

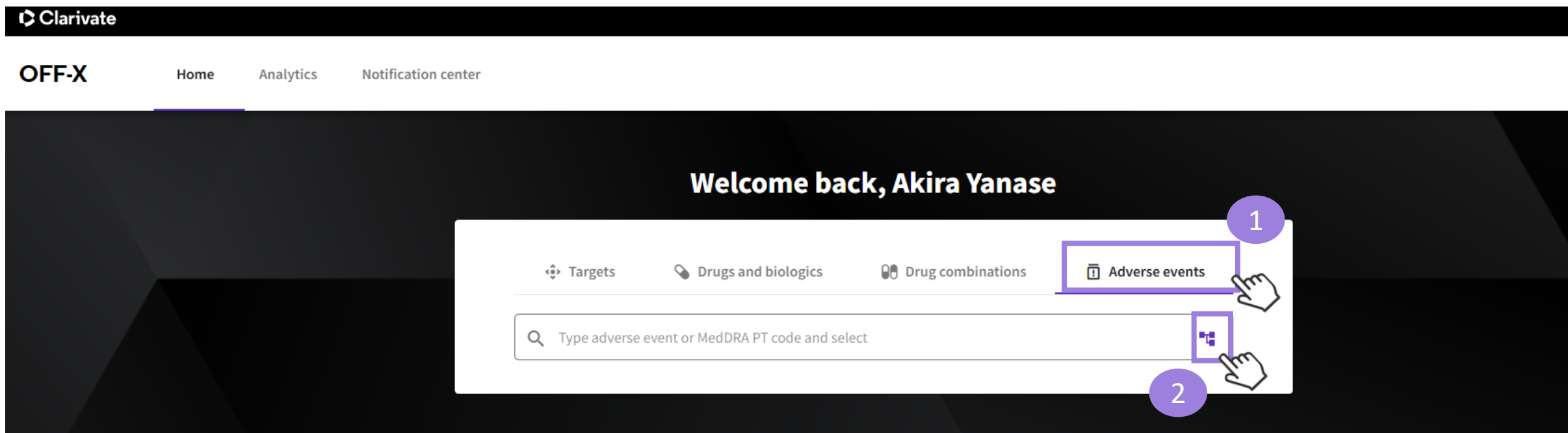
OFF-X

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

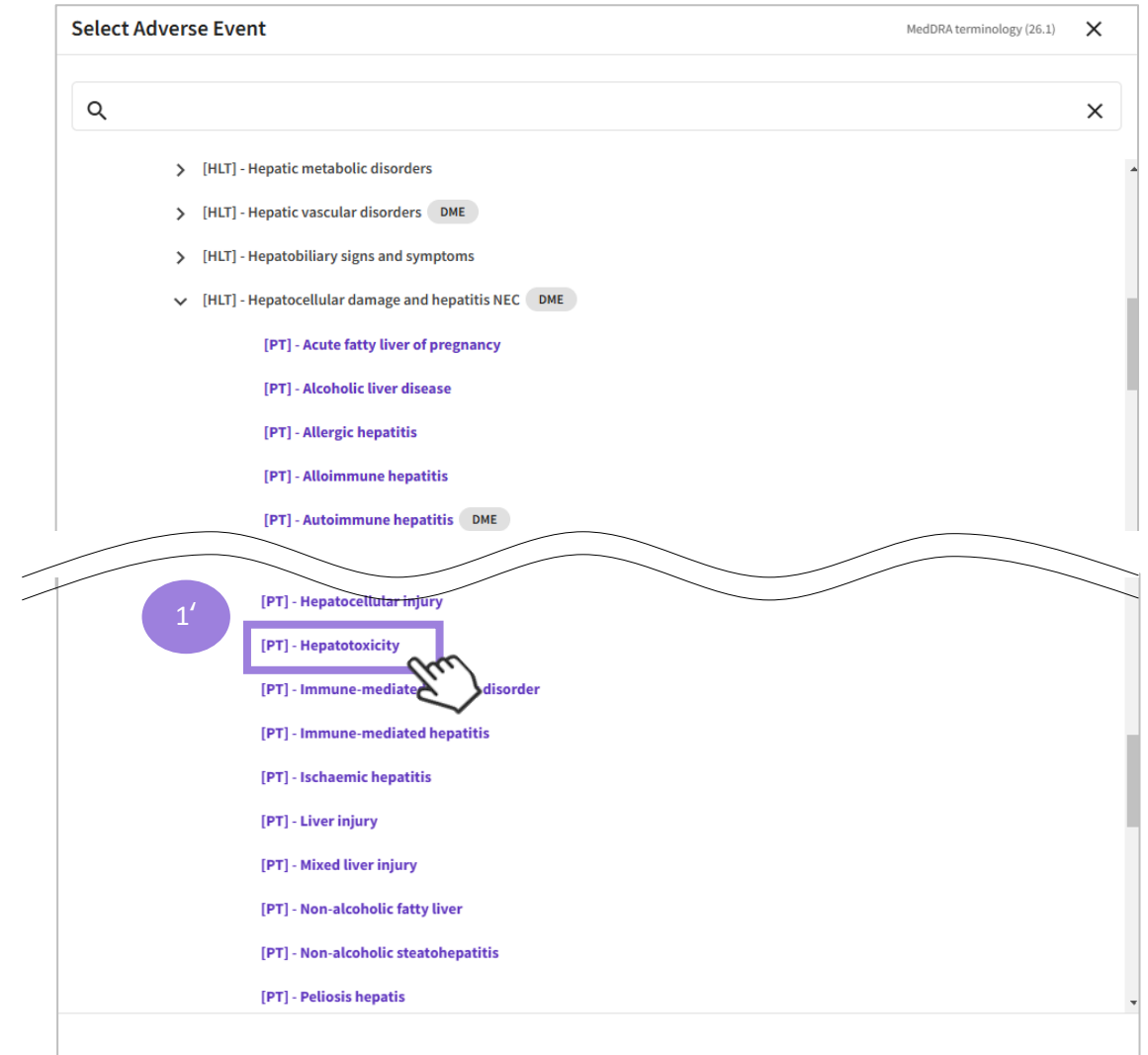
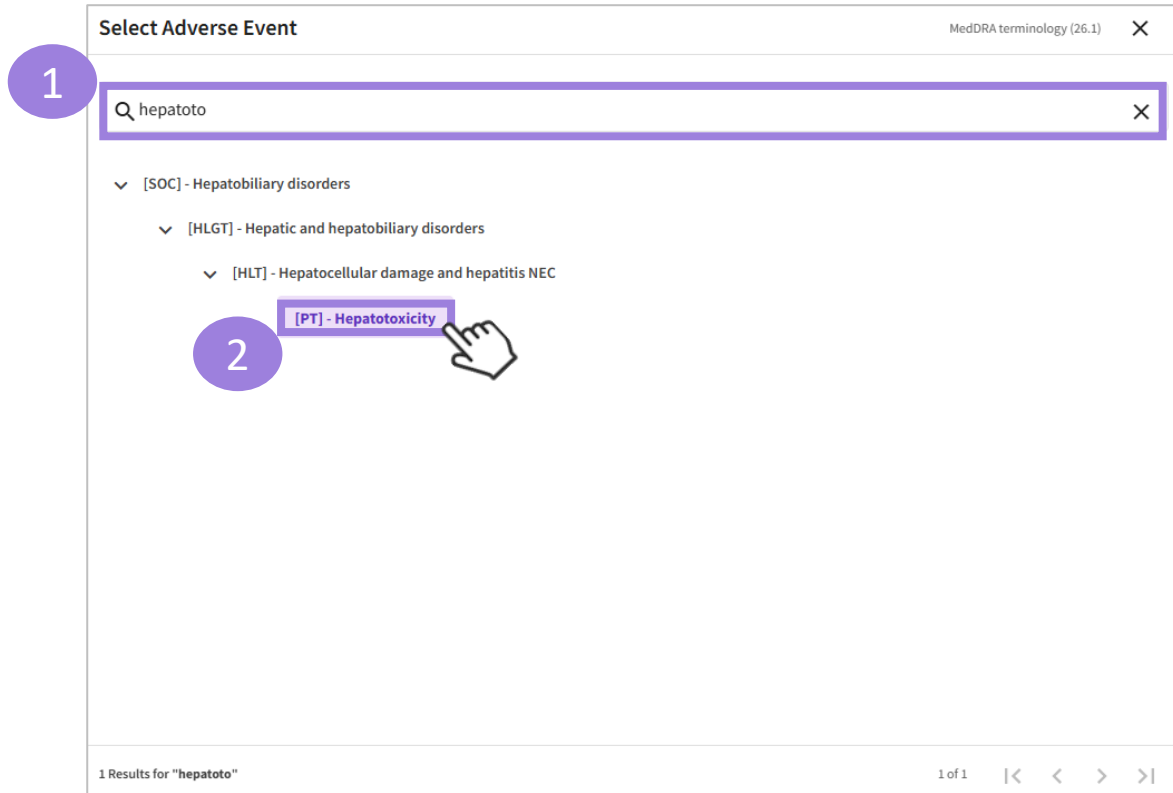
- ① TOP画面の「Adverse events」をクリック
- ② 「MedDRA hierarchy search」をクリック



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>HLGT>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

Adverse event
Hepatotoxicity

Comparative table builder

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	Alert type				Alert phase				Label Reference				
				Number of alerts	Class alerts	Drug alerts		Preclinical	Clinical		Text mining FDA SBA	FDA	EMA	PMDA	Tools	
asparaginase • Launched	Very high	Causality Severity Pharmacogenomics	≥ 10%	20	1	0	0	20	1	2	1	18	1	0		
fasiglifam • Discontinued	Very high	Causality Severity		16	1	0	0	16	1	5	1	11	1	0		
gemtuzumab ozogamicin • Launched	Very high	Causality Severity		23	1	0	0	23	1	2	1	21	1	5		
ketoconazole • Launched	Very high	Causality Severity	≥ 0.01 - <0.1%	28	1	6	0	22	1	8	1	20	1	0		
lapatinib • Launched	Very high	Causality Severity Pharmacogenomics	<1%	32	1	11	1	21	1	5	1	27	1	0		
mercaptopurine • Launched	Very high	Causality Severity Pharmacogenomics	≥ 1 - <10%	32	1	6	1	26	1	1	1	31	1	0		
methotrexate • Launched	Very high	Causality Severity Pharmacogenomics	≥ 0.01 - <0.1%	109	1	0	0	109	1	11	1	98	1	0		
nevirapine • Launched	Very high	Causality Severity Pharmacogenomics	≥ 1 - <10%	33	1	4	1	29	1	3	1	30	1	1		
pazopanib • Launched	Very high	Causality Severity Pharmacogenomics	≥ 1 - <10%	59	1	16	1	43	1	8	1	51	1	3		
pegaspargase • Launched	Very high	Causality Severity	≥ 1 - <10%	19	1	0	0	19	1	1	1	18	1	0		
pexidartinib • 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

Adverse event
Hepatotoxicity

Targets ▾ Drugs and biologics ▾

Translation Master view
Showing 1,471 items
Translational safety 1

Filter Columns

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（詳細はP.10）

市販後安全性報告をFARES、JADER毎に確認が可能（詳細はP.7-8）

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表示（詳細はP.6）

DrugのTarget Action毎にAEの報告件数を前臨床から市販後までの各ステージ毎に表示

Mounting evidence chartでDrug Scoreの推移を確認（詳細はP.9）

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

	Preclinical Evidence		Clinical Pharmacological Evidence								Text mining FDA SBA	Tools
	In vitro Data / Patient samples	Preclinical	Phase I	Phase II	Phase III	Clinical Regulatory	Postmarketing	Phase not specified				
acetaminophen <small>Small molecule</small> • Launched	14 Species 2	28 Species 5				1 1	18 1	9 1	0			
triptolide <small>Small molecule</small> • Clinical	4 Species 3	12 Species 2					1 1	1 1	0			
methotrexate <small>Small molecule</small> • Launched	2 Species 2	9 Species 3		1 1	2 1	5 1	65 1	25 1	0			
cannabidiol <small>Small molecule</small> • Launched	6 Species 2	8 Species 3					1 1	2 1	2			
isoniazid <small>Small molecule</small> • Launched	4 Species 2	6 Species 3			1 1	1 1	22 1	5 1	0			
rifampicin <small>Small molecule</small> • Launched	5 Species 1	5 Species 2				2 1	11 1	4 1	0			
urelumab <small>Biologic</small> • Phase II		5 Species 2		1 1				7 1	0			

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 1,477 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 • Launched	High	Species 2 14 1	Species 5 28 1		
triptolide • Clinical	Medium	Species 3 4 1	Species 2 12 1		
methotrexate • Launched	Very high	Species 1 9 1	Species 3 9 1	1 1	2 1
cannabidiol • Launched	Medium	Species 2 6 1	Species 3 8 1		
isoniazid • Launched	High	Species 2 4 1	Species 3 6 1	1 1	1 1
rifampicin • Launched	High	Species 1 5 1	Species 2 5 1	2 1	11 1
urelumab • Phase II	High		Species 2 5 1	1 1	7 1

cannabidiol 2

Alerts Read across

Showing 8 preclinical alerts for Hepatotoxicity and cannabidiol

Expand all

1

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

Causality

Adverse Event Hepatotoxicity

Alert Phase Preclinical

Species zebrafish

安全性報告の概要、動物種、報告開発段階、関連医薬品の構造、因果関係、重篤性、エビデンスレベル等の確認が可能

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

PubMed 39134136

PubMed® Search

Advanced User Guide

Save Email Send to Display options

> Food Chem Toxicol. 2024 Nov;193:114929. doi: 10.1016/j.fct.2024.114929. Epub 2024 Aug 10.

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

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

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

FULL TEXT LINKS ELSEVIER FULL TEXT ARTICLE

ACTIONS Cite Collections

SHARE

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 ▾
Showing 1,47
Filter Columns

Drug/combination • Highest phase
OFF-X Drug Score

acetaminophen	Small molecule • Launched	High
triptolide	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
Filter Columns View AE/SOC

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

Adverse event • System Organ Class	Label Reference	FAERS	JADER
Hepatotoxicity • Hepatobiliary disorders	OFF-X Drug Score Medium	18,771 case IDs (all drug roles) Last update: Q1 2024	case IDs (all drug roles) Last update:
		Number of reports 7	Number of reports
		% of reports 0	% of reports
		First reported >5 years	
		Evans X-squared PRR025 ROR025 GPS (EB05) IC025	Tools

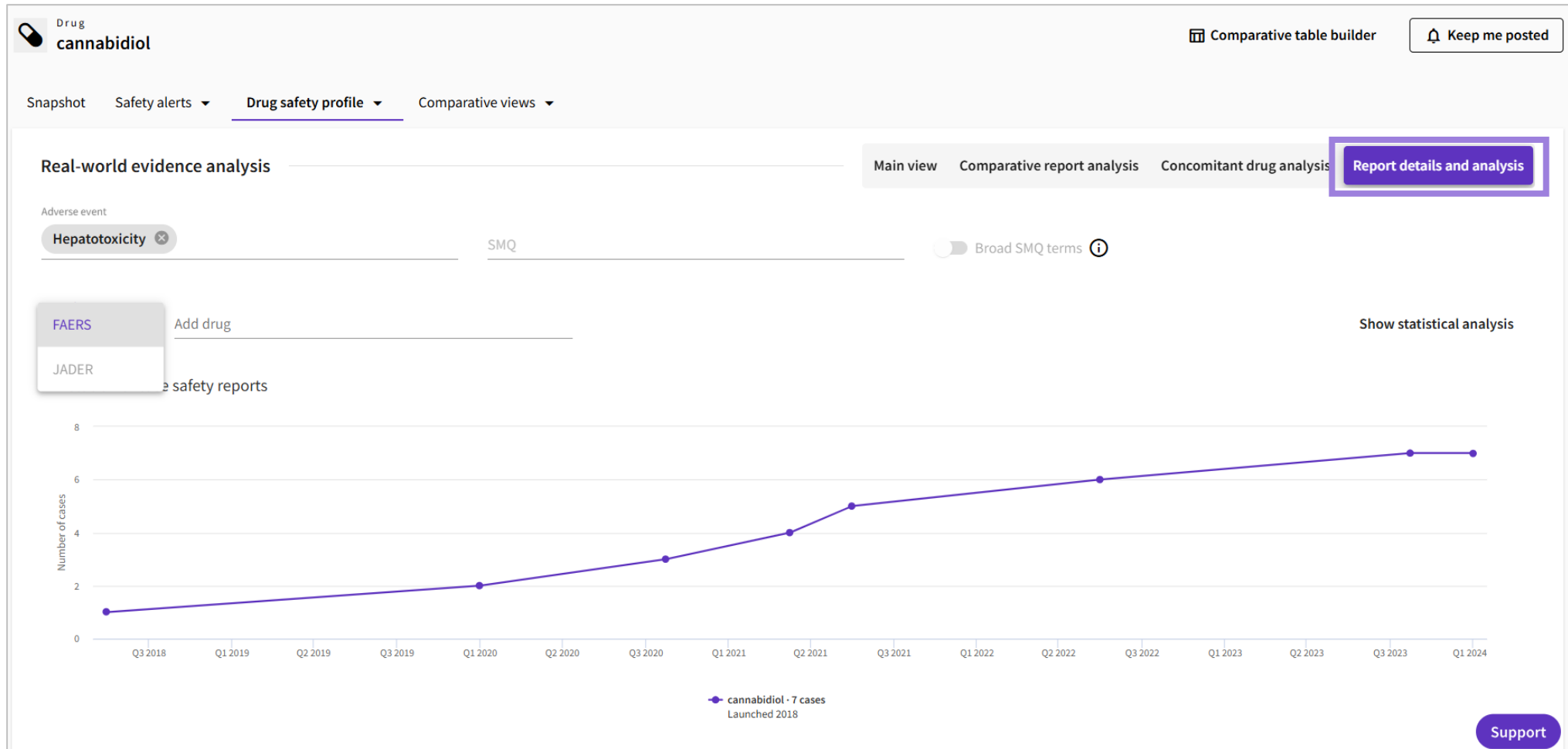
FARES, JADERに分けての確認が可能

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

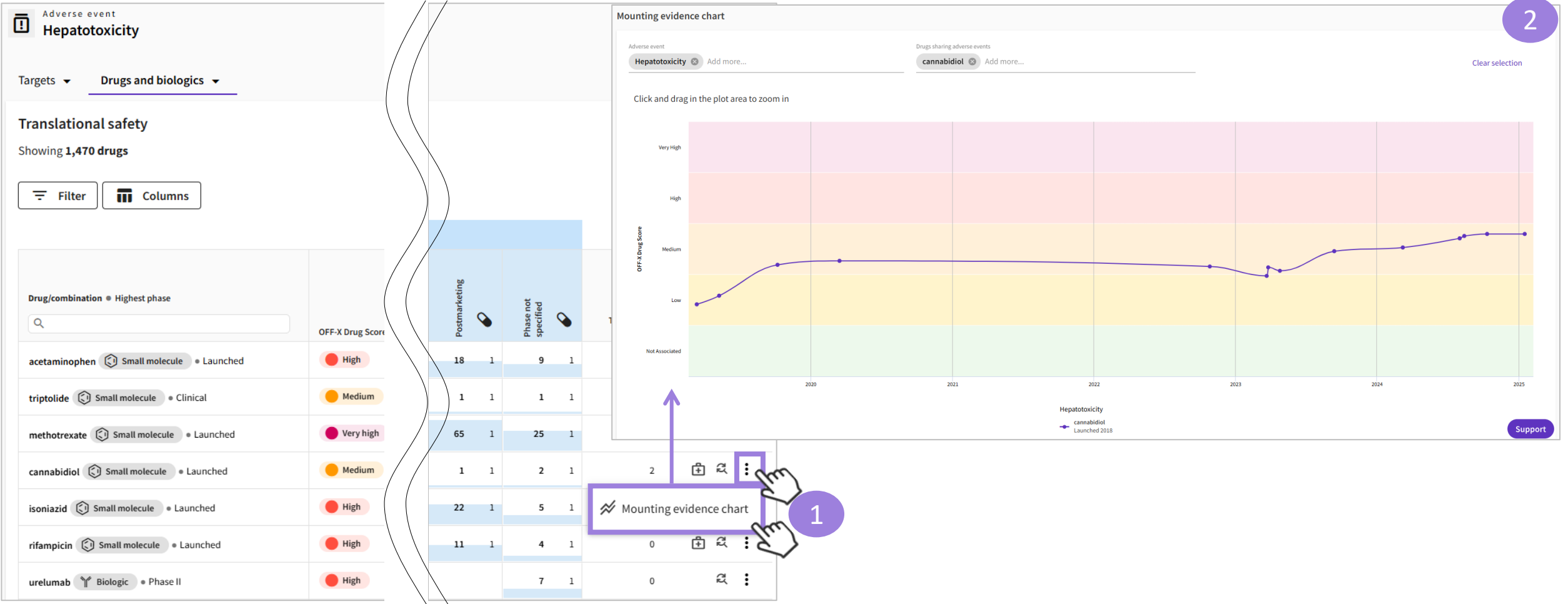
1



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 interface displays a list of drugs and biologics with their associated adverse events. The 'cannabidiol' entry is highlighted, and its 'Text mining FDA SBA' is being viewed. The 'Source' link in the table is clicked, leading to the document viewer.

Adverse event: Hepatotoxicity

Targets: Drugs and biologics

Translation: Master view, Translational safety

Showing 1,47

Filter Columns

Drug/combination • Highest phase	OFF-X Drug Score	Phase	Postmarketing	Phase not specified	Text mining FDA SBA	Tools
acetaminophen • Small molecule • Launched	High	1	18	9	0	
triptolide • Small molecule • Clinical	Medium	1	1	1	0	
methotrexate • Small molecule • Launched	Very high	1	65	25	0	
cannabidiol • Small molecule • Launched	Medium	1	1	2	2	
isoniazid • Small molecule • Launched	High	1	22	5	0	
rifampicin • Small molecule • Launched	High	1	11	4	0	
urelumab • Biologic • Phase II	High			7	0	

OFF-X text mining FDA Summary Basis of Approval (SBA)

The following table lists FDA Summary Basis of Approval (SBA) documents where particular adverse event terms have been found by our proprietary text mining tools. The original document with the adverse event terms highlighted is accessible via the Source link.

Adverse Event	Document type	Term	Number of occurrences	Source
Hepatotoxicity	Medical Review	hepatotoxicity	7	
	Risk Assessment and Risk Mitigation Review	hepatotoxicity	1	

cannabidiol

Text mining FDA SBA

Search by: Adverse event, Document type

Adverse event: Hepatotoxicity, Document type: Medical Review, 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

1

Adverse event
Hepatotoxicity

Comparative table builder

Targets ▾
Master view
Translational safety

Drugs and biologics ▾


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	Alert type				Alert phase				
					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

Adverse event
Hepatotoxicity

Targets ▾ Drugs and biologics ▾

1 Master view
Translational safety
Filter Columns

2

Target • Action	OFF-X Target/Class Score	Target Expression	Human Genetic variants	KO/KD Animal data	In vitro Data / Patient samples	Preclinical	Phase I	Phase II	Phase III	Clinical Regulatory	Postmarketing	Phase not specified	Tools
COX-2 • Inhibitors	Very high	ND			20 Species 5 10	43 Species 7 13				20 14	59 40	25 18	
COX-1 • Inhibitors	High	ND			20 Species 5 9	41 Species 6 11				14 10	58 35	22 15	
Tyrosine kinase • Inhibitors	Very high	ND			25 Species 4 20	27 Species 6 15	10 5	27 10	28 9	42 21	106 28	43 18	
4-1BB • Activators	Medium	ND				24 Species 3 14	2 2	2 2				8 3	
Tubulin • Polymerization inhibitors	Low	ND				17 Species 3 28	5 5	8 4	9 5	9 5	35 12	20 14	
DNA topoisomerase 1 • Inhibitors	Very low	ND			2 Species 2 1	14 Species 3 11	5 2	4 3	1 1		2 1	1 1	
HER • Inhibitors	High	ND			5 Species 3 7	12 Species 5 10	6 5	10 5	10 6	20 10	49 15	31 11	

THE HUMAN PROTEIN ATLAS

PTGS2

TISSUE BRAIN SINGLE CELL SUBCELL CANCER BLOOD CELL LINE STRUCT & INT

RNA AND PROTEIN EXPRESSION SUMMARY

RNA expression (nTPM)¹

Protein expression (score)²

Brain

Eye

Endocrine tissues

Respiratory system

Proximal digestive tract

Gastrointestinal tract

Liver & Gallbladder

Cerebral cortex

Cervix

Liver

Kidney

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 displays the OFF-X Analytics dashboard. At the top, the navigation bar includes 'OFF-X', 'Home', 'Analytics' (highlighted with a purple box and a hand cursor), and 'Notification center'. To the right is a search bar labeled 'Targets' with a dropdown arrow and a search icon, followed by the text 'Type target or gene or UniProt ID and select'. Below the navigation bar, the main section is titled 'Data in action to de-risk your R&D programs'. It features a row of filter buttons: 'All use cases' (highlighted), '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 filters is a grid of eight tool cards. The cards are: 'Comparative table builder' (Anticipate safety issues of new compounds and combinations, benchmark drugs and targets and assess the mechanisms behind adverse events.), 'Mounting evidence chart' (Discover and compare drug-safety trends to anticipate emerging concerns. - highlighted with a purple box and a hand cursor), 'Pathway maps New' (Anticipate and understand safety issues of targets based on upstream or downstream genes in their signaling cascade.), 'Real-world evidence analysis' (Assess and validate potential pharmacovigilance signals to optimize risk management plans. - highlighted with a purple box and a hand cursor), 'Secondary pharmacology panels New' (Explore an integrated view of safety-related targets to keep your in vitro panels updated.), 'Structure-toxicity explorer New' (Correlate chemical structures with safety liabilities.), 'Translational safety' (Assess the correlation of safety insights of targets and drugs from discovery to clinical. - highlighted with a purple box and a hand cursor), and 'Unexpected toxicity evaluation' (Assess the mechanisms behind unpredicted adverse events.).

※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。

ご案内 Cortellis Drug Discovery Intelligenceへ最大3日間の無料アクセスが可能です。ぜひこの機会にお試ください！

- 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時間お試しでお使いいただくことが可能です。
Cortellis Drug Discovery Intelligenceは前臨床プラットフォームであり、生物学、化学、薬理学データを統合した最も包括的な科学的パイプラインデータベースです。この24時間の無料トライアルは最大3回までご利用いただけます。
※本キャンペーンは、予告なく変更または終了させていただく場合がございます。あらかじめご了承ください。

ドラッグレコード

OFF-X Home Analytics Notification center Drugs and biologics Type drug and select

Drug nivolumab Comparative table builder Keep me posted

Snapshot Safety alerts Drug safety profile Comparative views

Drug type	Highest phase	OFF-X drug ID	Cortellis Drug Discovery Intelligence (4) 1243105, 421460, 1132935, 1049604
Biologic	Launched 2014	140816	
Product category/modality	Drug names (8)	Organizations (6)	Cortellis Competitive Intelligence (2) 108155, 54804
Cancer Immunotherapy	Nivolumab BMS	Amgen Inc.	
Follow-on Products	Opdivo	Bristol-Myers Squibb Co.	
Human Monoclonal Antibodies	Xdivane	Luye Pharma Group Ltd.	
Monoclonal Antibodies	ABP-206	National Cancer Institute (NCI)	
	BMS-936558	Ono Pharmaceutical Co., Ltd.	
	LY-01015	Xbrane Biopharma AB	
	MDX-1106		
	...		

Support

ターゲットレコード

OFF-X Home Analytics Notification center Targets Type target or gene or UniProt ID and select

Target COX-2 / Inhibitors Comparative table builder Keep me posted

Snapshot Safety alerts Target safety profile Comparative views Biological context

Class	Superfamily	OFF-X target ID	UniProt ID (1) P35354
Enzymes	Oxidoreductases	367	
Aliases (11)	Family	Gene (1) PTGS2	Cortellis Drug Discovery Intelligence (1) New G5743
COX2	Acting on paired donors, with incorporation or reduction of molecular oxygen		MetaCore (1) 153
Cyclooxygenase 2			
Cyclooxygenase-2			
PGH synthase 2			
PGHS-2			
PHS II			
PTGS2			
...			

Support



Think forward™

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