the top, there is a navigation bar with 'OFF-X' on the left, followed by 'Home', 'Analytics' (which is highlighted with a purple box and has a hand cursor icon over it), and 'Notification center'. To the right of the navigation bar is a search bar labeled 'Targets' with a dropdown arrow and a search icon, and a text input field 'Type target or gene or UniProt ID and select'. Below the navigation bar, the text 'Data in action to de-risk your R&D programs' is displayed. Underneath this, there is a row of buttons for 'All use cases' (highlighted in black), 'Target safety assessment', 'Toxicity exploration', 'Secondary pharmacology profiling', 'Preclinical to clinical translation', 'Structure-toxicity assessment', 'Mechanistic toxicity evaluation', 'Drug vs class assessment', and 'Safety profile benchmark'. Below these buttons is another button for 'Safety risk evaluation'. The main content area contains several cards, each with an icon and a title. Four of these cards are highlighted with purple boxes and have hand cursor icons over them: 'Mounting evidence chart' (with a chart icon), 'Real-world evidence analysis' (with a briefcase icon), 'Translational safety' (with a double-headed arrow icon), and 'Unexpected toxicity evaluation' (with a magnifying glass icon). The other cards are: 'Comparative table builder' (with a table icon), 'Pathway maps' (with a wrench icon), and 'Structure-toxicity explorer' (with a pencil icon).

※OFF-Xには枠で囲った以外の分析ツールも多く搭載されています。ぜひご活用ください。

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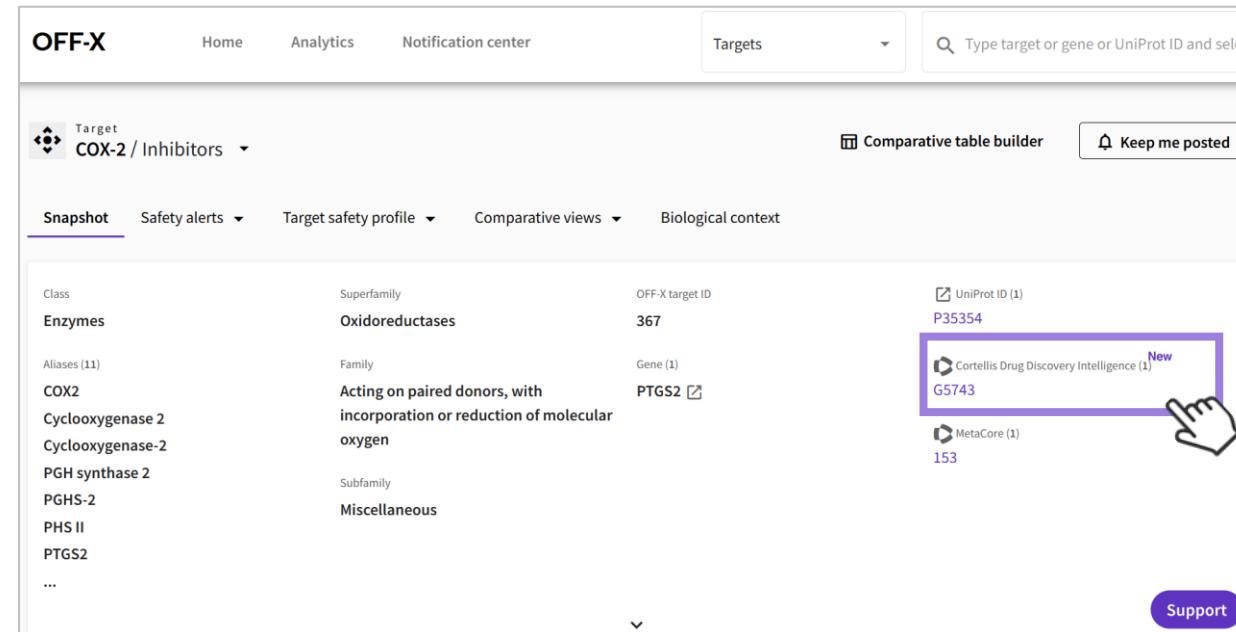
- ドラッグレコード、ターゲットレコードにある「Cortellis Drug Discovery Intelligence」リンクをクリックすることでCortellis Drug Discovery Intelligenceを24時間お試してお使いいただくことが可能です。  
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## ドラッグレコード



The screenshot shows the OFF-X platform interface for the drug Nivolumab. At the top, there are navigation links for Home, Analytics, and Notification center. A search bar is present with the placeholder "Type drug and select". Below the search bar, a section titled "Drug nivolumab" is displayed. The main content area includes tabs for Snapshot, Safety alerts, Drug safety profile, Comparative views, and Biological context. Under the Snapshot tab, detailed information is provided about Nivolumab, including its drug type (Biologic), highest phase (Launched 2014), OFF-X drug ID (140816), and various aliases like Amgen Inc., Bristol-Myers Squibb Co., Luye Pharma Group Ltd., National Cancer Institute (NCI), Ono Pharmaceutical Co., Ltd., and Xbrane Biopharma AB. A call-to-action button "Keep me posted" is located at the top right of this section. A purple box highlights the "Cortellis Drug Discovery Intelligence (4) 1243105, 421460, 1132935, 1049604" link, which is also being clicked by a cursor icon.

## ターゲットレコード



The screenshot shows the OFF-X platform interface for the target COX-2 / Inhibitors. At the top, there are navigation links for Home, Analytics, and Notification center. A search bar is present with the placeholder "Type target or gene or UniProt ID and select". Below the search bar, a section titled "Target COX-2 / Inhibitors" is displayed. The main content area includes tabs for Snapshot, Safety alerts, Target safety profile, Comparative views, and Biological context. Under the Snapshot tab, detailed information is provided about COX-2, including its class (Enzymes), superfamily (Oxidoreductases), OFF-X target ID (367), and various aliases like COX2, Cyclooxygenase 2, Cyclooxygenase-2, PGH synthase 2, PGHS-2, PHS II, PTGS2, and PTGS2. A call-to-action button "Keep me posted" is located at the top right of this section. A purple box highlights the "Cortellis Drug Discovery Intelligence (1) G5743" link, which is also being clicked by a cursor icon.



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