Introduction to PharmaPendium: Leveraging FDA and EMA drug approval data

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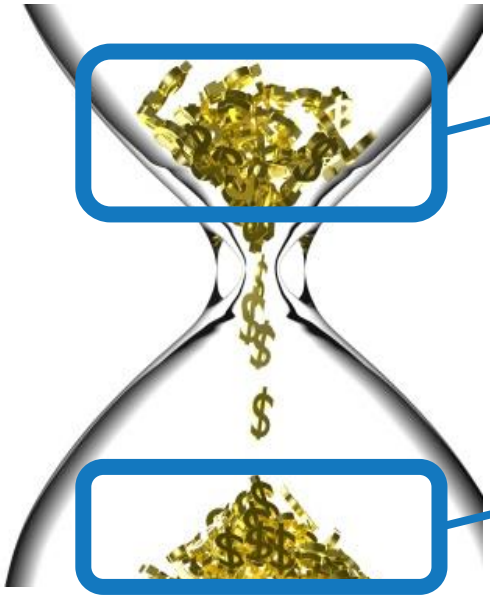
Empowering Knowledge

We suggest viewing the presentation in full screen

Agenda

- Overview
- Focus on:
  - Content
  - Taxonomies
- Text searching vs extracted information
- Example use cases showing:
  - Types of searching (extracted vs text)
  - Drug safety search
  - FAERS

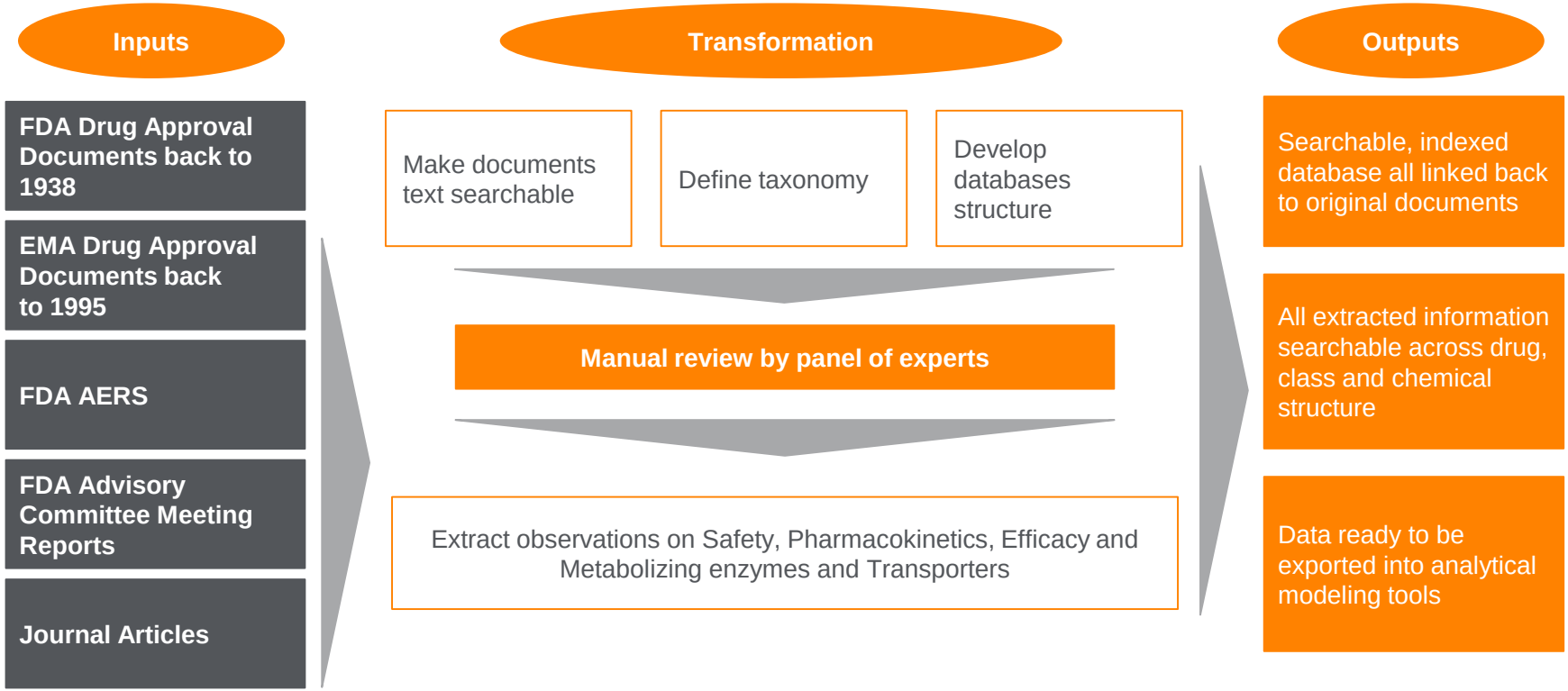
Critical decision-support



- ✓ Leverage past drug approvals to inform bottleneck issues
- ✓ Design studies that provide the most meaningful data
- ✓ Reduce unnecessary preclinical and clinical costs by comparing your drug to successful ones
- ✓ Rapidly evaluate potential DDI risks

PharmaPendium

Our Process and Industry's challenge –
making regulatory documents accessible



A critical decision-support tool

searchable FDA/EMA Drug Approval Docs, extracted data, expert taxonomies and prediction tools

Text searchable Content

- FDA approval packages (1938 – now)
- EMA approval packages (1995 – now)
- FDA Advisory Committee Meetings
- DESI (Drug Efficacy Study Implement'n)
- Meyler's, Mosby's
- FAERS (FDA Adverse Event Reporting System)

Summary Table and Visualization Analysis

Preclinical AND Clinical

- Drug Safety data
- Pharmacokinetic data
- Met. Enzymes and Transporters data
- Efficacy data
- Activity data

Prediction Tools

- DDI Risk Calculator

Drugs/Drug Classes	Indications	Concomitants *(coming soon!)*
Targets/Target Classes	Chemical Structures/Substructure	Endpoints
MedDRA (Adverse Events)	Species	…..and more!

Our users report that PharmaPendium *supports confident decision-making and informs product positioning*

Why is that critical?

72% of surveyed research organizations agree that PharmaPendium provides important **insights that impact the success of a project**.

How PharmaPendium supports phases along the Drug Development pipeline

R&D Phase	Information in PharmaPendium helps you to:
Preclinical	• Determine Drug Safety assessments on lead candidates • Anticipate drug-drug interactions and other adverse events • Optimize *in vivo / in vitro* study designs, select and prioritize leads • Increase chances of successful submissions to regulatory authorities based on past precedents • Leverage drug precedents to help translate preclinical data into human effects / outcomes
Clinical	• Examine on- and off-target effects to predict adverse events • Examine drug approval packages to inform clinical study designs (population, indications, endpoints, etc)

Post-launch	• Leverage lessons learned to:
	  • Develop risk management and strategic programs,
	  • Improve clinical trial design
	• Monitor AERS reports for to identify post marketing safety concerns

How can PharmaPendium be used?

Example User Questions:

- Can I find safety, efficacy and DMPK data to support my analysis of in vitro and in vivo test results?
- Can I compare my drug to approved drugs to help optimize my drug safety analyses and trial design?
- How can I assess PK parameters and potential drug-drug interaction risks for my drug candidate?
- What support can I get for making my case to the regulatory authorities?
- What are the efficacy benchmarks that must be met to compete?
- Which primary endpoints were used during Phase III clinical trials for similar drugs?
- Can I cite a previously-run experiment from a similar drug?

Possible use cases:

Content and value is continually growing

Source Documents

2.4M+
pages of FDA approval documents

215K+
pages of EMA approval documents

10.4M+
FDA AERS reports

690K+
Pages from FDA Advisory Committee Meetings

Extracted Data

4527
Drugs indexed & fully searchable

1.64M+
PK data lines

315K+
Metabolizing enzyme and transporter data lines

1.78M+
safety data lines

2.71M+
efficacy data lines

115K
activity data lines

Information is organised around unique taxonomies

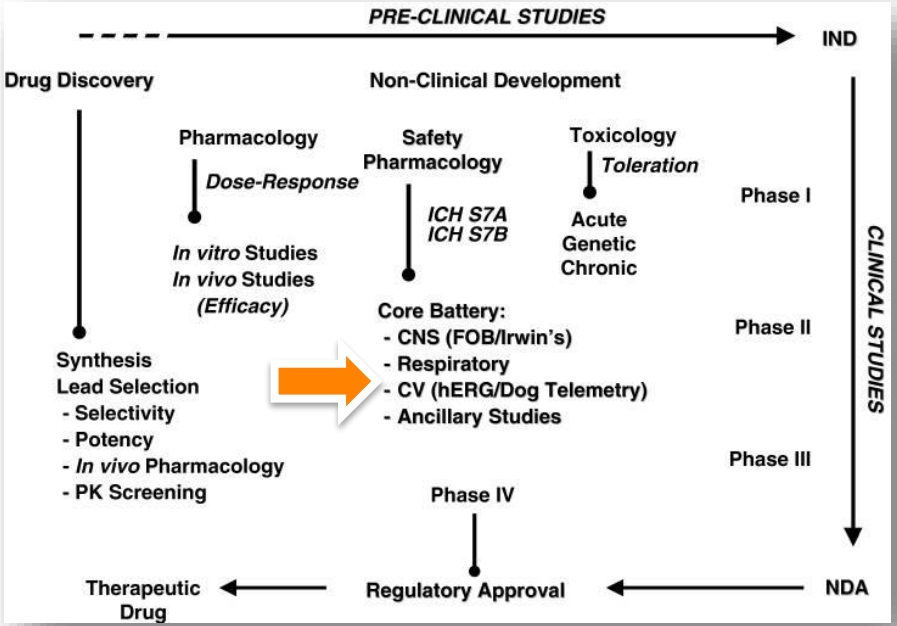
- Adverse effects taxonomy
  - Taxonomy contains MedDRA preferred terms and synonyms linked to MedDRA preferred terms
- Targets taxonomy
  - Target information and the relationship between targets and drugs comes from xPharm, drug labels and FDA Approval Packages
- Endpoint taxonomy
  - Developed in-house
- Indications taxonomy
  - Based on MedDRA with additional indications from Mosby's
- Drug names
  - FDA generic drug names are the main PharmaPendium drug name
  - European drug names are taken primarily from Meyler's
  - Synonyms are linked to the main drug name
  - Excerpted PK, MET and efficacy data based on defined thesauri/parameters

Demo

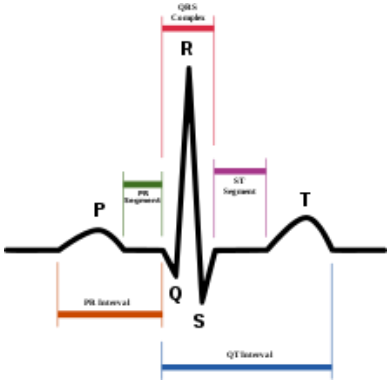
ELSEVIER

Empowering Knowledge

Safety pharmacology – QT prolongation studies

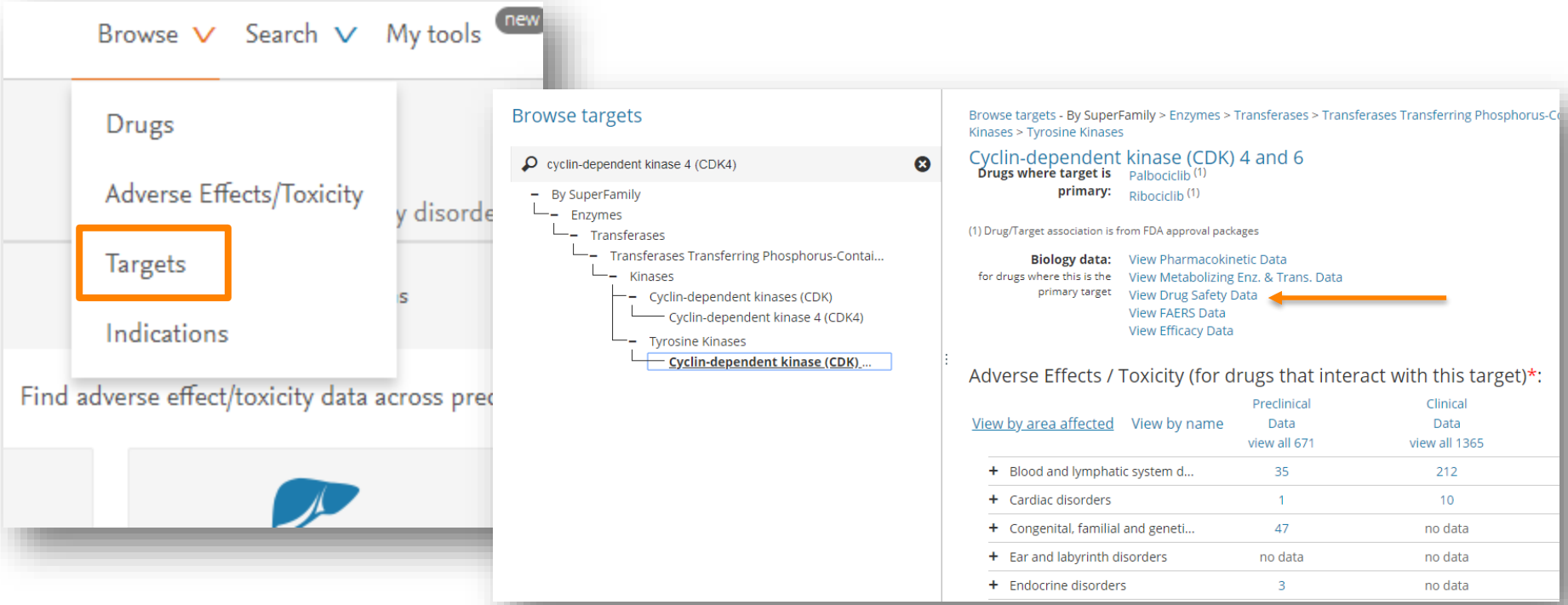


QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. A lengthened QT interval is a marker for the potential of ventricular tachyarrhythmias like **torsades de pointes** and a **risk factor for sudden death**

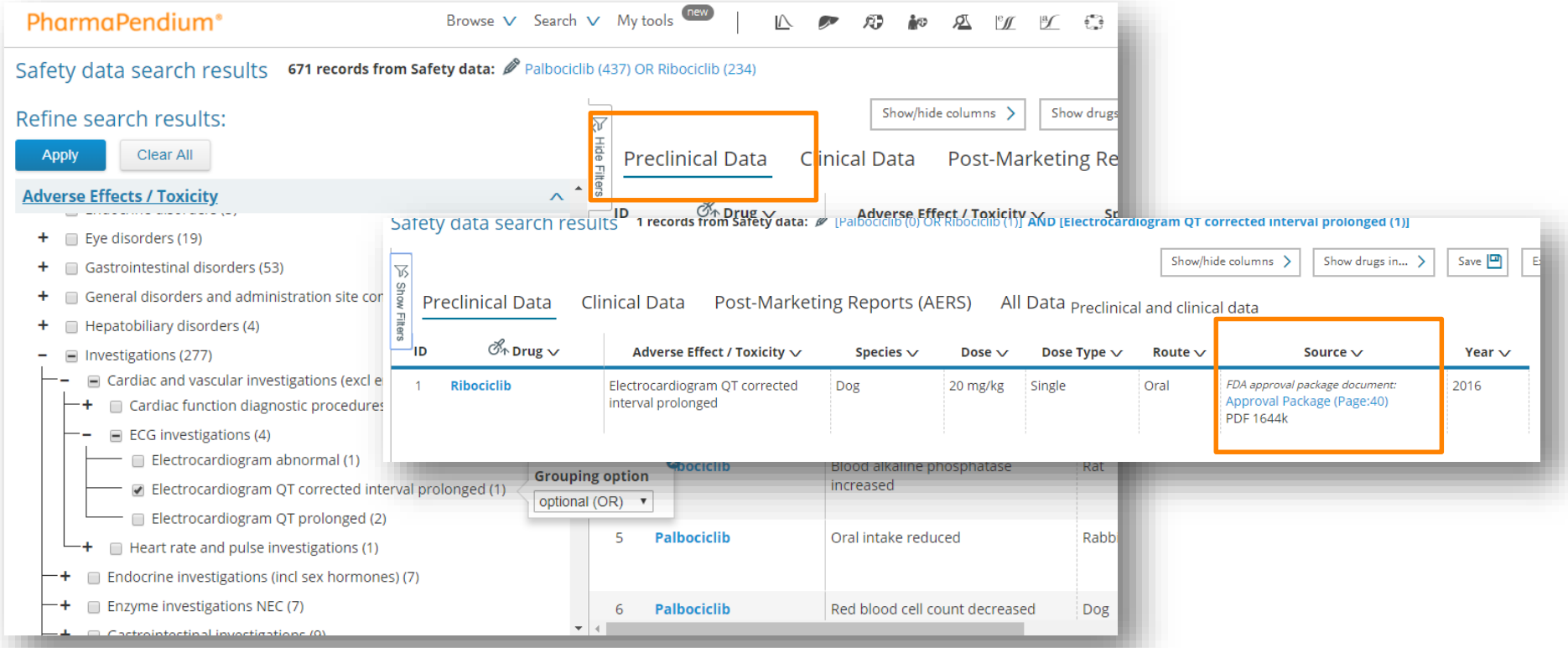


Since 2005, the FDA and EMA have required that **nearly all new molecular entities be evaluated in a Thorough QT (TQT) study** to determine a drug's effect on the QT interval.

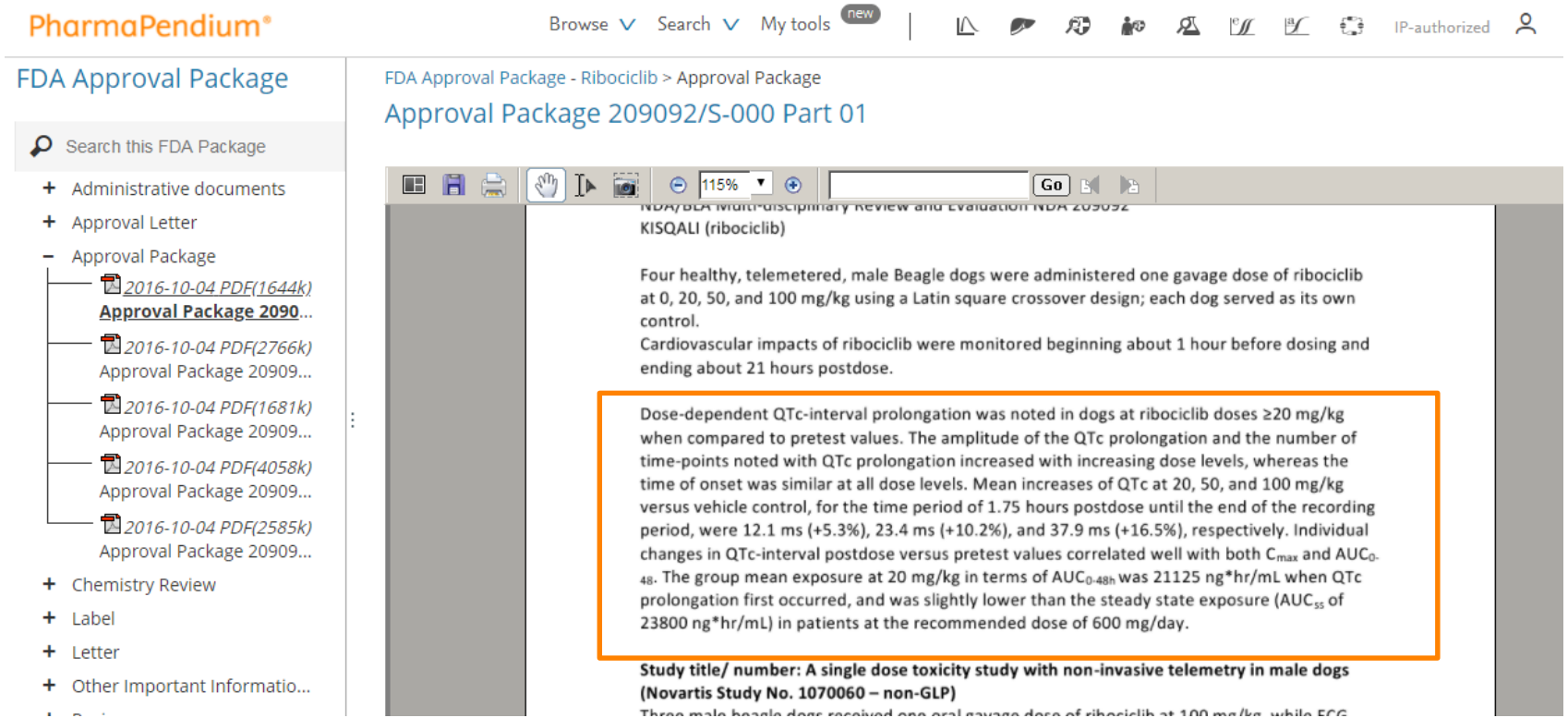
What effects on QT prolongation have been observed in drugs that act on the same target?



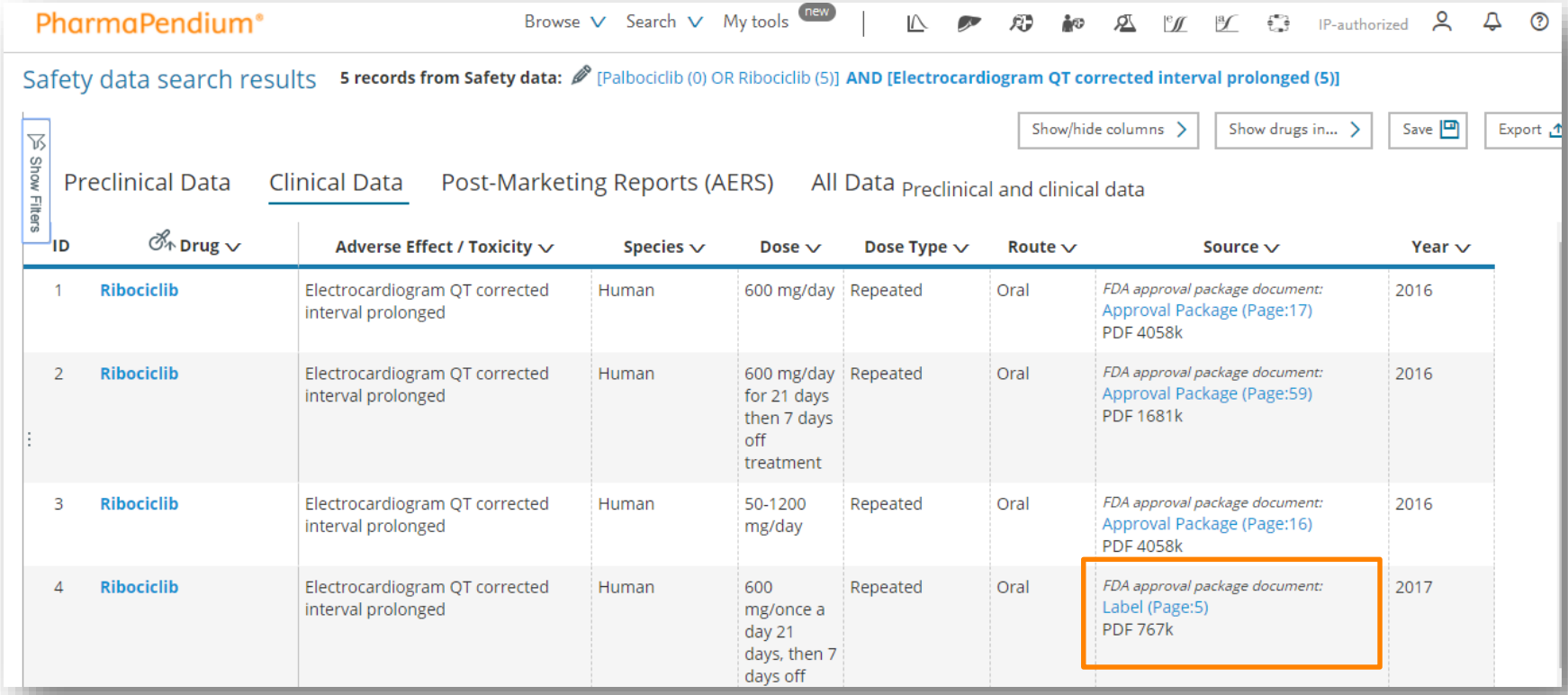
First, look at preclinical data



Dose-dependent QT prolongation was seen

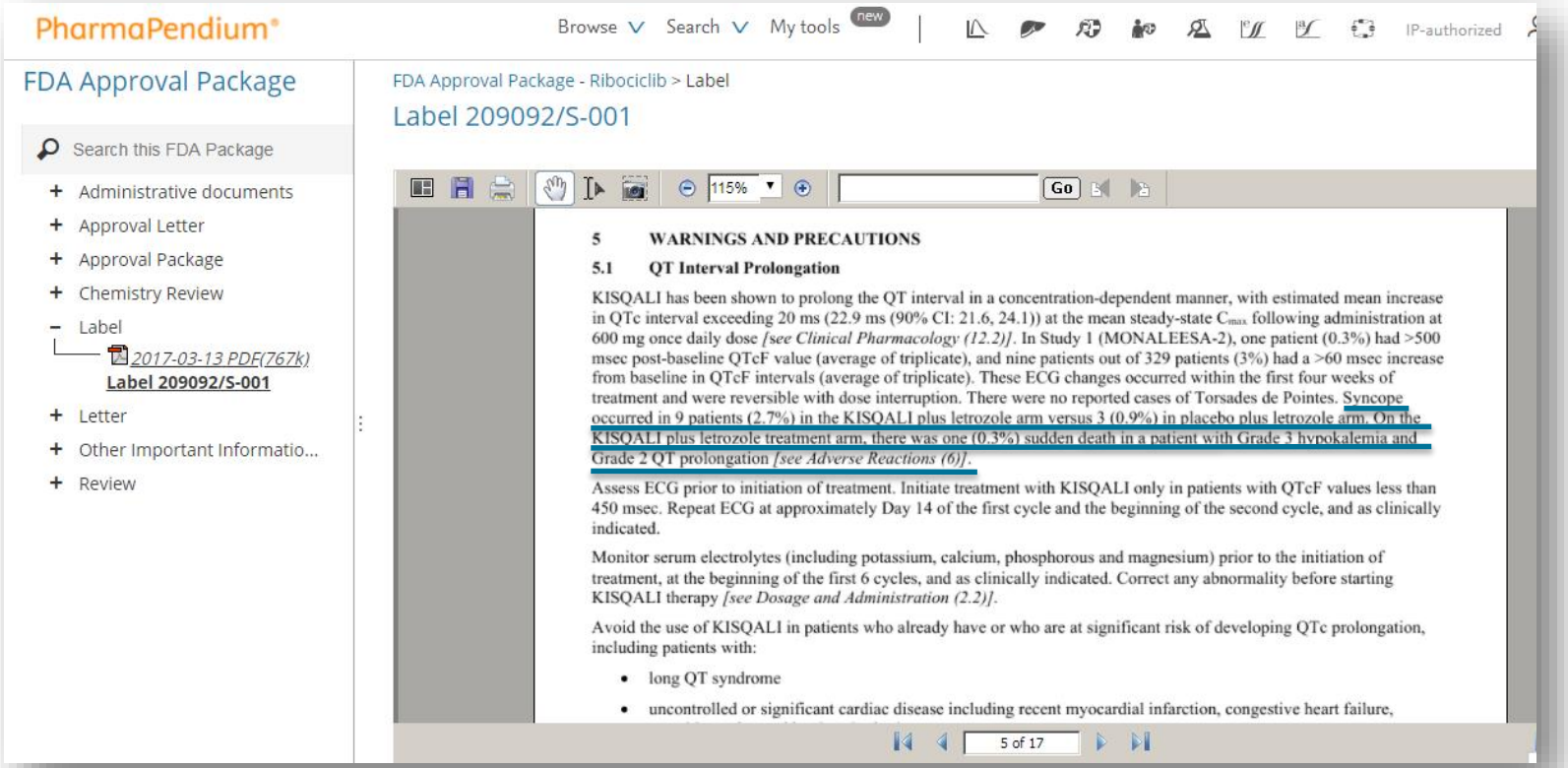


Next, look at clinical studies (keep ECG filter applied)

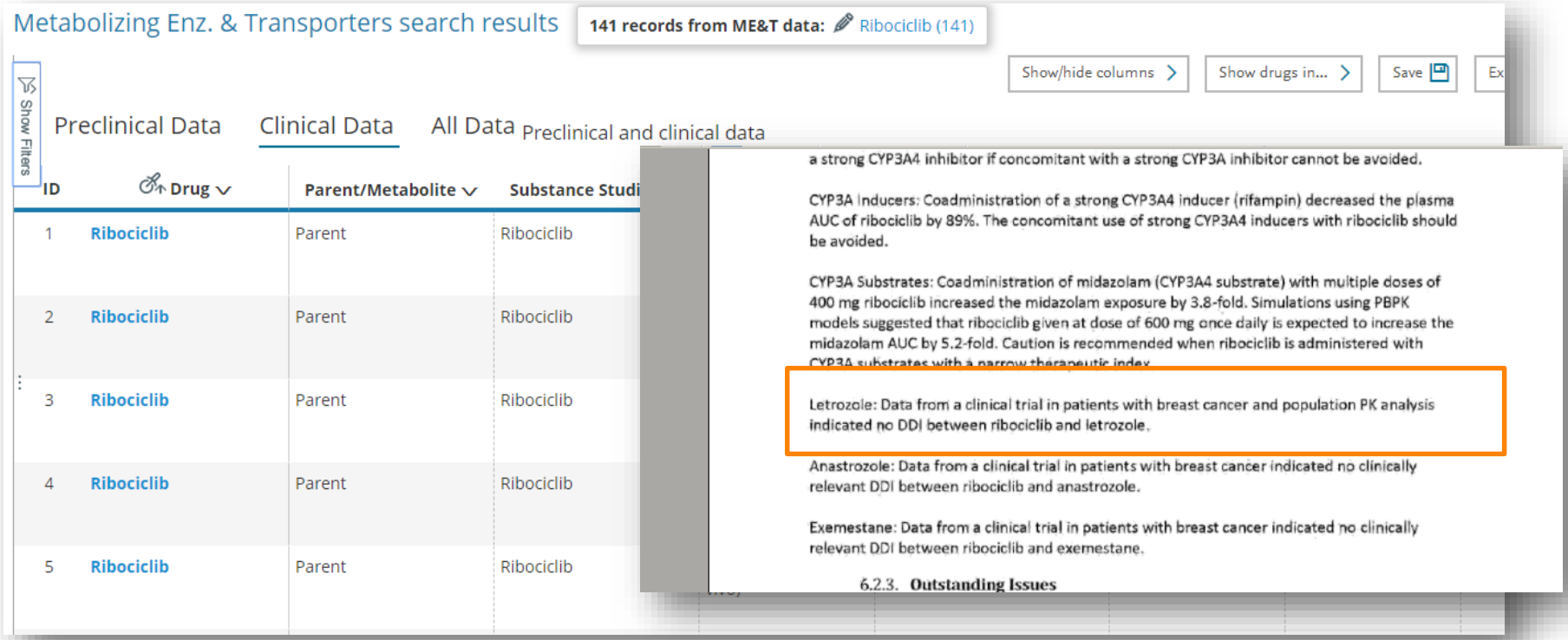


ID	Drug	Adverse Effect / Toxicity	Species	Dose	Dose Type	Route	Source	Year
1	Ribociclib	Electrocardiogram QT corrected interval prolonged	Human	600 mg/day	Repeated	Oral	*FDA approval package document:* Approval Package (Page:17) PDF 4058k	2016
2	Ribociclib	Electrocardiogram QT corrected interval prolonged	Human	600 mg/day for 21 days then 7 days off treatment	Repeated	Oral	*FDA approval package document:* Approval Package (Page:59) PDF 1681k	2016
3	Ribociclib	Electrocardiogram QT corrected interval prolonged	Human	50-1200 mg/day	Repeated	Oral	*FDA approval package document:* Approval Package (Page:16) PDF 4058k	2016
4	Ribociclib	Electrocardiogram QT corrected interval prolonged	Human	600 mg/once a day 21 days, then 7 days off	Repeated	Oral	*FDA approval package document:* Label (Page:5) PDF 767k	2017

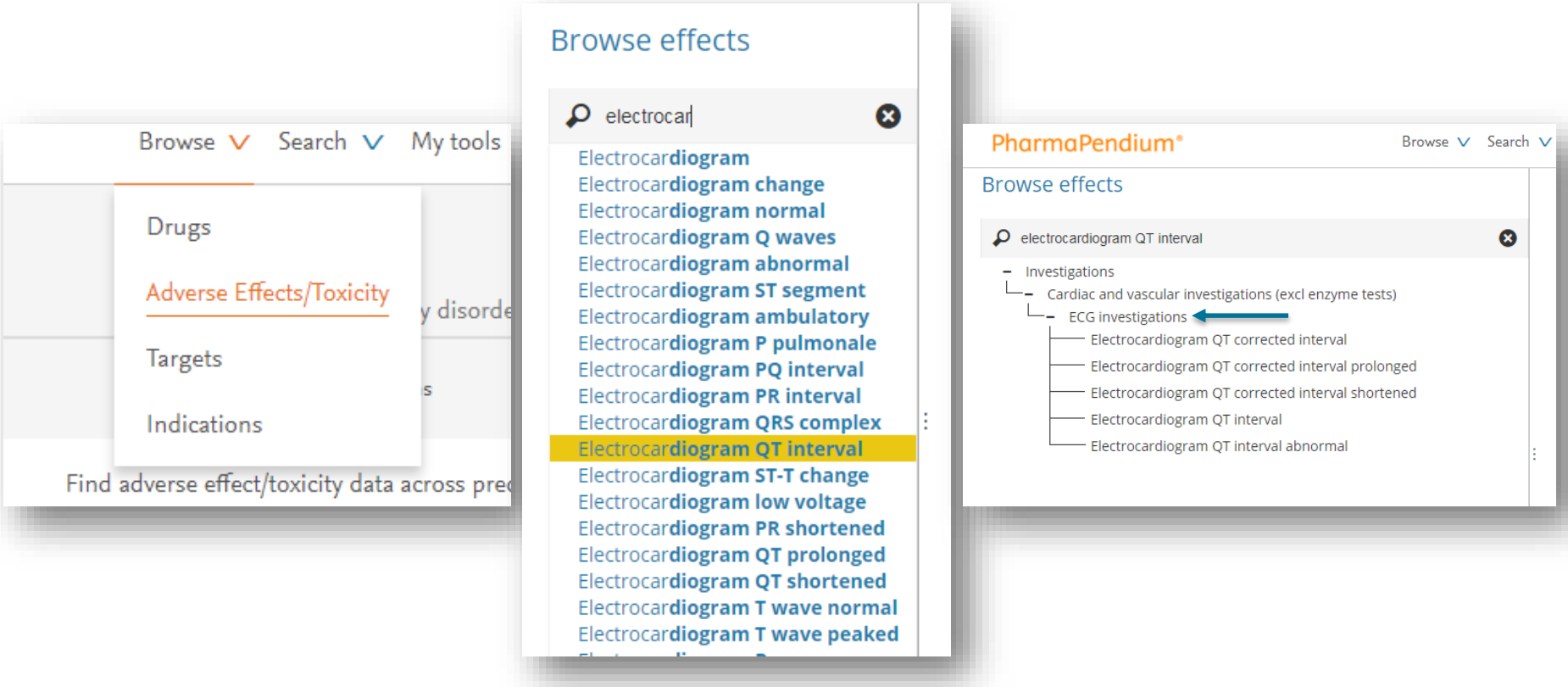
Dose dependent QT prolongation plus potential DDI was seen



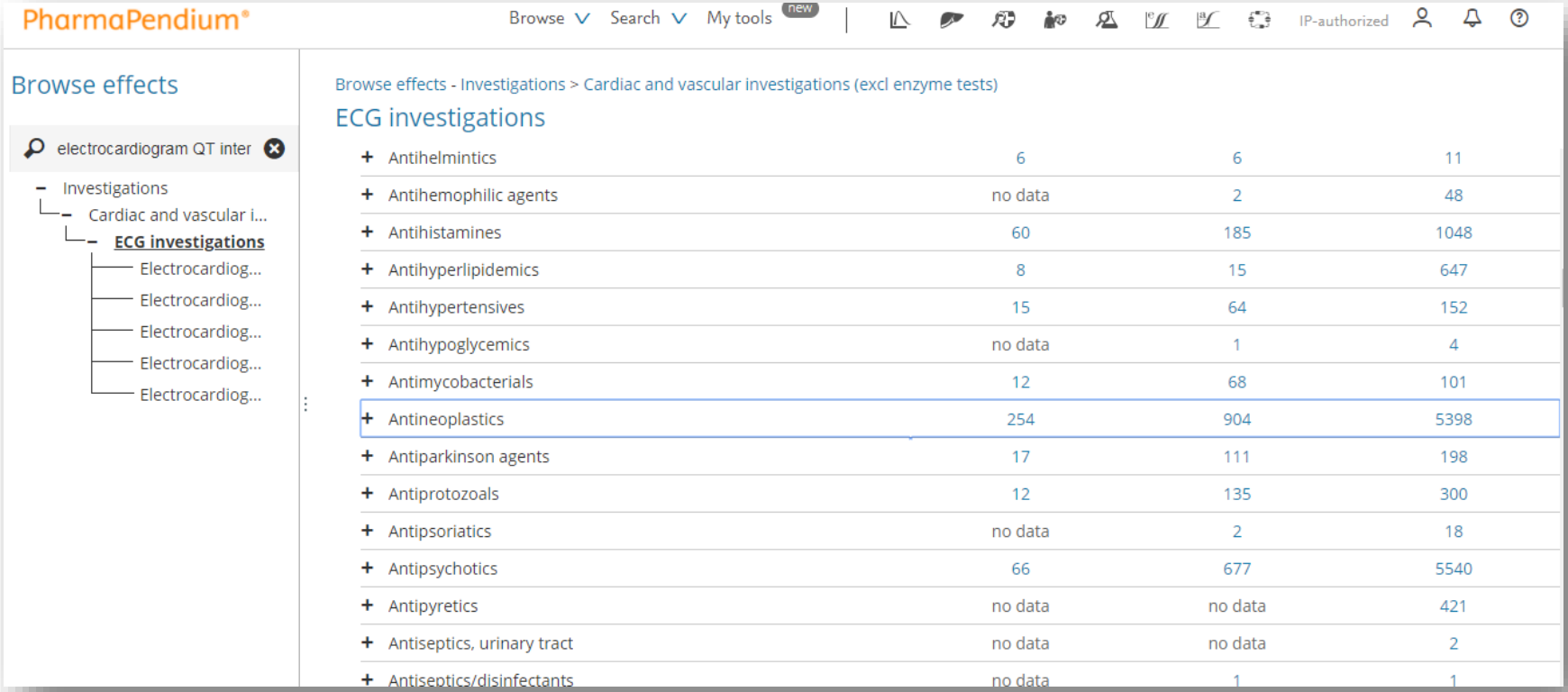
Further investigation shows more information on the potential DDI



See all QT interval AEs reported for antineoplastics

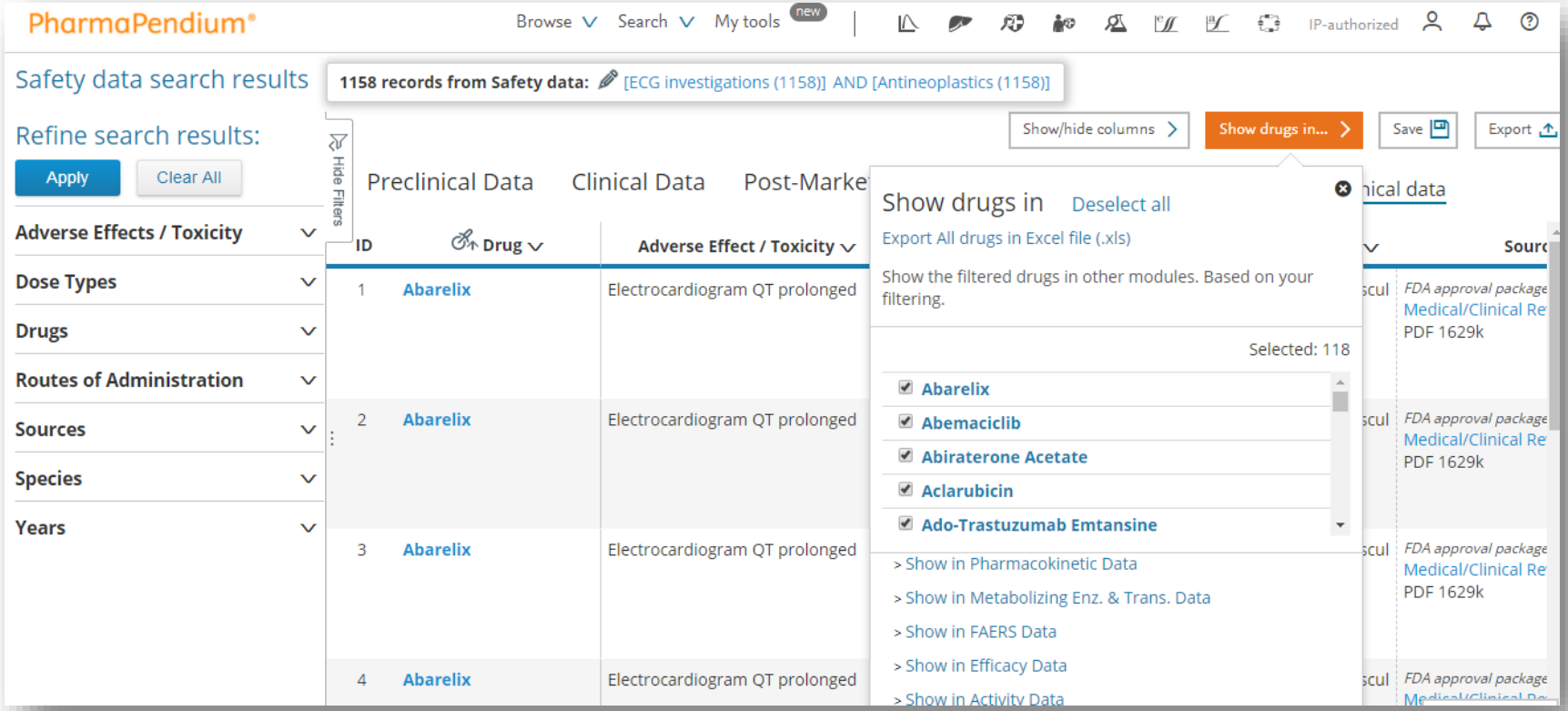


See all QT interval AEs reported for antineoplastics



+ Antihelmintics	6	6	11
+ Antihemophilic agents	no data	2	48
+ Antihistamines	60	185	1048
+ Antihyperlipidemics	8	15	647
+ Antihypertensives	15	64	152
+ Antihypoglycemics	no data	1	4
+ Antimycobacterials	12	68	101
+ Antineoplastics	254	904	5398
+ Antiparkinson agents	17	111	198
+ Antiprotozoals	12	135	300
+ Antipsoriatics	no data	2	18
+ Antipsychotics	66	677	5540
+ Antipyretics	no data	no data	421
+ Antiseptics, urinary tract	no data	no data	2
+ Antiseptics/disinfectants	no data	1	1

→1158 preclinical/clinical records for 118 drugs



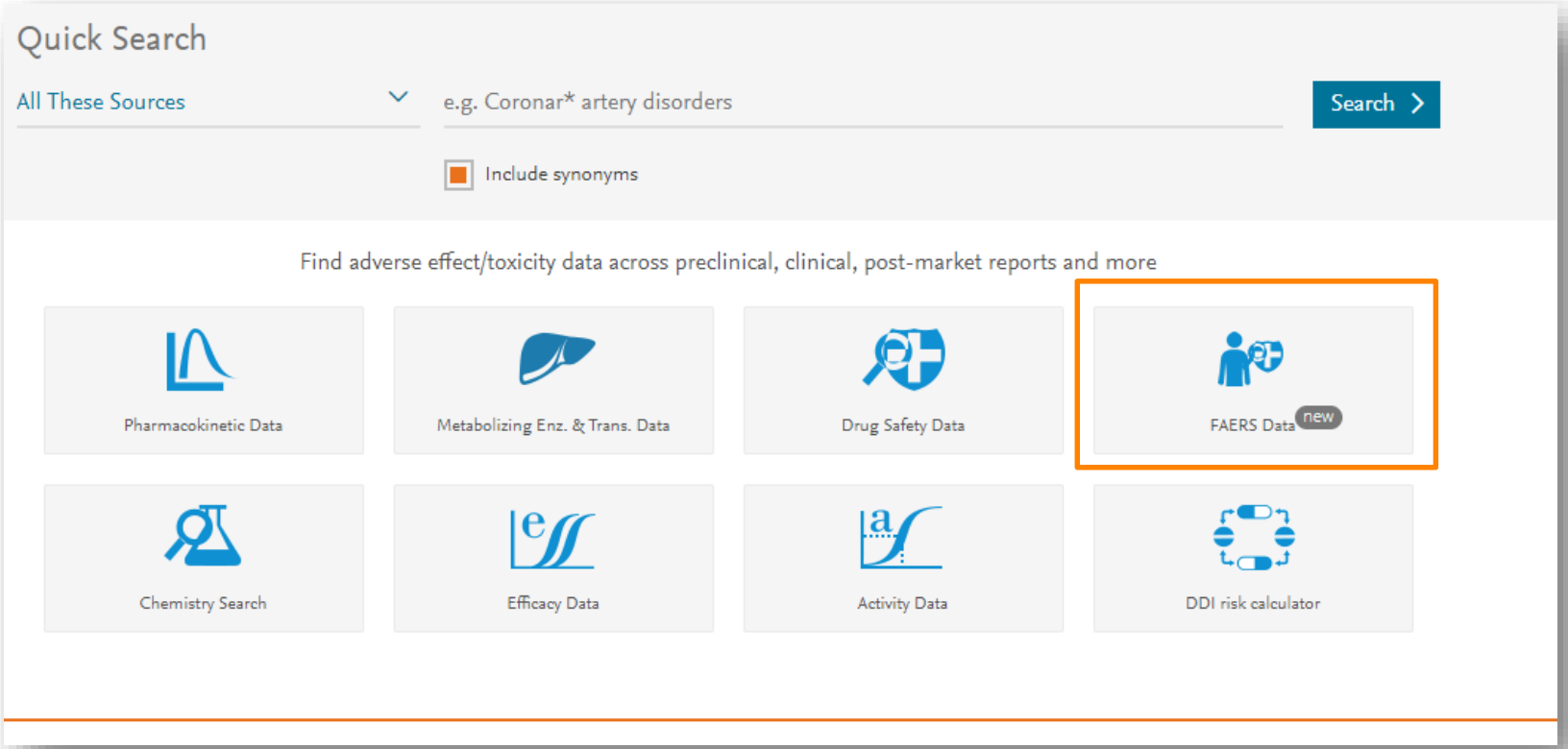
What evidence can we look at in PharmaPendium to evaluate a potential DDI signal?

Example

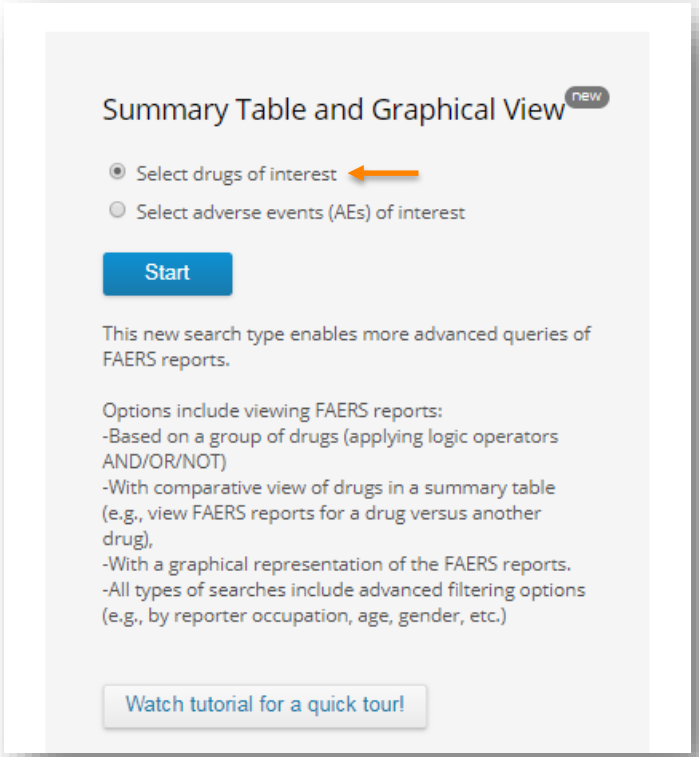
- Routine literature monitoring identified an intracranial hemorrhage in a patient taking theophylline + ciprofloxacin

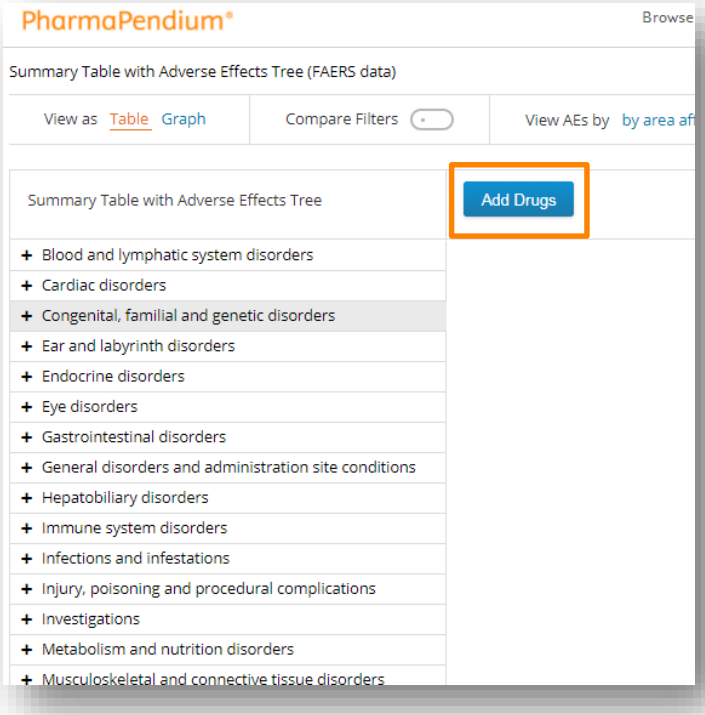
➢ What information can PharmaPendium provide to help confirm (or refute) causality?

Was there an increase in post-market reports for this AE and drug combination?

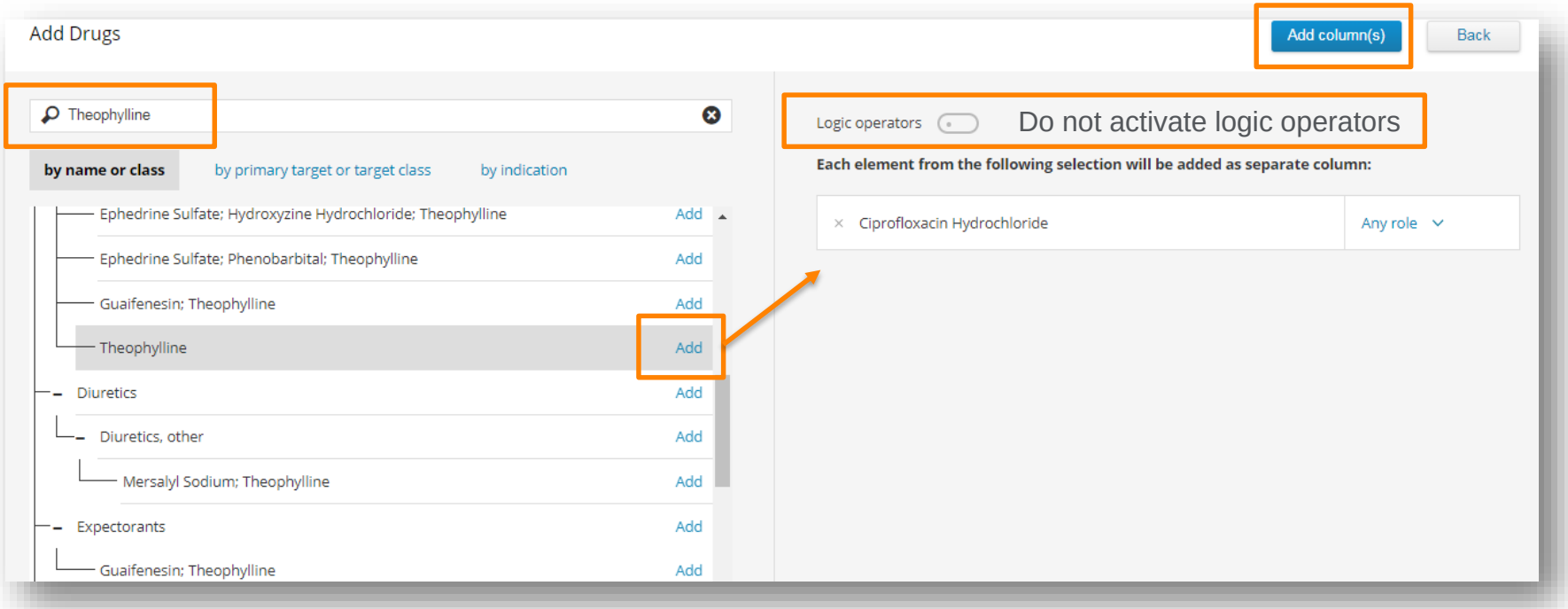


Add drugs to populate the FAERS table

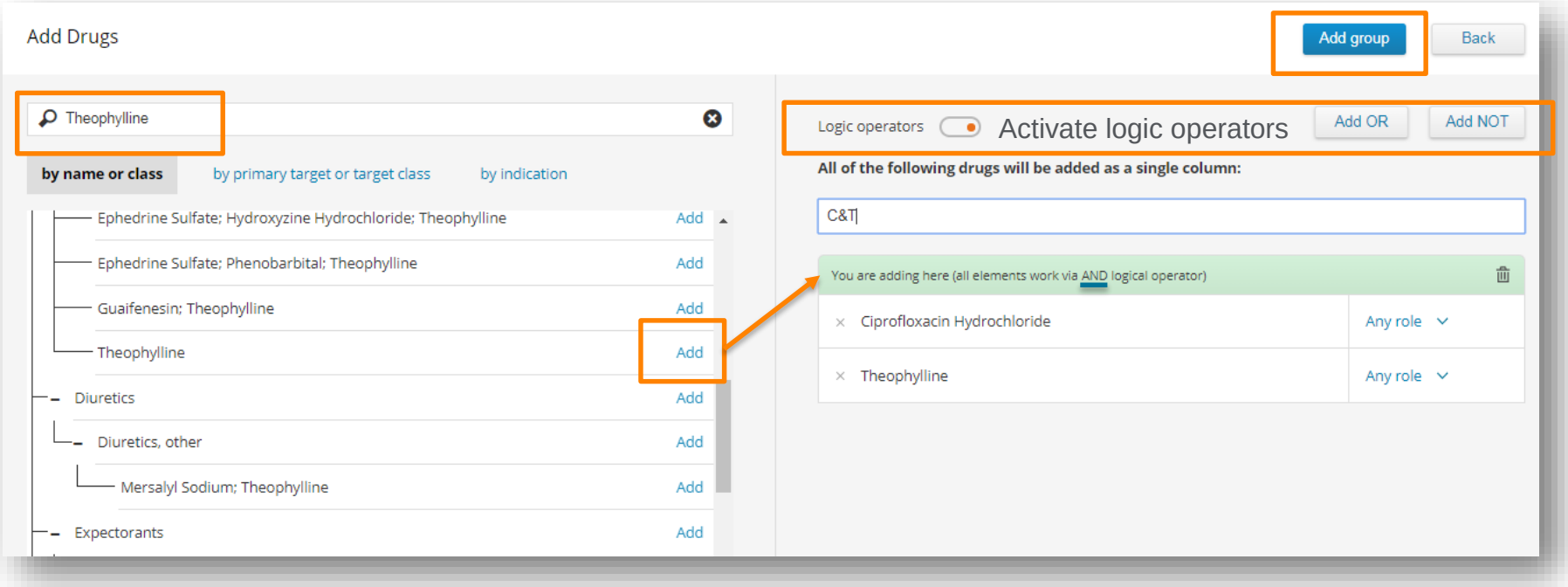




First, add drugs individually



Then, add drugs in a group



Even looking at total cases, there seems to be a peak – next convert to percent of total cases

PharmaPendium®

Browse Search My tools

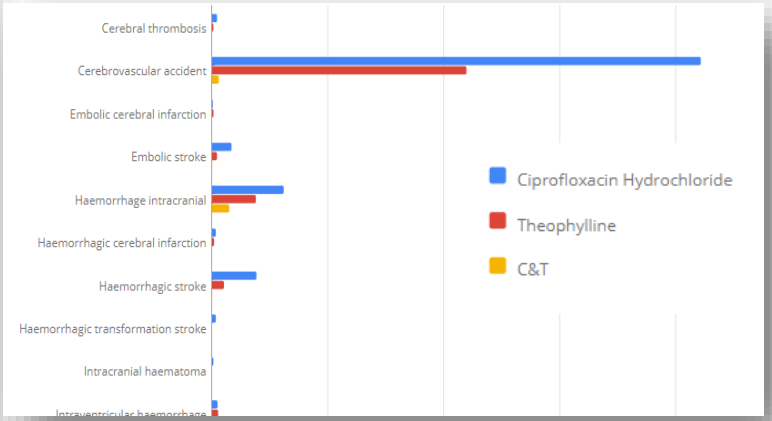
Summary Table with Adverse Effects Tree (FAERS data)

View as Table Graph | Compare Filters | View AEs by by area affected | Export | Save

Summary Table with Adverse Effects Tree	Ciprofloxacin ...	Theophylline	C&T	Add Drugs
Total	77575	26948	672	
+ Blood and lymphatic system disorders	11031	2303	125	
+ Cardiac disorders	9591	4824	160	
+ Congenital, familial and genetic disorders	934	231	5	
+ Ear and labyrinth disorders	2666	393	33	
+ Endocrine disorders	1229	397	19	
+ Eye disorders	5581	1292	44	
+ Gastrointestinal disorders	20913	6030	217	
+ General disorders and administration site conditions	31616	10966	309	
+ Hepatobiliary disorders	6551	1476	80	
+ Immune system disorders	6298	1216	38	
+ Infections and infestations	20459	5793	265	
+ Injury, poisoning and procedural complications	4056	2773	69	
+ Investigations	17371	6983	204	
+ Metabolism and nutrition disorders	9323	3275	128	
+ Musculoskeletal and connective tissue disorders	17335	3561	115	

Drill down into the graph view:

1) Nervous system disorders
2) Central nervous system vascular disorders
3) Central nervous system haemorrhages and cerebrovascular accidents



Export data, expand the relevant part of the AE taxonomy and copy the rows of data

	A	B	C	D
5		Ciprofloxacin Hydrochloride	Theophylline	C&T
6	Total	77575	26948	672
7	Blood and lymphatic system disorders	11031	2303	125
196	Cardiac disorders	9591	4824	160
447	Congenital, familial and genetic disorders	934	231	5
784	Ear and labyrinth disorders	2666	393	33
857	Endocrine disorders			
960	Eye disorders			
1315	Gastrointestinal disorders			
1958	General disorders and administration site cond			
2350	Hepatobiliary disorders			
2495	Immune system disorders			
2592	Infections and infestations			
3524	Injury, poisoning and procedural complications			
3603	Investigations			
4957	Metabolism and nutrition disorders			
5179	Musculoskeletal and connective tissue disorder			
5563	Neoplasms benign, malignant and unspecified			
6288	Nervous system disorders			
6905	Pregnancy, puerperium and perinatal condition			
7037	Psychiatric disorders			
7421	Renal and urinary disorders			
7677	Reproductive system and breast disorders			
7972	Respiratory, thoracic and mediastinal disorders			
8337	Skin and subcutaneous tissue disorders			
8663	Social circumstances			
8790	Surgical and medical procedures			
8794	Vascular disorders			
9054				

6325	Cerebral haematoma	24	2	0
6326	Cerebral haemorrhage	244	64	3
6327	Cerebral haemorrhage neonatal	1	2	0
6328	Cerebral infarction	223	144	1
6329	Cerebral ischaemia	145	28	0
6330	Cerebral thrombosis	10	3	0
6331	Cerebrovascular accident	844	440	13
6332	Embolic cerebral infarction	2	4	0
6333	Embolic stroke	35	10	1
6334	Haemorrhage intracranial	125	77	31
6335	Haemorrhagic cerebral infarction	8	5	0
6336	Haemorrhagic stroke	78	22	1
6337	Haemorrhagic transformation stroke	8	0	0
6338	Intracranial haematoma	3	0	0
6339	Intraventricular haemorrhage	11	12	0
6340	Intraventricular haemorrhage neonatal	0	9	0
6341	Ischaemic cerebral infarction	18	5	0
6342	Ischaemic stroke	67	18	1
6343	Meningorrhagia	2	0	0
6344	Post procedural stroke	0	2	0
6345	Precerebral artery occlusion	0	2	0
6346	Putamen haemorrhage	0	3	0
6347	Ruptured cerebral aneurysm	2	11	0
6348	Spinal haematoma	1	0	0
6349	Subarachnoid haemorrhage	118	38	0
6350	Thalamic infarction	9	1	0
6351	Thalamus haemorrhage	1	3	0
6352	Thrombotic stroke	1	6	0
6353	Vertebral artery occlusion	0	1	0
6354	Vertebral artery thrombosis	1	0	0

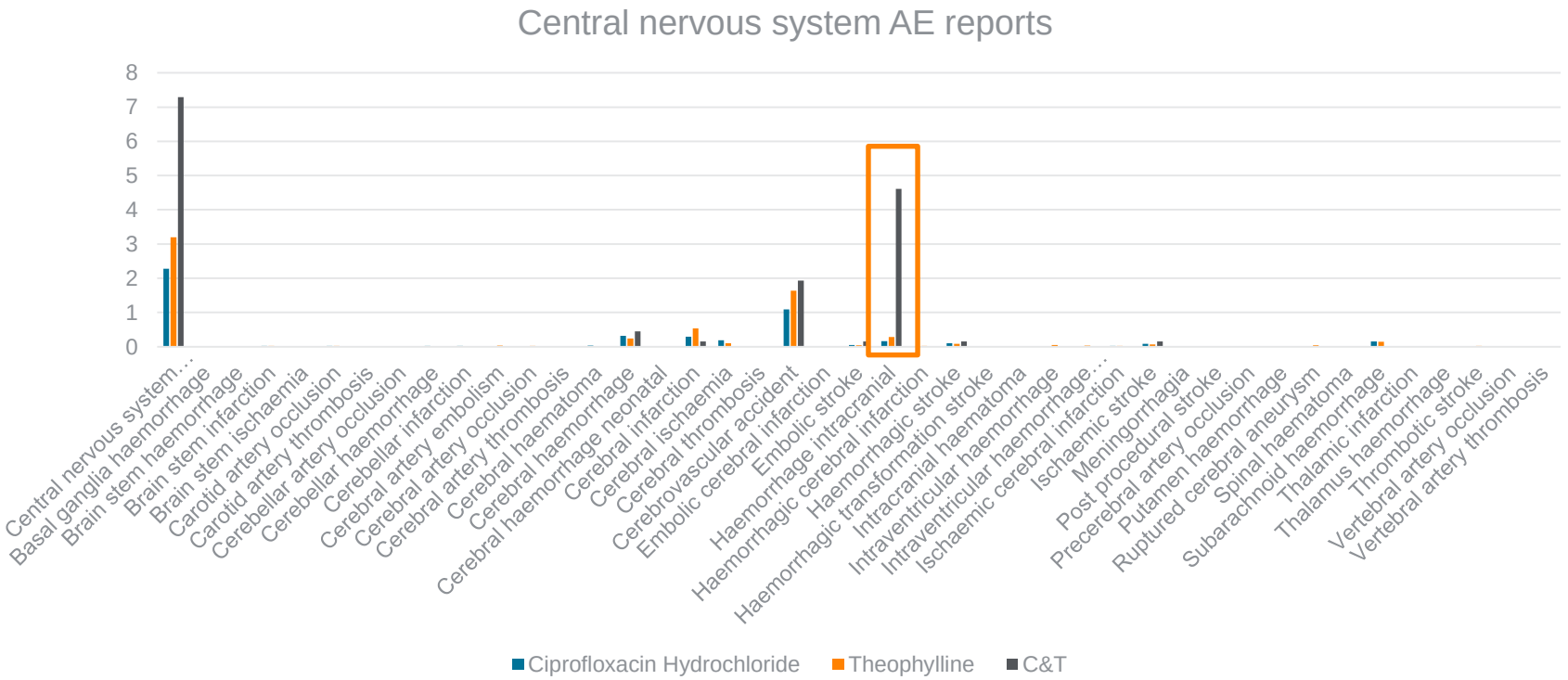
Convert to % (of total AEs), then create a chart

	Ciprofloxacin Hydrochloride	Theophylline	C&T
Central nervous system haemorrhages and cerebrovascular accidents	1762	662	49
Basal ganglia haemorrhage	1	0	0
Brain stem haemorrhage	6	1	0
Brain stem infarction	16	6	0
Brain stem ischaemia	3	1	0
Carotid artery occlusion	19	7	0
Carotid artery thrombosis	5	1	0
Cerebellar artery occlusion	0	1	0
Cerebellar haemorrhage	15	3	0
Cerebellar infarction	20	3	0
Cerebral artery embolism	13	5	0
Cerebral artery occlusion	5	6	0
Cerebral artery thrombosis	6	3	0
Cerebral haematoma	24	2	0
Cerebral haemorrhage	244	64	3
Cerebral haemorrhage neonatal	1	2	0
Cerebral infarction	223	144	1
Cerebral ischaemia	145	25	0
Cerebral thrombosis	10	2	0

Total Aes reported	77575	26945	672
	Ciprofloxacin Hydrochloride	Theophylline	C&T
Central nervous system haemorrhages and cerebrovascular accidents	2.269373632	3.195753154	7.291667
Basal ganglia haemorrhage	0.001289075	0	0
Brain stem haemorrhage	0.007734451	0.003710851	0
Brain stem infarction	0.020625201	0.022265103	0
Brain stem ischaemia	0.003867225	0.003710851	0
Carotid artery occlusion	0.024492427	0.025975954	0
Carotid artery thrombosis	0.006445375	0.003710851	0
Cerebellar artery occlusion	0	0.003710851	0
Cerebellar haemorrhage	0.019336126	0.011132552	0
Cerebellar infarction	0.025781502	0.011132552	0
Cerebral artery embolism	0.016757976	0.029656504	0
Cerebral artery occlusion	0.006445375	0.022265103	0
Cerebral artery thrombosis	0.007734451	0.011132552	0
Cerebral haematoma	0.030937803	0.007421701	0
Cerebral haemorrhage	0.314534222	0.237494434	0.446429
Cerebral haemorrhage neonatal	0.001289075	0.007421701	0
Cerebral infarction	0.287463745	0.534363476	0.14881
Cerebral ischaemia	0.186915888	0.103903815	0
Cerebral thrombosis	0.012890751	0.011132552	0

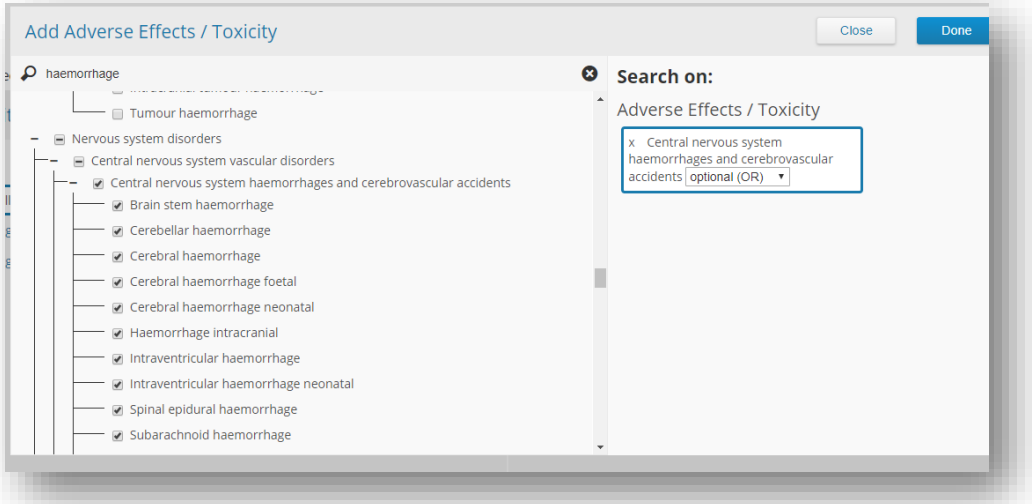
Cerebrovascular accident	544	440	13	Cerebrovascular accident	1.057979375	1.632774232	1.934524
Embolic cerebral infarction	2	4	0	Embolic cerebral infarction	0.00257515	0.014843402	0
Embolic stroke	33	10	1	Embolic stroke	0.045117626	0.037106503	0.14881
Haemorrhage intracranial	125	77	21	Haemorrhage intracranial	0.161134356	0.285725491	4.613095
Haemorrhagic cerebral infarction	8	5	0	Haemorrhagic cerebral infarction	0.010312601	0.018554253	0
Haemorrhagic stroke	76	22	1	Haemorrhagic stroke	0.100547537	0.081638712	0.14881
Haemorrhagic transformation stroke	8	0	0	Haemorrhagic transformation stroke	0.010312601	0	0
Intracranial haematoma	3	0	0	Intracranial haematoma	0.003867225	0	0
Intraventricular haemorrhage	11	12	0	Intraventricular haemorrhage	0.014179526	0.044530206	0
Intraventricular haemorrhage neonatal	0	9	0	Intraventricular haemorrhage neonatal	0	0.033397655	0
Ischaemic cerebral infarction	16	5	0	Ischaemic cerebral infarction	0.022203352	0.018554253	0
Ischaemic stroke	67	18	1	Ischaemic stroke	0.086368031	0.066726309	0.14881
Meningorrhagia	2	0	0	Meningorrhagia	0.00257515	0	0
Post procedural stroke	0	2	0	Post procedural stroke	0	0.007421701	0
Precerebral artery occlusion	0	2	0	Precerebral artery occlusion	0	0.007421701	0
Putamen haemorrhage	0	3	0	Putamen haemorrhage	0	0.011132552	0
Ruptured cerebral aneurysm	2	11	0	Ruptured cerebral aneurysm	0.00257515	0.040812356	0
Spinal haematoma	1	0	0	Spinal haematoma	0.001289075	0	0
Subarachnoid haemorrhage	116	38	0	Subarachnoid haemorrhage	0.15211056	0.14101222	0
Thalamic infarction	9	1	0	Thalamic infarction	0.011601676	0.003710851	0
Thalamus haemorrhage	1	3	0	Thalamus haemorrhage	0.001289075	0.011132552	0
Thrombotic stroke	1	6	0	Thrombotic stroke	0.001289075	0.022265103	0
Vertebral artery occlusion	0	1	0	Vertebral artery occlusion	0	0.003710851	0
Vertebral artery thrombosis	1	0	0	Vertebral artery thrombosis	0.001289075	0	0

PharmaPendium lets you drill down to see how different AEs may be reported for drug combinations

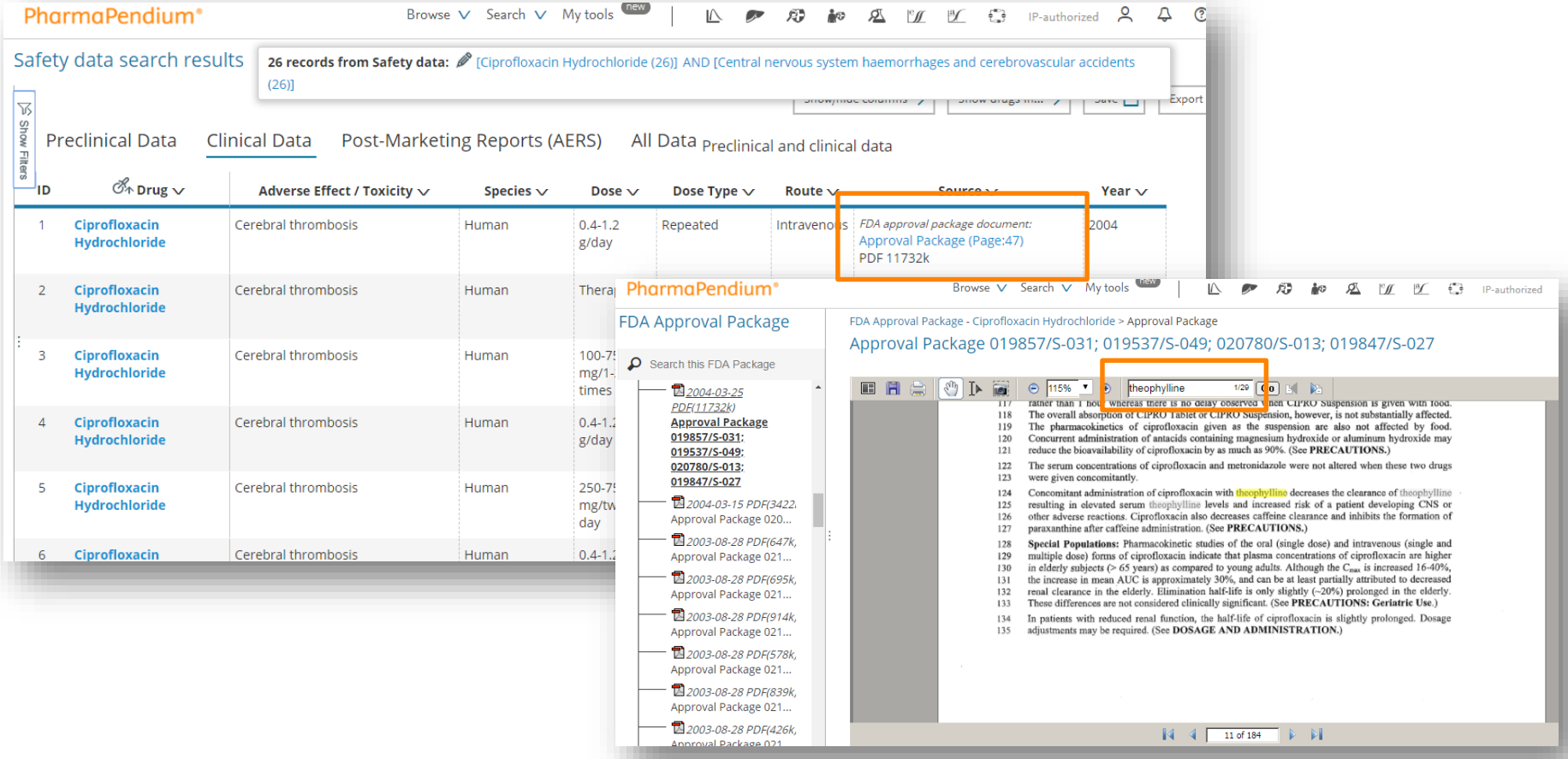


What other information in PP can be examined to answer this question?

1) Drug safety module:
    1) Search theophylline + Central nervous system haemorrhages and cerebrovascular accidents = 0 results
    2) Search Ciprofloxacin Hydrochloride + Central nervous system haemorrhages and cerebrovascular accidents = 26 results



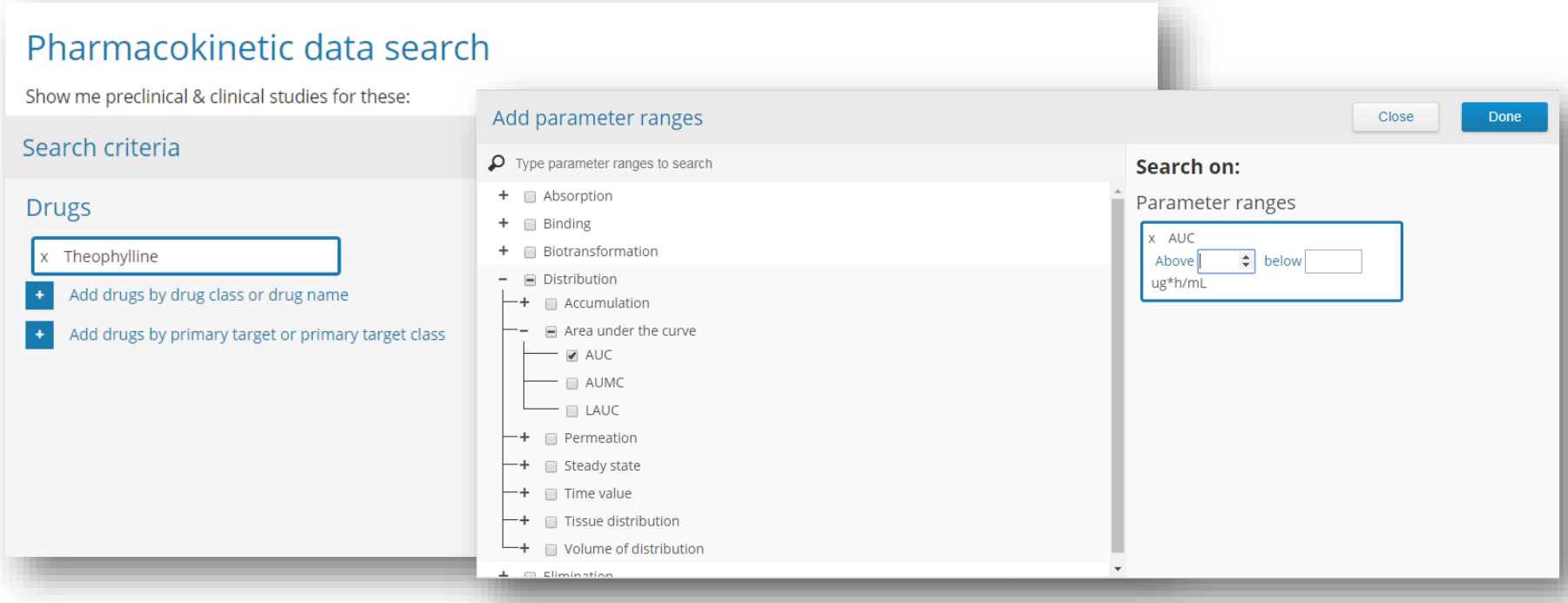
Click on the first result, search text for theophylline



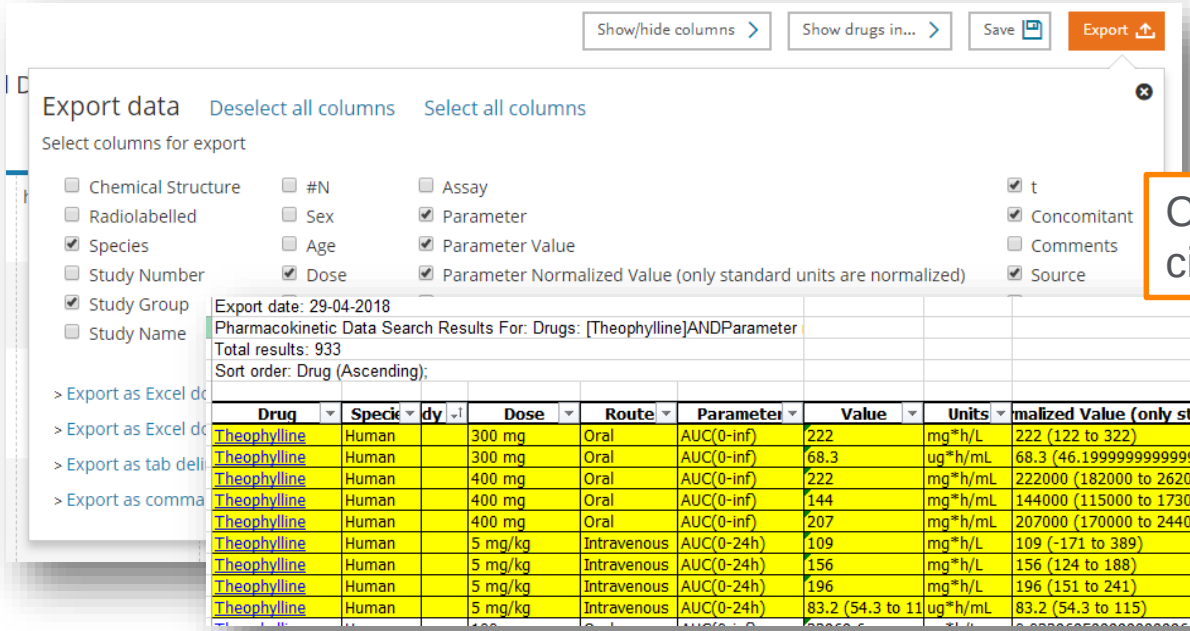
What other information in PP can be examined to answer this question?

2) Pharmacokinetic module:

1) Search theophylline and limit parameter to AUC



Export data. Filter results to those with ciprofloxacin as a concomitant & theophylline (same dose, no concomitant)



Export date: 29-04-2018
Pharmacokinetic Data Search Results For: Drugs: [Theophylline]ANDParameter
Total results: 933
Sort order: Drug (Ascending);

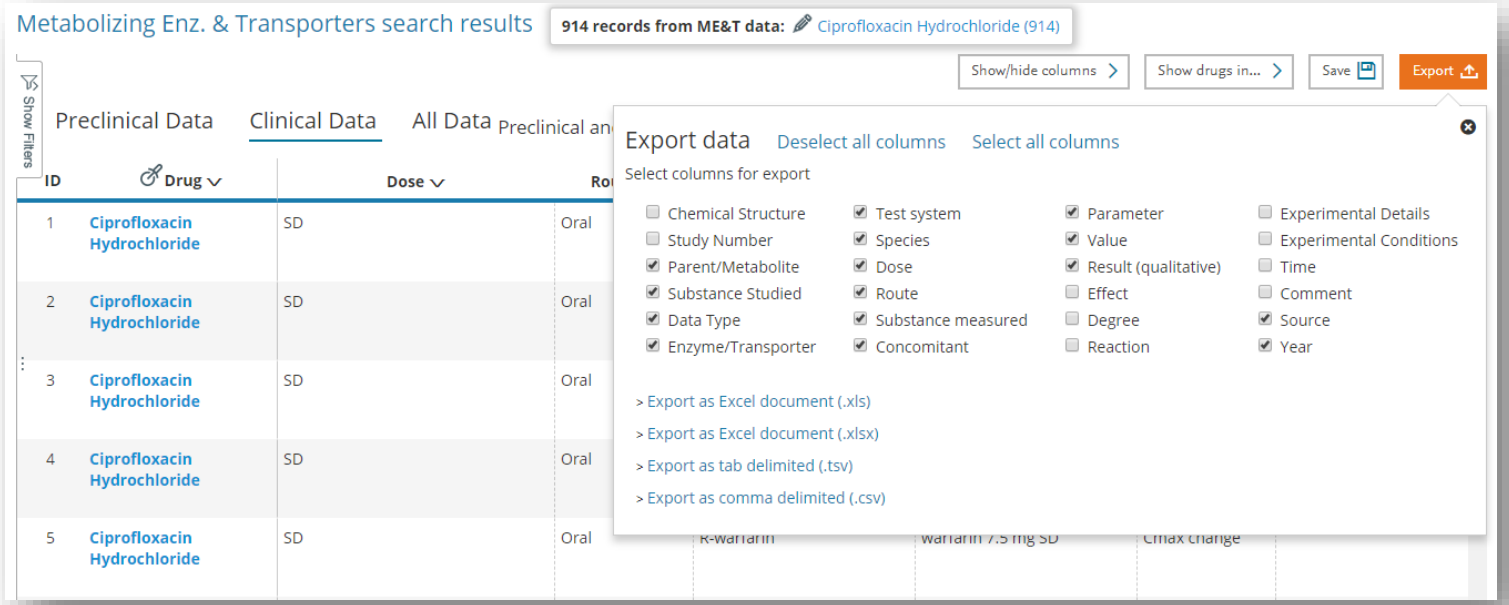
Drug	Specie	dy	Dose	Route	Parameter	Value	Units	malized Value (only standard units	nit (only stan	SD		Concomitant
Theophylline	Human		300 mg	Oral	AUC(0-inf)	222	mg*h/L	222 (122 to 322)	ug*h/mL	100.0		Ciprofloxacin 500 mg
Theophylline	Human		300 mg	Oral	AUC(0-inf)	68.3	ug*h/mL	68.3 (46.199999999999996 to 90.4)	ug*h/mL	22.1		
Theophylline	Human		400 mg	Oral	AUC(0-inf)	222	mg*h/mL	222000 (182000 to 262000)	ug*h/mL	40.0		Ciprofloxacin 500 mg
Theophylline	Human		400 mg	Oral	AUC(0-inf)	144	mg*h/mL	144000 (115000 to 173000)	ug*h/mL	29.0		
Theophylline	Human		400 mg	Oral	AUC(0-inf)	207	mg*h/mL	207000 (170000 to 244000)	ug*h/mL	37.0		Ciprofloxacin 500 mg
Theophylline	Human		5 mg/kg	Intravenous	AUC(0-24h)	109	mg*h/L	109 (-171 to 389)	ug*h/mL	280.0		
Theophylline	Human		5 mg/kg	Intravenous	AUC(0-24h)	156	mg*h/L	156 (124 to 188)	ug*h/mL	32.0		Ciprofloxacin 500 mg
Theophylline	Human		5 mg/kg	Intravenous	AUC(0-24h)	196	mg*h/L	196 (151 to 241)	ug*h/mL	45.0		Ciprofloxacin 500 mg
Theophylline	Human		5 mg/kg	Intravenous	AUC(0-24h)	83.2 (54.3 to 11	ug*h/mL	83.2 (54.3 to 115)	ug*h/mL			

Clear increase in AUC when ciprofloxacin is co-administered

What other information in PP can be examined to answer this question?

3) Metabolising enzyme & transporter module:

1) Search ciprofloxacin with no limits (goal is to identify all studies where theophylline was a concomitant). Export data



Filter results for theophylline as concomitant

Export date: 29-04-2018
Metabolizing Enzymes And Transporters Data Search Results For: Drugs: [Ciprofloxacin Hydrochloride]
Total results: 914
Sort order: Concomitant (Descending); Drug (Ascending);

Drug	nt/Me	Substance Stud	Data Type	nzyme/Transpo	Test syste	Speci	Dose	Route	bstance mea	Concomitant	Parameter	Result (qualitative
Ciprofloxacin Hydrochloride	Parent	Ciprofloxacin hydroc	Enzyme Inhibitor (in vivo)	Enzyme unspecified	Not applicable	Human	Unreported		Theophylline	theophylline	C increase	Yes
Ciprofloxacin Hydrochloride	Parent	Ciprofloxacin	Enzyme Inhibitor (in vivo)	Enzyme unspecified	Not applicable	Human	Unreported		Theophylline	theophylline	C increase	Yes
Ciprofloxacin Hydrochloride	Parent	Ciprofloxacin hydroc	Enzyme Inhibitor (in vivo)	CYP1A2	Not applicable	Human	Unreported		Theophylline	theophylline	C increase	Yes
Ciprofloxacin Hydrochloride	Parent	Ciprofloxacin hydroc	Enzyme Inhibitor (in vivo)	Enzyme unspecified	Not applicable	Human	Unreported		Theophylline	theophylline	C increase	Yes
Ciprofloxacin Hydrochloride	Parent	Ciprofloxacin hydroc	Inhibitor (in vivo)	Unreported	Not applicable	Human	Unreported	Oral	Theophylline	theophylline	CL decrease	Yes
Ciprofloxacin Hydrochloride	Parent	Ciprofloxacin hydroc	Enzyme Inhibitor (in vivo)	Enzyme unspecified	Not applicable	Human	Unreported	Oral	Theophylline	theophylline	C increase	Yes
Ciprofloxacin Hydrochloride	Parent	Ciprofloxacin	Enzyme Inhibitor (in vivo)	CYP1A2	Not applicable	Human	Unreported		Theophylline	theophylline	C increase	Yes
Ciprofloxacin Hydrochloride	Parent	Ciprofloxacin	Enzyme Inhibitor (in vivo)	CYP1A2	Not applicable	Human	Unreported		Theophylline	theophylline	C increase	Yes
Ciprofloxacin Hydrochloride	Parent	Ciprofloxacin	Enzyme Inhibitor (in vivo)	Enzyme unspecified	Not applicable	Human	Unreported		Theophylline	theophylline	T1/2 increase	Yes
Ciprofloxacin Hydrochloride	Parent	Ciprofloxacin hydroc	Enzyme Inhibitor (in vivo)	CYP1A2	Not applicable	Human	Unreported		Theophylline	theophylline	C increase	Yes
Ciprofloxacin Hydrochloride	Parent	Ciprofloxacin	Enzyme Inhibitor (in vivo)	CYP1A2	Not applicable	Human	Unreported	Oral	Theophylline	theophylline	Cmax increase	Yes
Ciprofloxacin Hydrochloride	Parent	Ciprofloxacin hydroc	Enzyme Inhibitor (in vivo)	Enzyme unspecified	Not applicable	Human	Unreported		Theophylline	theophylline	T1/2 increase	Yes
Ciprofloxacin Hydrochloride	Parent	Ciprofloxacin	Enzyme Inhibitor (in vivo)	CYP1A2	Not applicable	Human	Unreported	Oral	Theophylline	theophylline	Cmax increase	Yes
Ciprofloxacin Hydrochloride	Parent	Ciprofloxacin	Enzyme Inhibitor (in vivo)	CYP1A2	Not applicable	Human	Unreported	Oral	Theophylline	theophylline	Cmax increase	Yes
Ciprofloxacin Hydrochloride	Parent	Ciprofloxacin	Enzyme Inhibitor (in vivo)	Enzyme unspecified	Not applicable	Human	Unreported		Theophylline	theophylline	C increase	Yes
Ciprofloxacin Hydrochloride	Parent	Ciprofloxacin hydroc	Enzyme Inhibitor (in vivo)	Enzyme unspecified	Not applicable	Human	Unreported		Theophylline	theophylline	C increase	Yes
Ciprofloxacin Hydrochloride	Parent	Ciprofloxacin hydroc	Enzyme Inhibitor (in vivo)	Enzyme unspecified	Not applicable	Human	Unreported		Theophylline	theophylline	CL decrease	Yes
Ciprofloxacin Hydrochloride	Parent	Ciprofloxacin hydroc	Enzyme Inhibitor (in vivo)	Enzyme unspecified	Not applicable	Human	Unreported		Theophylline	theophylline	Enzyme activity decrease	Yes
Ciprofloxacin Hydrochloride	Parent	Ciprofloxacin	Enzyme Inhibitor (in vivo)	CYP1A2	Not applicable	Human	Unreported		Theophylline	theophylline	C increase	Yes
Ciprofloxacin Hydrochloride	Parent	Ciprofloxacin hydroc	Enzyme Inhibitor (in vivo)	CYP1A2	Not applicable	Human	Unreported	Oral	Theophylline	theophylline	C increase	Yes
Ciprofloxacin Hydrochloride	Parent	Ciprofloxacin hydroc	Enzyme Inhibitor (in vivo)	Enzyme unspecified	Not applicable	Human	Unreported		Theophylline	theophylline	C increase	Yes
Ciprofloxacin Hydrochloride	Parent	Ciprofloxacin hydroc	Enzyme Inhibitor (in vivo)	Enzyme unspecified	Not applicable	Human	Unreported		Theophylline	theophylline	T1/2 increase	Yes
Ciprofloxacin Hydrochloride	Parent	Ciprofloxacin	Enzyme Inhibitor (in vivo)	CYP1A2	Not applicable	Human	Unreported	Oral	Theophylline	theophylline	Cmax increase	Yes
Ciprofloxacin Hydrochloride	Parent	Ciprofloxacin hydroc	Enzyme Inhibitor (in vivo)	Enzyme unspecified	Not applicable	Human	Unreported		Theophylline	theophylline	CL decrease	Yes
Ciprofloxacin Hydrochloride	Parent	Ciprofloxacin	Enzyme Inhibitor (in vivo)	CYP1A2	Not applicable	Human	Unreported	Oral	Theophylline	theophylline	Cmax increase	Yes
Ciprofloxacin Hydrochloride	Parent	Ciprofloxacin hydroc	Inhibitor (in vivo)	Unreported	Not applicable	Human	Unreported	Oral	Theophylline	theophylline	C increase	Yes
Ciprofloxacin Hydrochloride	Parent	Ciprofloxacin	Enzyme Inhibitor (in vivo)	CYP1A2	Not applicable	Human	Unreported		Theophylline	theophylline	C increase	Yes

94 lines of data with qualitative changes to MET parameter being measured

Example result

fluoroquinolones, including ciprofloxacin. CIPRO IV should be avoided in patients with known prolongation of the QT interval, risk factors for QT prolongation or torsade de pointes (for example, congenital long QT syndrome, uncorrected electrolyte imbalance, such as hypokalemia or hypomagnesemia and cardiac disease, such as heart failure, myocardial infarction, or bradycardia), and patients receiving Class IA antiarrhythmic agents (quinidine, procainamide), or Class III antiarrhythmic agents (amiodarone, sotalol), tricyclic antidepressants, macrolides, and antipsychotics).. Elderly patients may also be more susceptible to drug-associated effects on the QT interval. (See **PRECAUTIONS**, **Drug Interactions** and **Geriatric Use.**)

Cytochrome P450 (CYP450)

Ciprofloxacin is an inhibitor of the hepatic CYP1A2 enzyme pathway. Coadministration of ciprofloxacin and other drugs primarily metabolized by CYP1A2 (for example, theophylline, methylxanthines, caffeine, tizanidine, ropinirole, clozapine, olanzapine) results in increased plasma concentrations of the coadministered drug and could lead to clinically significant pharmacodynamic side effects of the coadministered drug. (See **PRECAUTIONS, Drug Interactions**.)

PRECAUTIONS

General

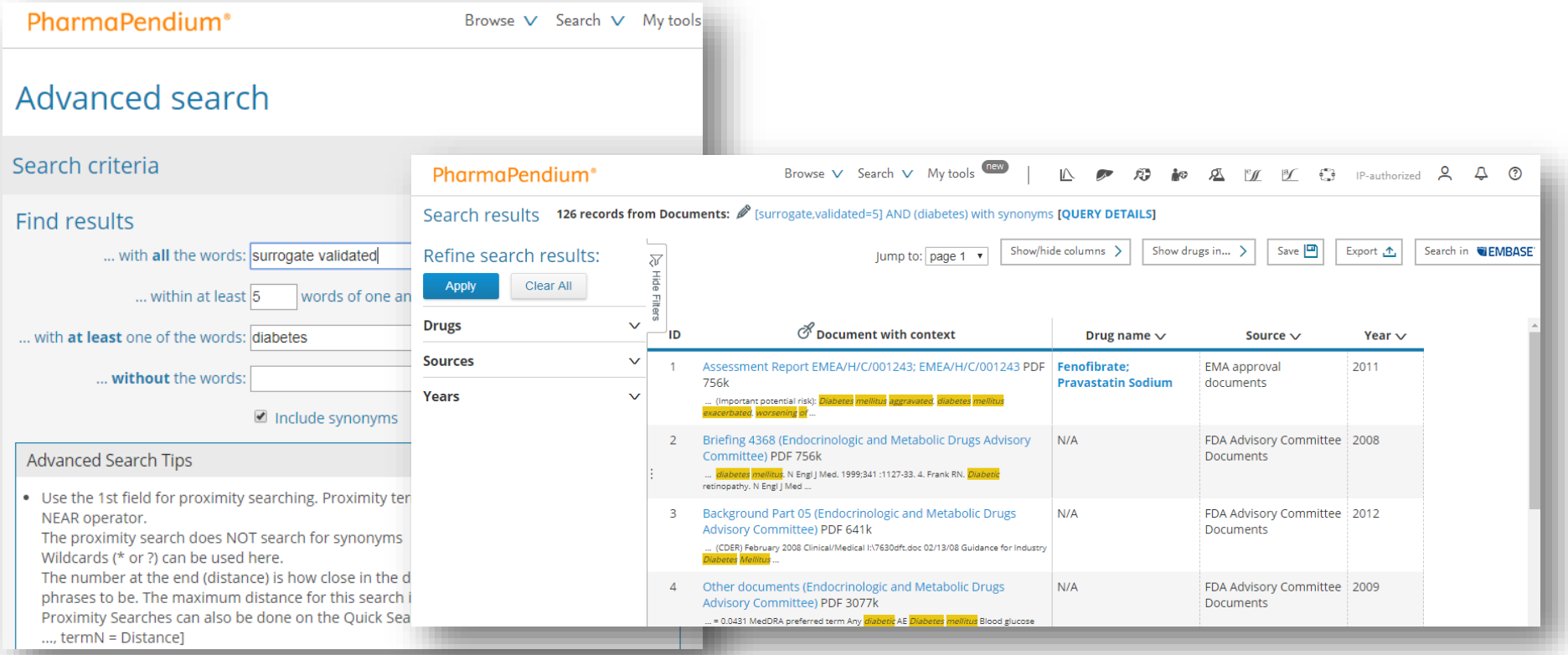
INTRAVENOUS CIPROFLOXACIN SHOULD BE ADMINISTERED BY SLOW INFUSION OVER A PERIOD OF 60 MINUTES. Local IV site reactions have been reported with the intravenous administration of ciprofloxacin. These reactions are more frequent if infusion time is 30 minutes or less or if small veins of the hand are used. (See **ADVERSE REACTIONS**.)

Central Nervous System

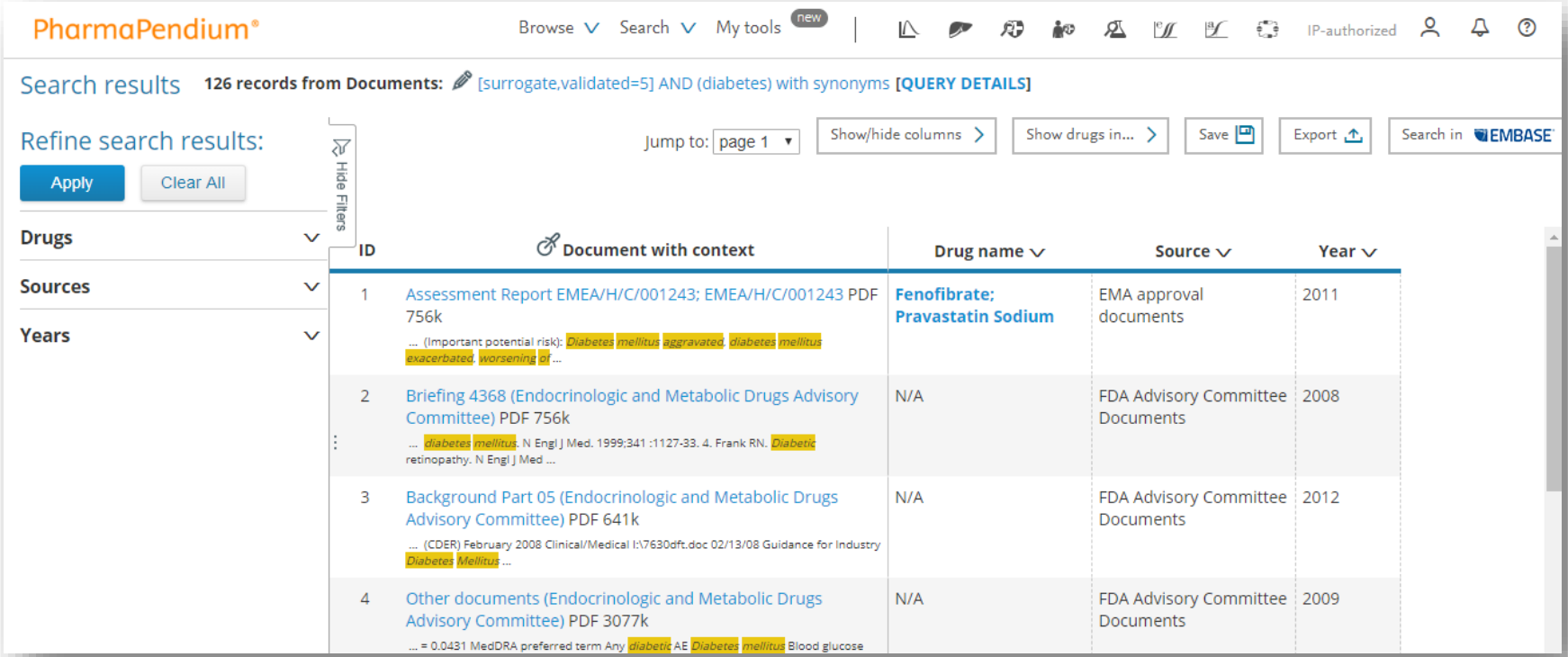
Example: what information is available on surrogate endpoints for diabetes

- 2 steps:
  - 1) Text search validated surrogate (within 5 words) and diabetes and unvalidated surrogate (within 5 words) and diabetes – do this to demonstrate information in FDA Advisory committee meeting reports
  - 2) Extracted information search: Look for information on specific surrogate endpoint (e.g., Hba1c) – search across endpoints

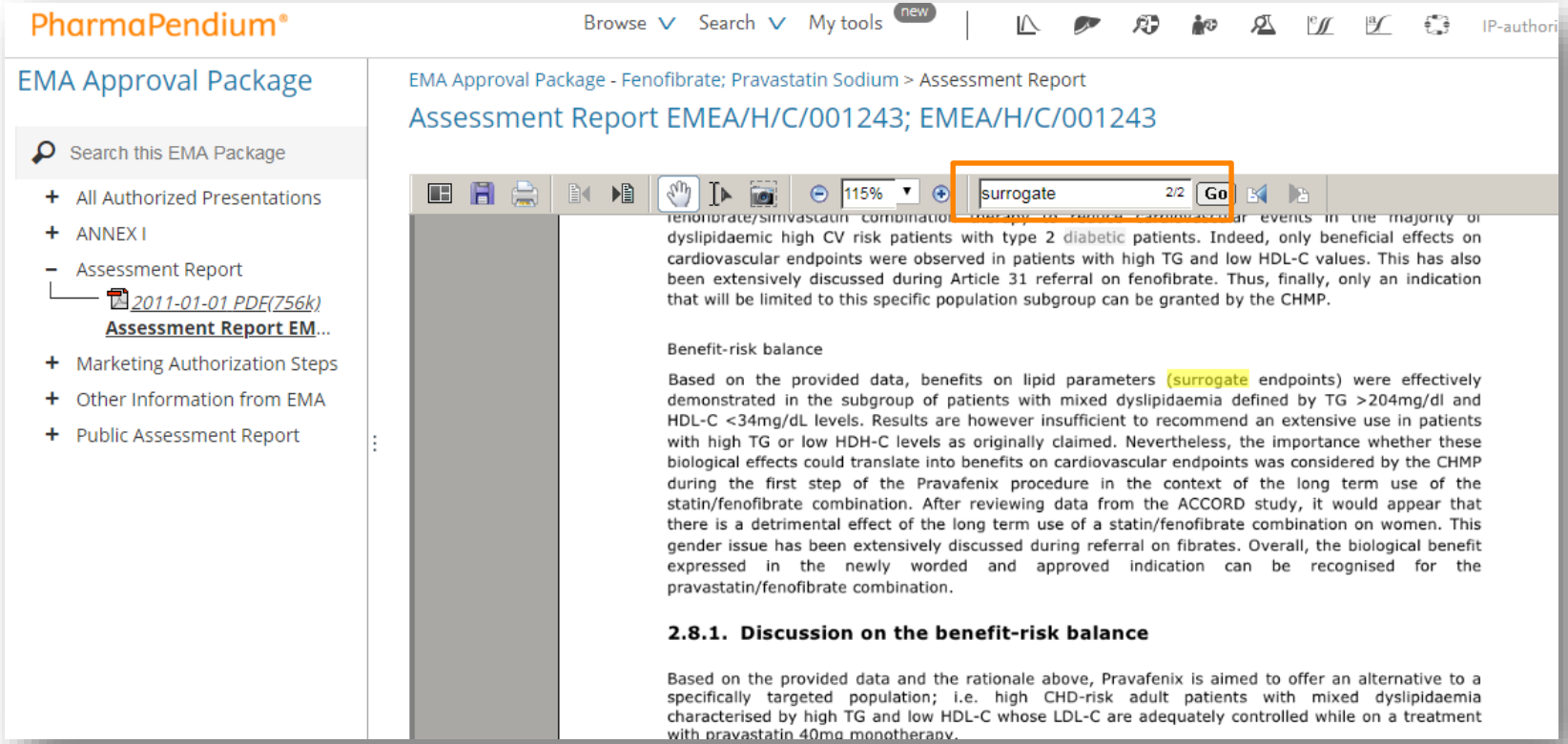
Search for validated surrogate endpoints for diabetes



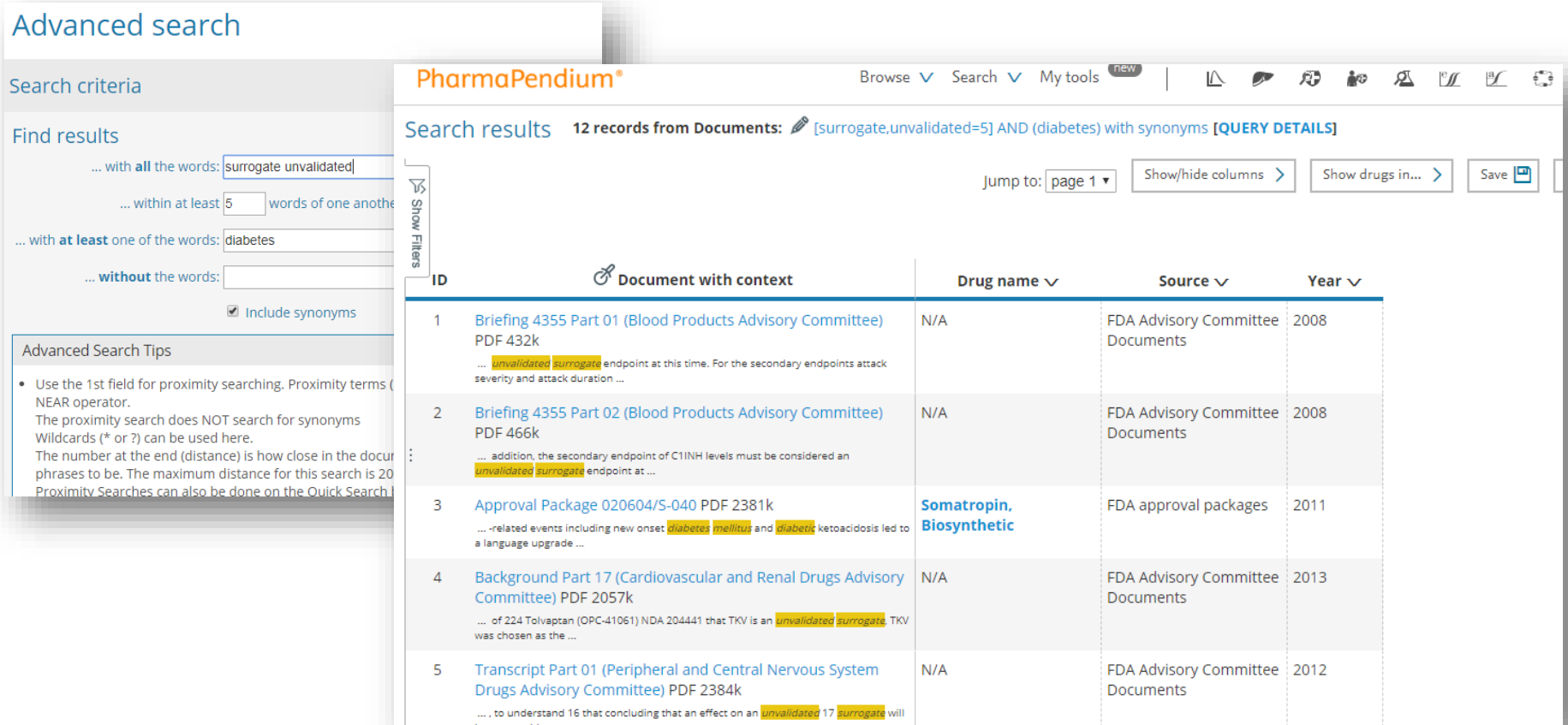
Explore AC documents



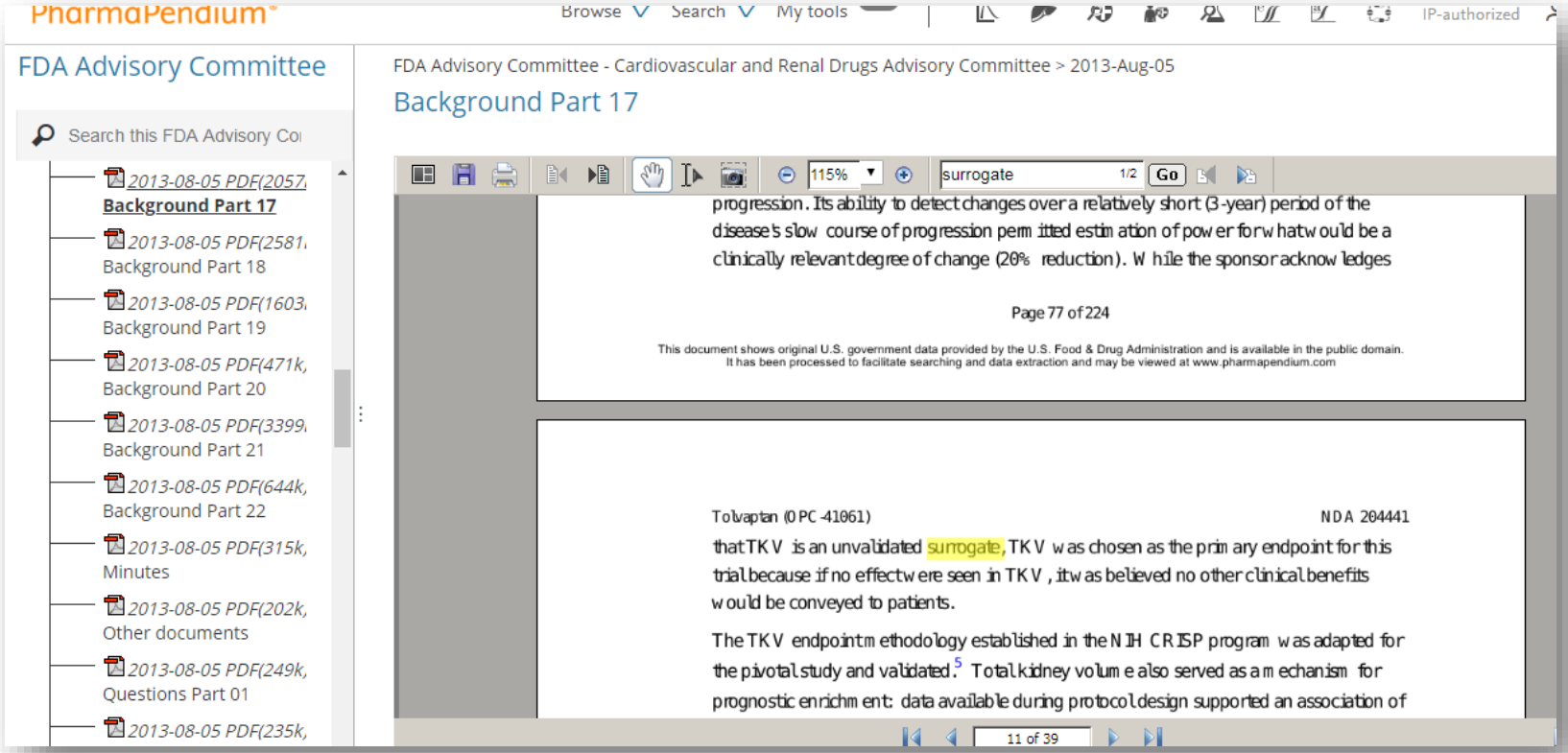
Need to text search ‘surrogate’



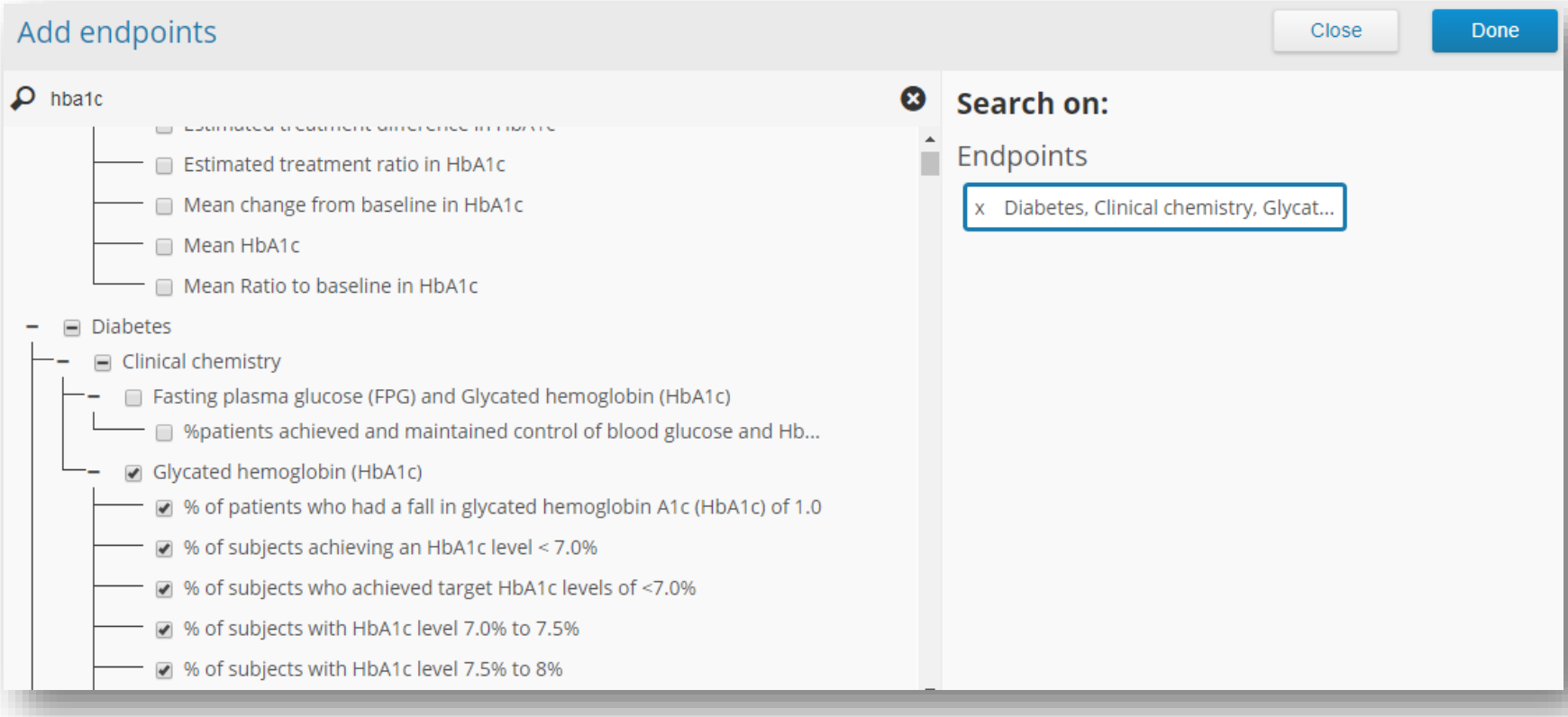
Change to unvalidated surrogate search



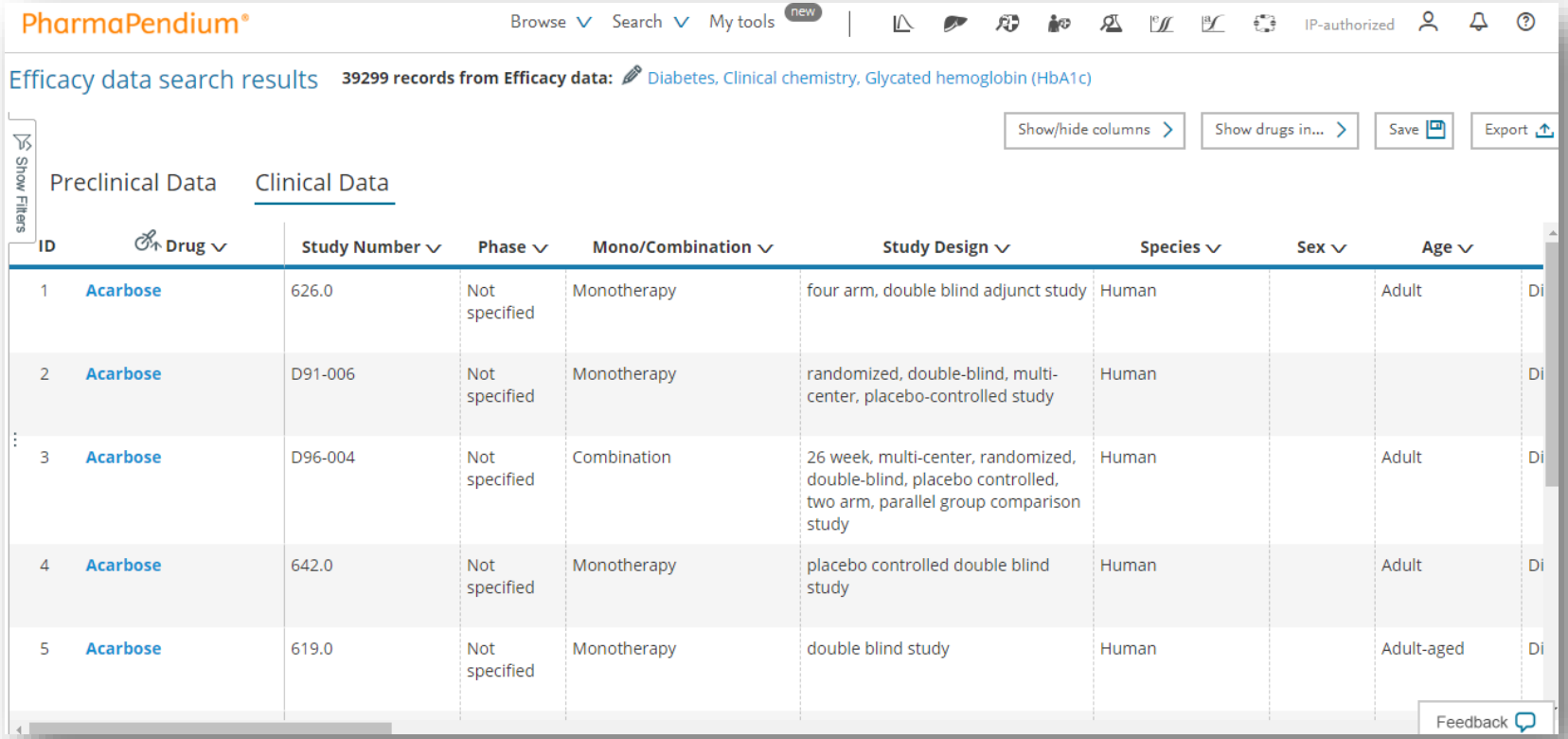
Again, need to search for ‘surrogate’ in the document



What values have been seen for a known endpoint?

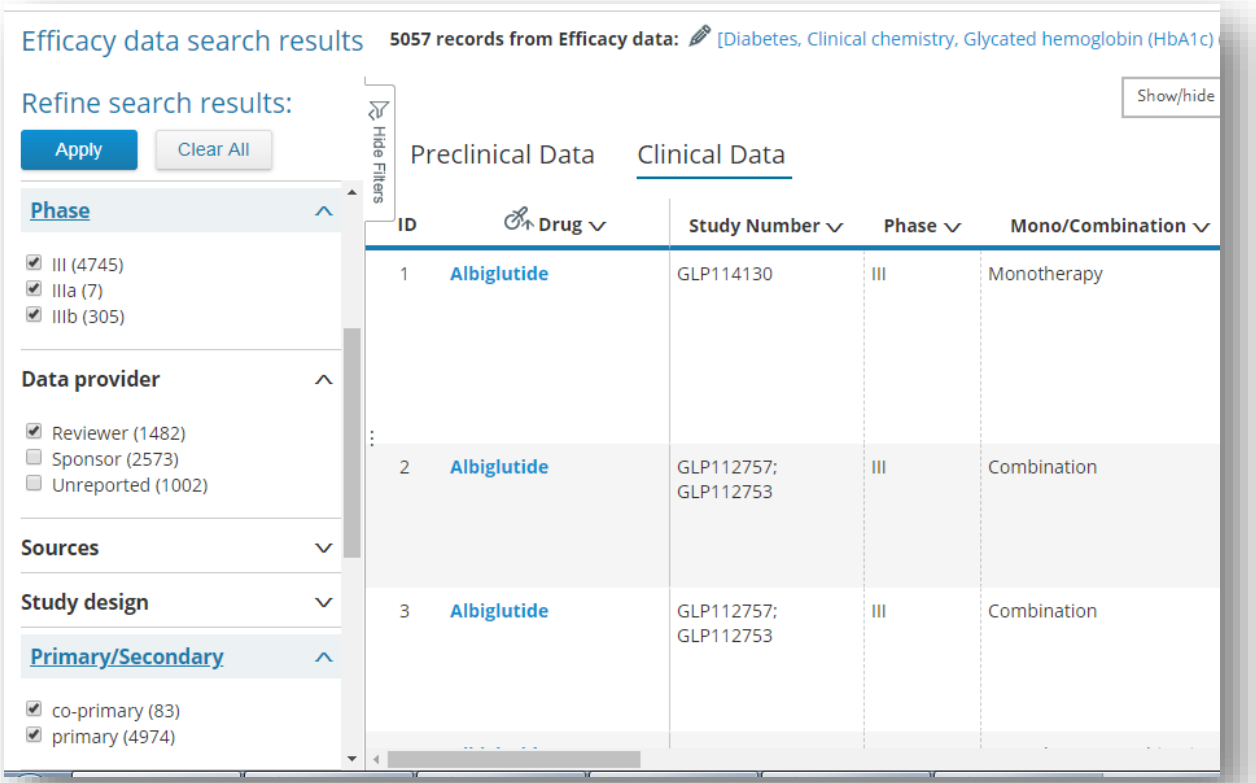


One step – see all clinical data for an endpoint



ID	Drug	Study Number	Phase	Mono/Combination	Study Design	Species	Sex	Age	
1	Acarbose	626.0	Not specified	Monotherapy	four arm, double blind adjunct study	Human		Adult	Di
2	Acarbose	D91-006	Not specified	Monotherapy	randomized, double-blind, multi-center, placebo-controlled study	Human			Di
3	Acarbose	D96-004	Not specified	Combination	26 week, multi-center, randomized, double-blind, placebo controlled, two arm, parallel group comparison study	Human		Adult	Di
4	Acarbose	642.0	Not specified	Monotherapy	placebo controlled double blind study	Human		Adult	Di
5	Acarbose	619.0	Not specified	Monotherapy	double blind study	Human		Adult-aged	Di

Apply filters to pinpoint to a relevant results set



Search for ‘endpoint’