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R&D Solutions

Reducing efficacy-related failures with PharmaPendium

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Agenda – focus on efficacy

- Clinical trial stages
  - Reasons for efficacy-related failure
- Intro to PharmaPendium:
  - Information on content, taxonomies and search capabilities of the Efficacy Module
  - Finding efficacy information
- Overcoming efficacy challenges using PharmaPendium
  - Showing significant improvement over existing treatment/placebo
  - Finding the correct choice of primary and/or secondary endpoints

Why is Efficacy data important in drug development?

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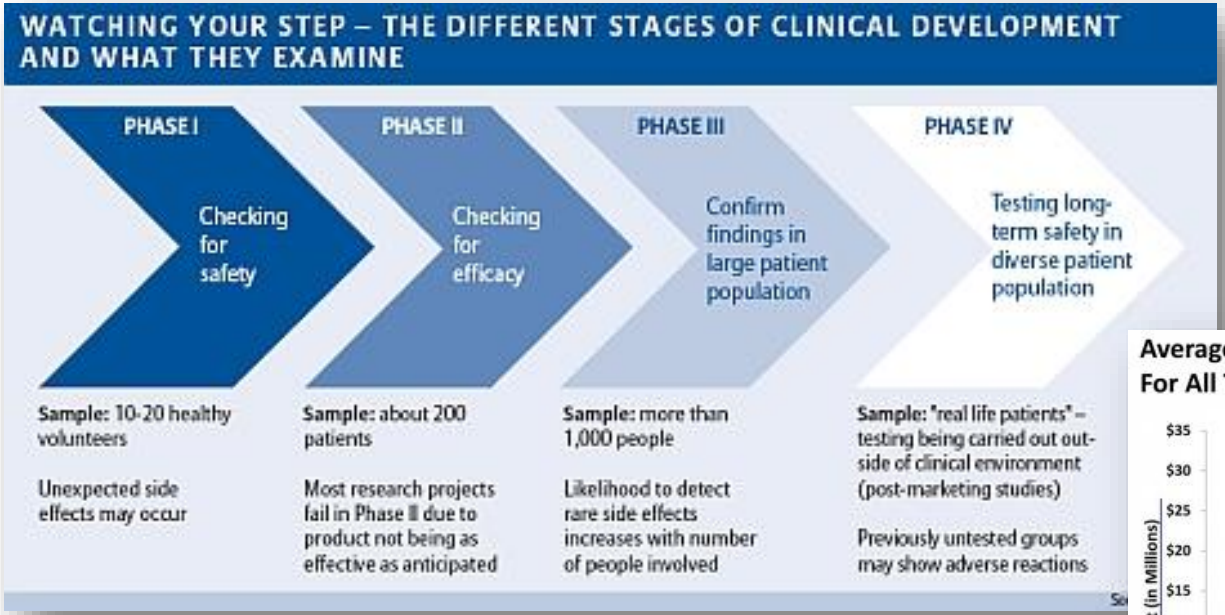
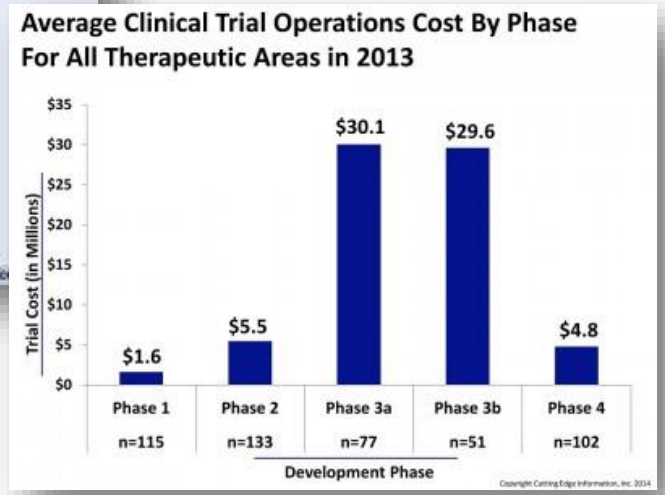
Stages, costs and challenges of clinical development





Mitigating the risk of efficacy-related failure "*Did not meet primary endpoint*"

- Of the top 13 Phase III failures highlighted by Genetic Engineering and Biotechnology News (GEN), 9 failed because they didn't meet the primary endpoint, 6 failed due to safety issues
- Using PharmaPendium could improve success rates of clinical trial designs by optimising selection of sample size, primary/secondary endpoint and study design

- Identify clinical and preclinical data that measures a specific endpoint
  - Search across drugs, drug classes, indications
  - Retrieve preclinical and clinical data
  - See details on study designs (type of study, dose regimen, etc.)
  - Compare with placebo data

http://www.genengnews.com/the-lists/unlucky-13-top-clinical-trial-failures-of-2016/77900787

What is a primary endpoint?

- All drugs have safety risks. Therefore, the only reason that a patient would want to take a drug would be if the drug:
  - improved survival
  - resulted in a benefit that was detectable by the patient (improvement in symptoms, improvement in functional capacity), or
  - decreased the chances of developing a condition or disease complication that is itself apparent to the patient and is undesirable (e.g. stroke)
- Therefore, a primary endpoint should be a direct measure of one of these. A primary endpoint should generally not be a measure of something that is not important to the patient (exception: validated surrogate endpoint).

FDA

https://www.fda.gov/downloads/Training/ClinicalInvestigatorTrainingCourse/UCM337268.pdf

Types of endpoints

- **Direct/true/clinically meaningful endpoints**:
  - Directly measure how a patient feels, functions, or survives
  - Can be **objective** (e.g., measurement of event like disease-free survival) or **subjective** (e.g., measurement of quality of life)
- **Surrogate endpoints**:
  - Laboratory measure or a physical sign that is intended to be used as a substitute for a clinically meaningful endpoint
  - Must be 'validated' –changes in the surrogate reflect changes in a clinically meaningful endpoint

Validated Surrogate Endpoint	Correlated Clinical Outcome
Systolic blood pressure (SBP)	Occurrence of stroke
Low density lipoprotein cholesterol (LDL) level	Occurrence of heart attack
Forced expiratory volume in 1 second (FEV1) *The amount of air that a person can blow out of his or her lungs in 1 second*	Improved breathing after taking medication for chronic lung diseases such as asthma
Human immunodeficiency virus (HIV) viral load *The amount of the human immunodeficiency virus that is present in the blood*	Development of an acquired immunodeficiency syndrome (AIDS) diagnosis

https://www.fda.gov/AboutFDA/Innovation/ucm512503.htm

Biomarkers

- Measured as indicators of health, disease, or a response to an exposure or intervention, including therapeutic interventions
  - Used to identify the best treatment for a patient, to monitor the safety of a therapy, or to find out if a treatment is having the desired effect
  - Can be used for patient stratification (to identify patients most likely to respond)
  - Can not be used to demonstrate clinically meaningful benefit

Examples of biomarker types or clinical trial end points and their relationship to drug efficacy.

Biomarker or clinical trial end point	Item measured	Example from sitagliptin	Degree of confidence on efficacy
TE	Fraction of drug target bound by drug	Plasma DPP-4 activity	+[a]
Proximal PD biomarker	Substrate or other molecule immediately downstream of target	Plasma GLP-1 (substrate)	+[a]
Distal PD biomarker	Further downstream biological effect	Plasma glucose, insulin, glucagon	++
Surrogate end point	Biological effect intimately associated with clinical outcome	Hemoglobin A_{1c}	++++[b]
Clinical outcome	Mortality, morbidity, symptoms, quality of life	Myocardial infarction (MI), stroke, death from MI	++++

Biomarkers in Pharmaceutical Research
X Zhao, et al. Laterza. Clinical Chemistry **61**(11): 1343. 2015.

PharmaPendium endpoint taxonomy

Endpoint Types	Endpoint Subtypes	Endpoint Tested (Descriptions are heterogeneous)
Physical Measurements	Change in Body Weight	• Cumulative Distribution of Weight Change from Baseline at Week 52: Percentile 70% • LS Mean Model-adjusted Change from Baseline in Body Weight
Risk	Patients at risk of discontinuation	• Number of patients at risk of discontinuation
Markers	Anti-drug Antibodies	• Subjects who had low antibody titers • Subjects who tested positive for anti-albiglutide antibodies • Subjects with positive pre-existing antibodies tested weakly positive for neutralizing antibodies
Clinical Response	Response	• Number of patients tested positive during the first 2 years of treatment when receiving Process 2 • Treatment Difference

Finding efficacy information in PharmaPendium

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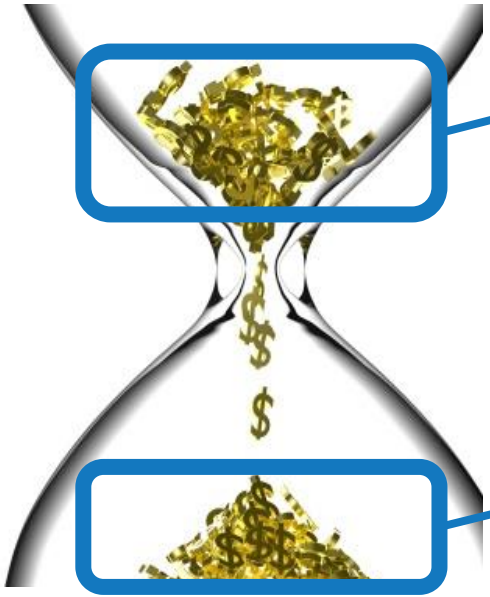
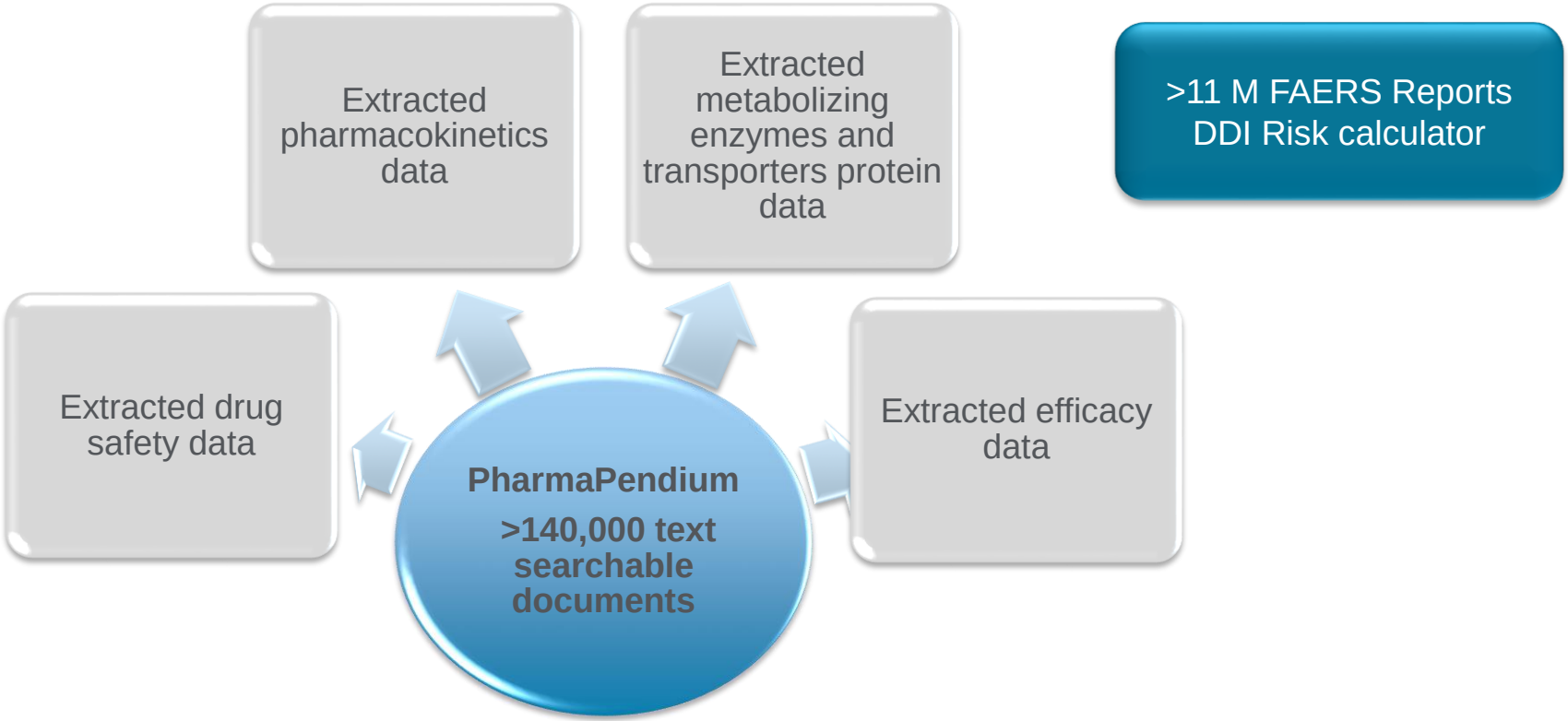
Critical decision-support



- ✓ 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

Integrated FDA/EMA Drug Approval Docs & extracted data



Content and value is continually growing*

Source Documents

2.4M+
pages of FDA Approval Documents

227K+
pages of EMA Approval Documents

11.1M+
FDA AERS reports

701K+
pages from FDA Advisory Committee Meetings

Extracted Data

4519
Drugs indexed & fully searchable

1.68M+
PK data lines

328K+
Metabolizing enzyme and transporter data lines

1.77M+
safety data lines

2.84M+
efficacy data lines

119K
activity data lines

* as of May 2018

Simplified data structure to quickly find relevant efficacy data

Efficacy Module data structure

- Extracted data from FDA documents (from 1938 till present) and EMA documents (from 1995 till present)
- Currently 2.84+ million lines of efficacy data from FDA/EMA approved drugs

1.Extract

2.Organize

- Taxonomies categorize drugs, targets, chemical substructures, **indications** and **endpoints** to reduce search times
- Normalized data across preclinical and clinical efficacy data

- Relevant filters and export functionality help retrieve critical data sets which can be used for further analysis
- Results table can be configured to users search needs

3. Gain critical insights

Search using a wide range of Efficacy parameters

Extracted information lets you limit search to specific parameters including:

Indication

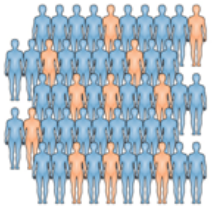
Includes:
- In-house taxonomy
- Search by indication
- Filter results by indication type

Endpoints

Includes:
- In-house taxonomy
- Filter by primary, secondary or other

Study design:

Includes:
- Sample size
- Phase
- Study design
- Baseline
- Study population
- Comparative group

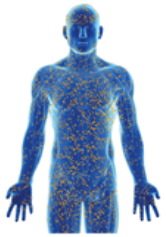


Treatment:

Includes:
- Dose
- Placebo
- Route of administration
- Dose frequency

Demographics

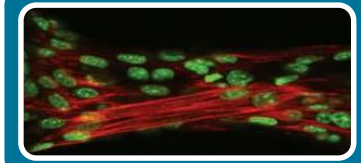
Includes:
- Study population
- Gender
- Age



Species

Includes:
- Human
- Vertebrates
  - Birds
  - Fish
  - Mammals
  - Etc.

Efficacy module supports critical workflows



In vivo modeling

- Can I find human correlate data to design a predictive model?
- Can this model be used with *in vitro* data (i.e.. before starting preclinical studies?)
- Can I use this predictive model for drug candidate selection?

Preclinical experimental design

- What precedent preclinical models were used to demonstrate efficacy? Were the outcomes translatable to the clinic?
- What endpoints have been tested for a particular therapeutic indication?
- What kind of efficacy data can I find across drugs/targets/chemical substructures?

Clinical trial design

- What primary/secondary endpoints have been tested?
- What do I need to do to achieve at least the same level of efficacy?
- What regulatory concerns do I need to know to mitigate the risk of repeating a clinical arm/trial?
- What kind of off-target effects can I anticipate?

Competitive drug positioning

- Can I compete on dose regimen?
- Can I achieve better efficacy in a subpopulation or indication?
- How can I achieve a better risk/benefit ratio compared to my competitors?

Demo: what information is available on surrogate endpoints for diabetes?

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Reminder - types of endpoints

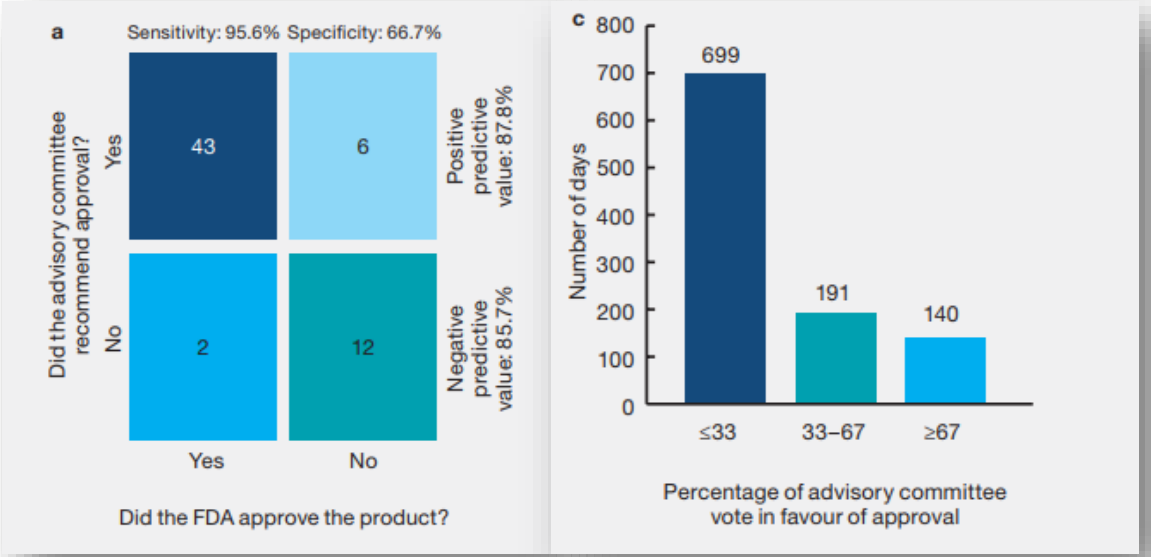
- Direct/true/clinically meaningful endpoints:
  - Directly measure how a patient feels, functions, or survives
  - Can be **objective** (e.g., measurement of event like disease-free survival) or **subjective** (e.g., measurement of quality of life)
- Surrogate endpoints:
  - Laboratory measure or a physical sign that is intended to be used as a substitute for a clinically meaningful endpoint
  - Must be 'validated' –changes in the surrogate reflect changes in a clinically meaningful endpoint… **but what if it's not?**

Validated Surrogate Endpoint	**Correlated Clinical Outcome**
Systolic blood pressure (SBP)	Occurrence of stroke
Low density lipoprotein cholesterol (LDL) level	Occurrence of heart attack
Forced expiratory volume in 1 second (FEV1) *The amount of air that a person can blow out of his or her lungs in 1 second*	Improved breathing after taking medication for chronic lung diseases such as asthma
Human immunodeficiency virus (HIV) viral load *The amount of the human immunodeficiency virus that is present in the blood*	Development of an acquired immunodeficiency syndrome (AIDS) diagnosis

https://www.fda.gov/AboutFDA/Innovation/ucm512503.htm

FDA Advisory Committee Meeting reports

- FDA reviewers complete an initial review of a product application and identify questions where external input is needed
- FDA reviewers take into account the input received when making product approval decisions

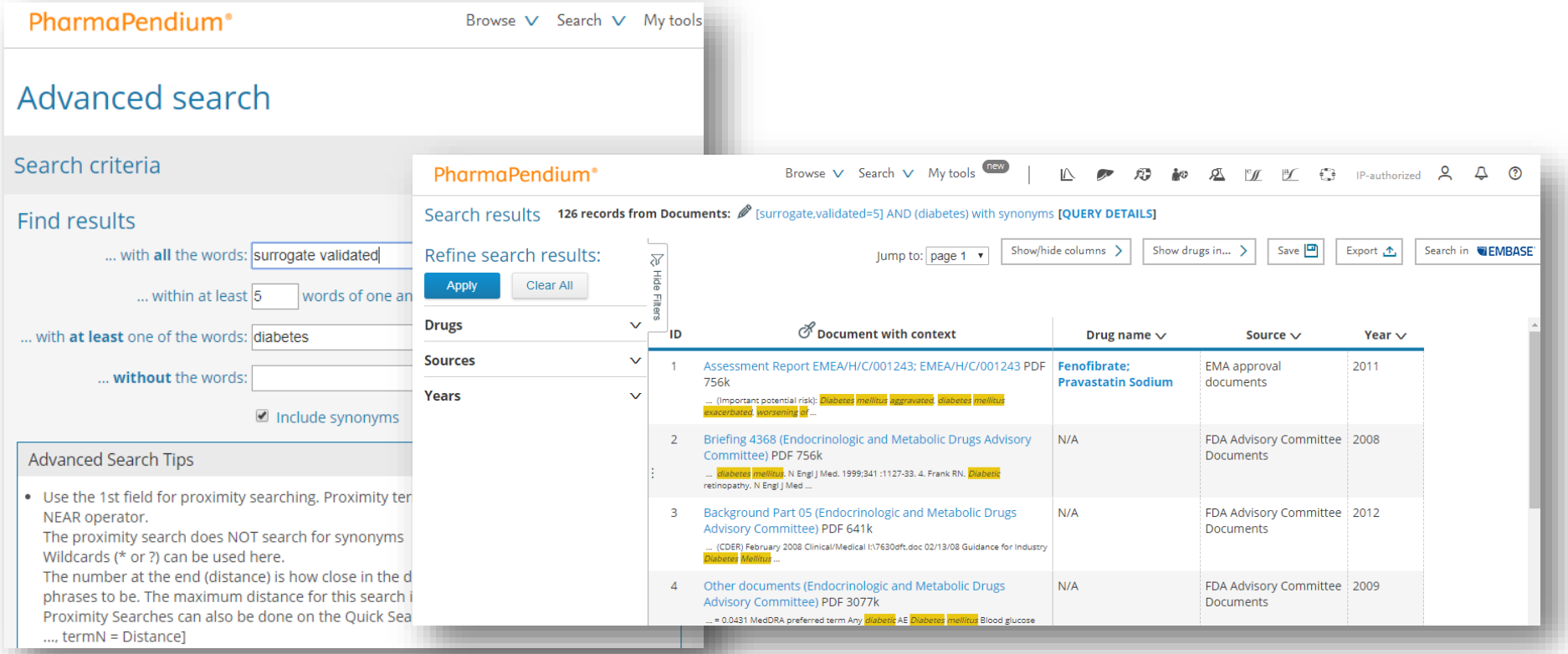


https://www.mckinsey.com/~/media/McKinsey/dotcom/client_service/%20Public%20Sector/Regulatory%20excellence/FDA_advisory_committee_outcomes.ashx

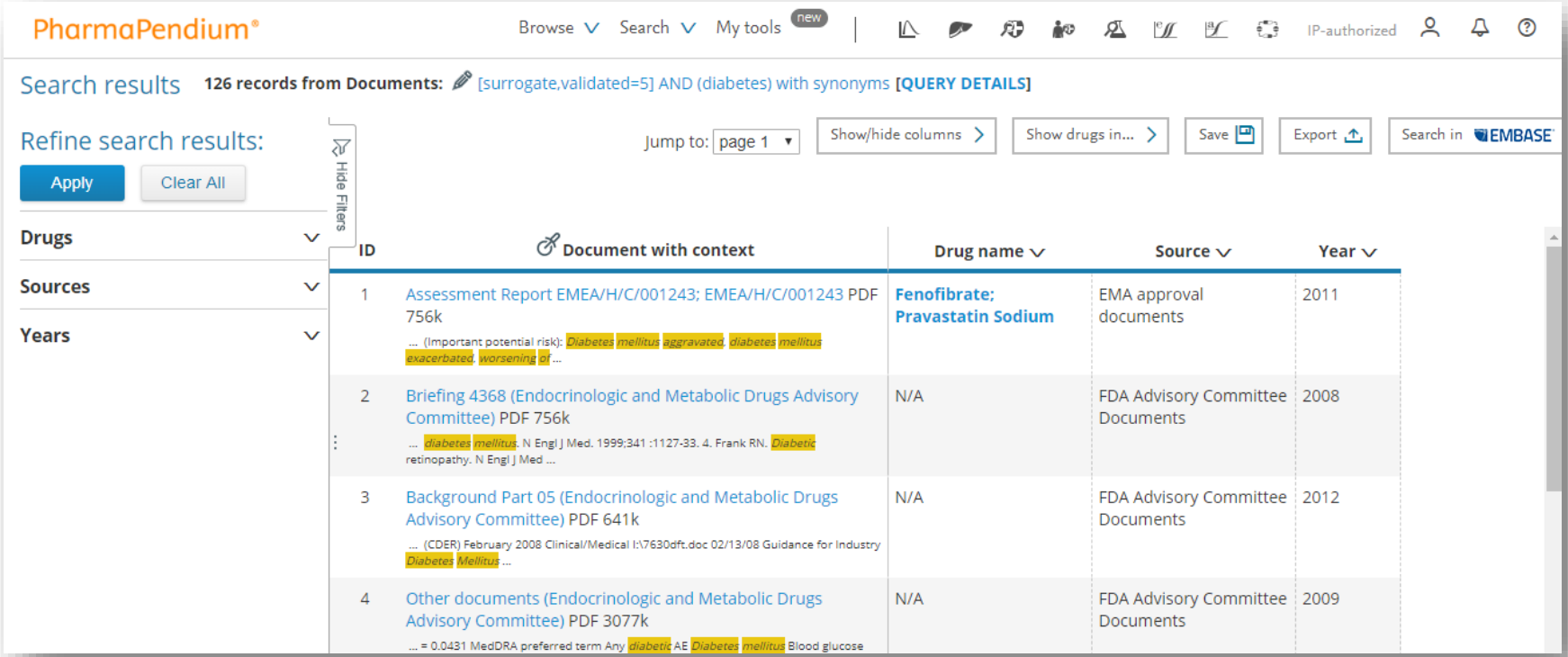
Workflow: Look for general information and also for a specific surrogate

- 2 steps:
  - 1) Test 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) Look for information on specific surrogate endpoint (e.g., Hba1c) – search across endpoints

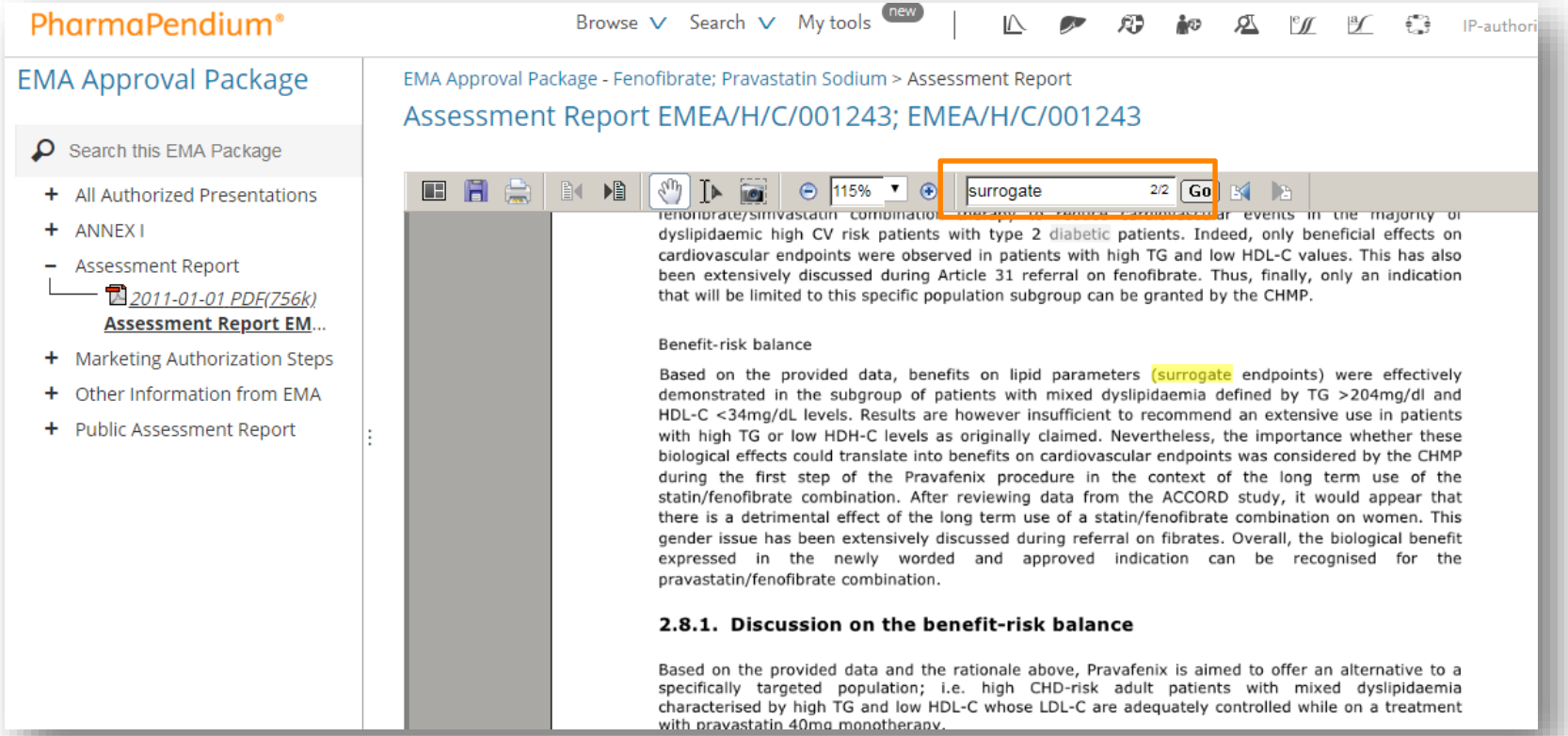
Search for validated surrogate endpoints for diabetes



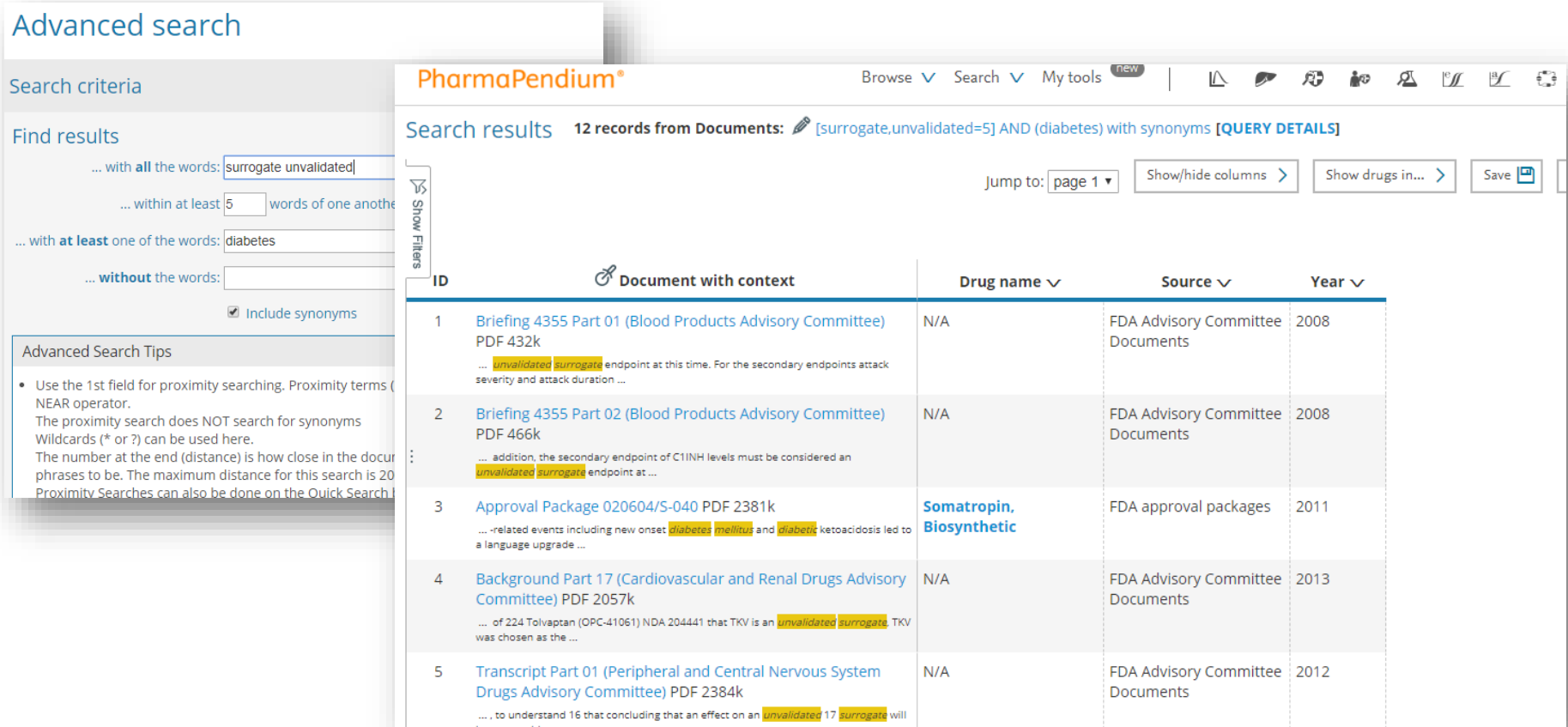
Explore AC documents



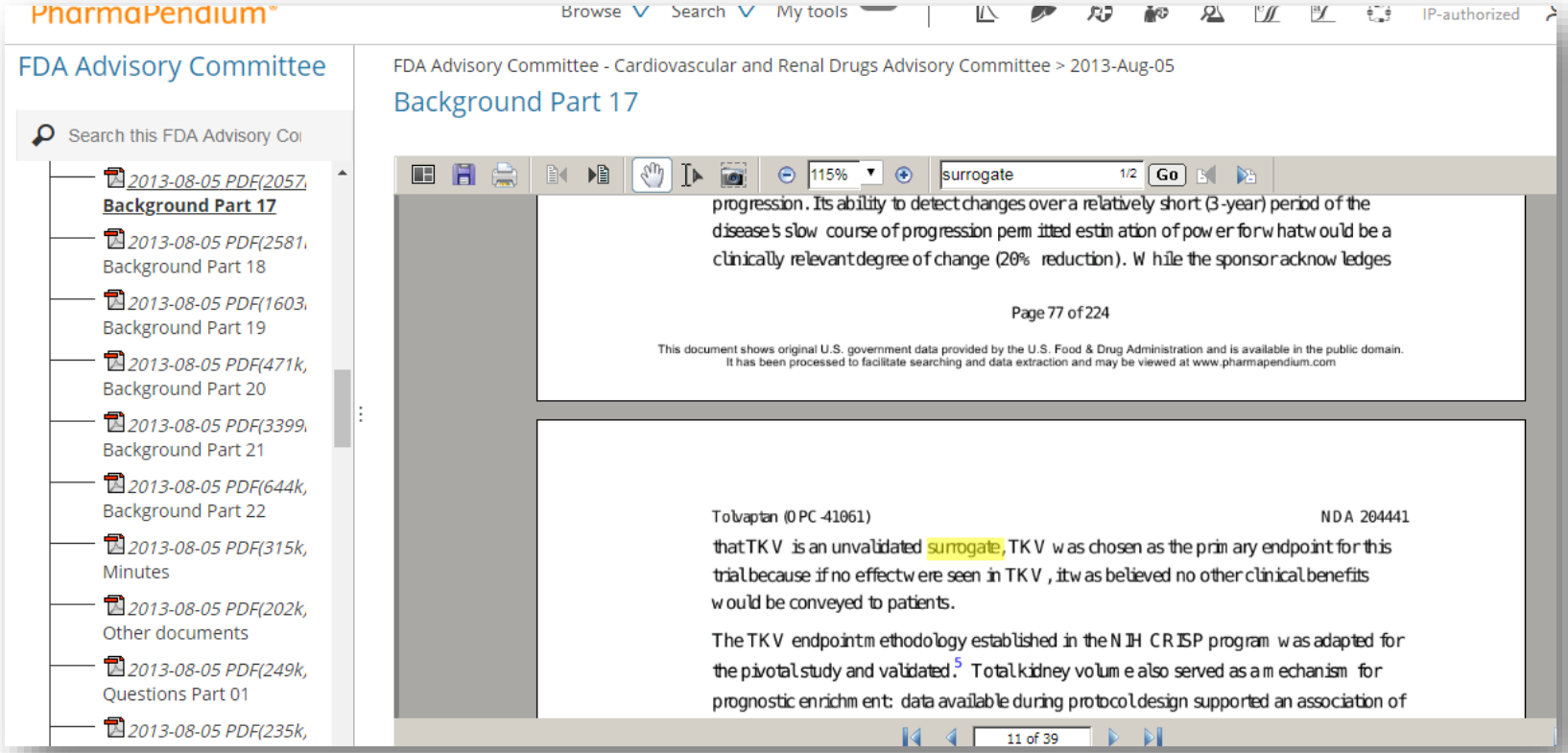
Need to text search ‘surrogate’



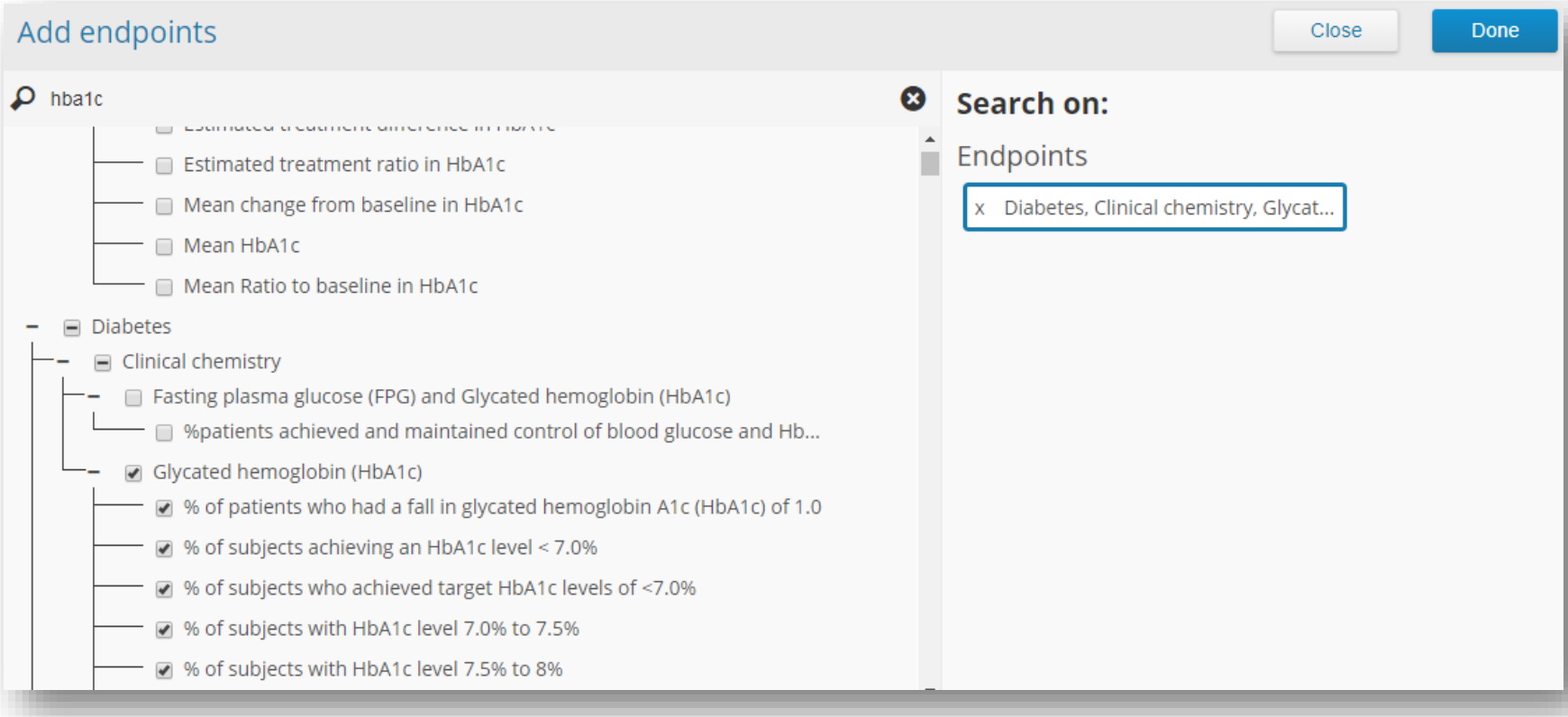
Change to unvalidated surrogate search



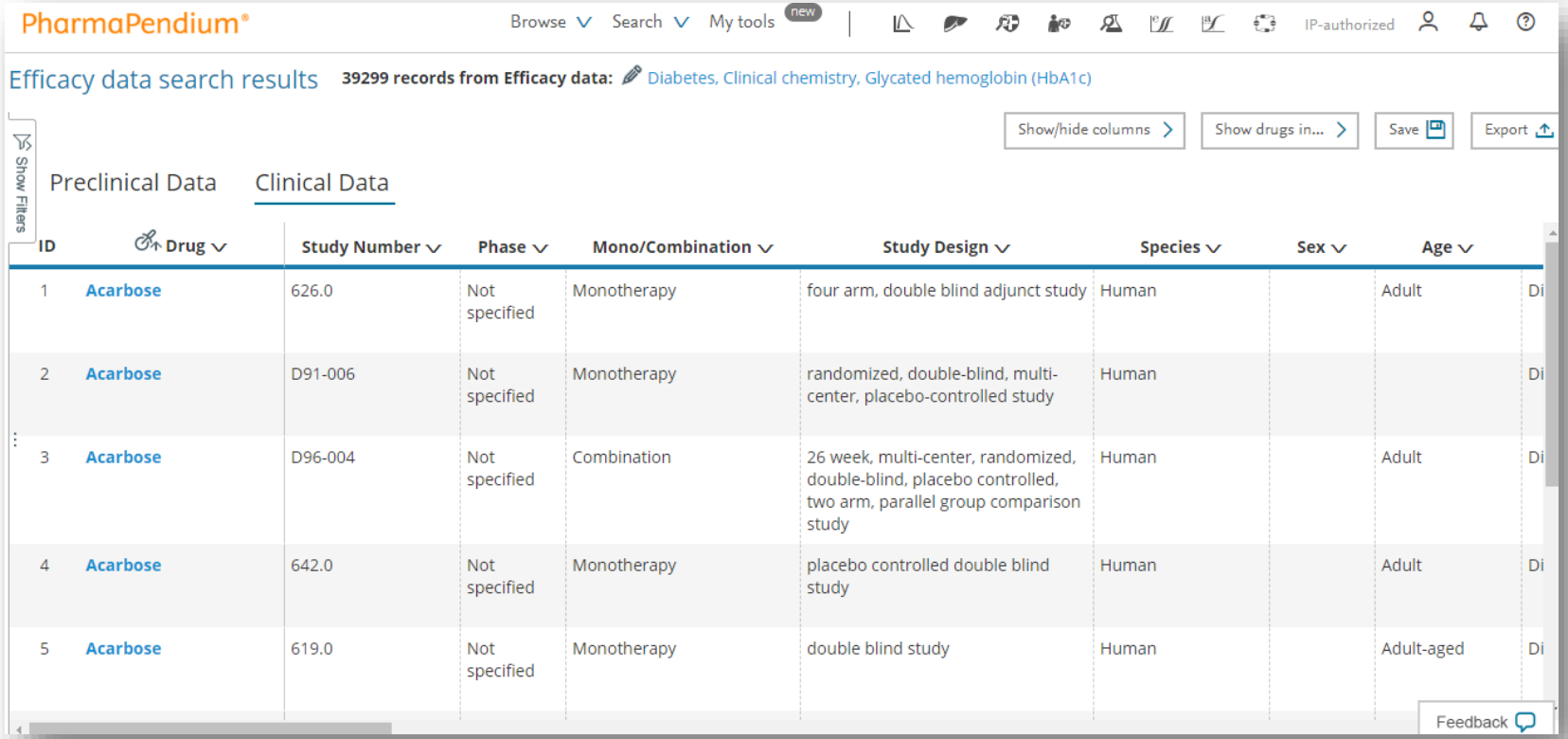
Again, need to search for 'surrogate' in the document



What values have been seen for a known endpoint?

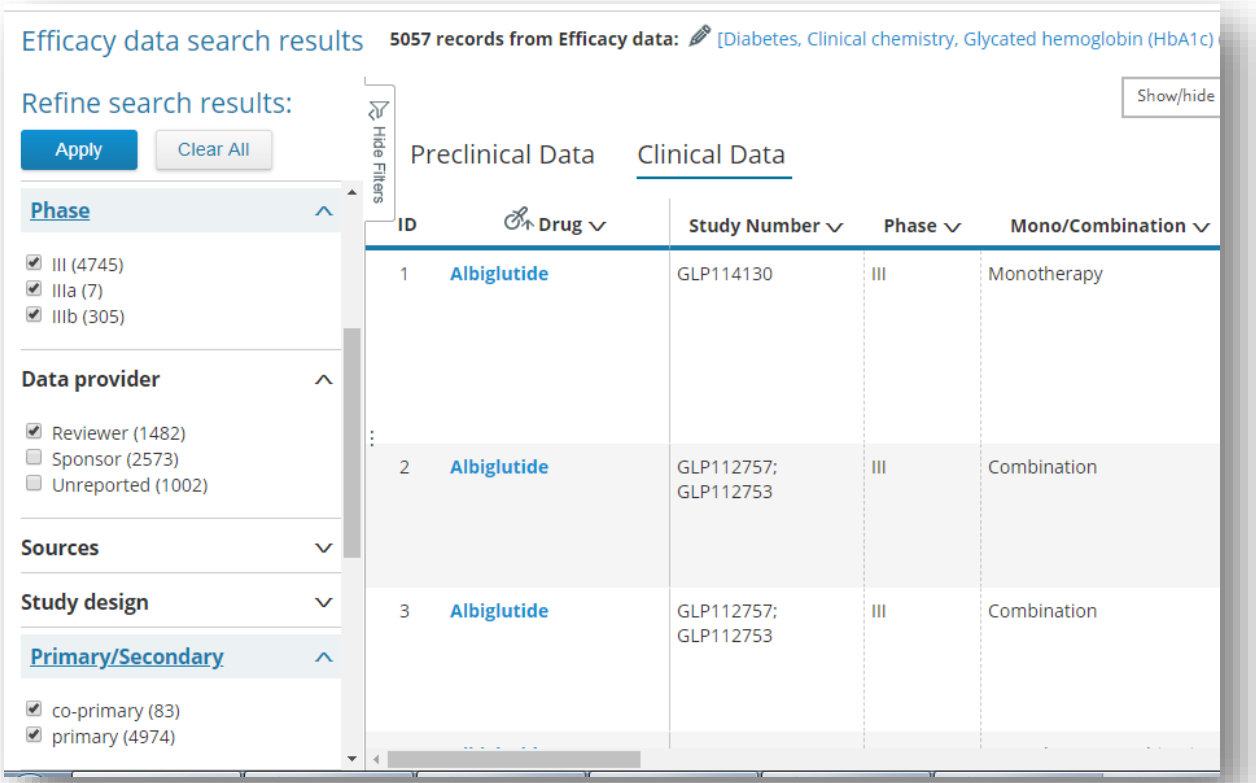


One step – see all clinical data for an endpoint

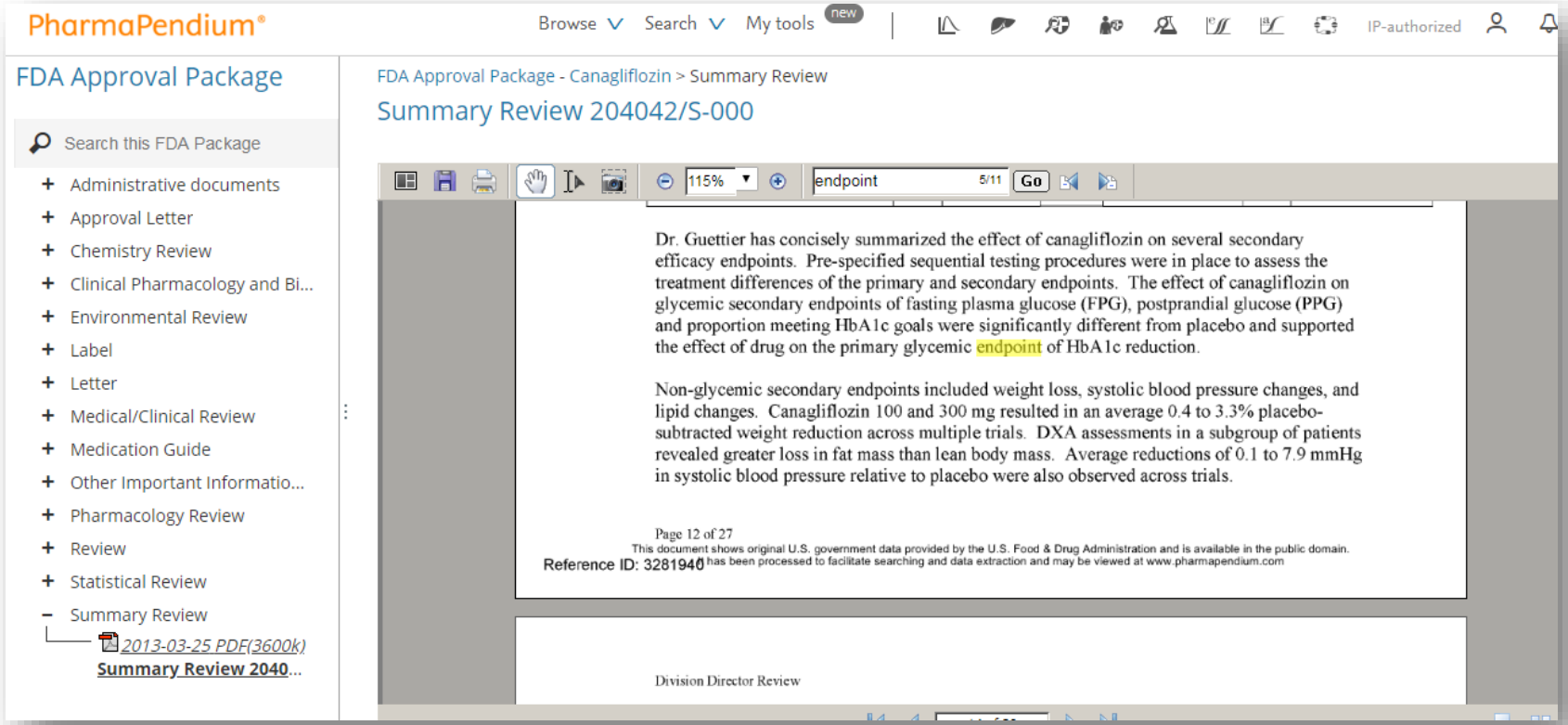


ID	Drug	Study Number	Phase	Mono/Combination	Study Design	Species	Sex	Age	
1	Acarbose	626.0	Not specified	Monotherapy	four arm, double blind adjunct study	Human		Adult	Di
2	Acarbose	D91-006	Not specified	Monotherapy	randomized, double-blind, multi-center, placebo-controlled study	Human			Di
3	Acarbose	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

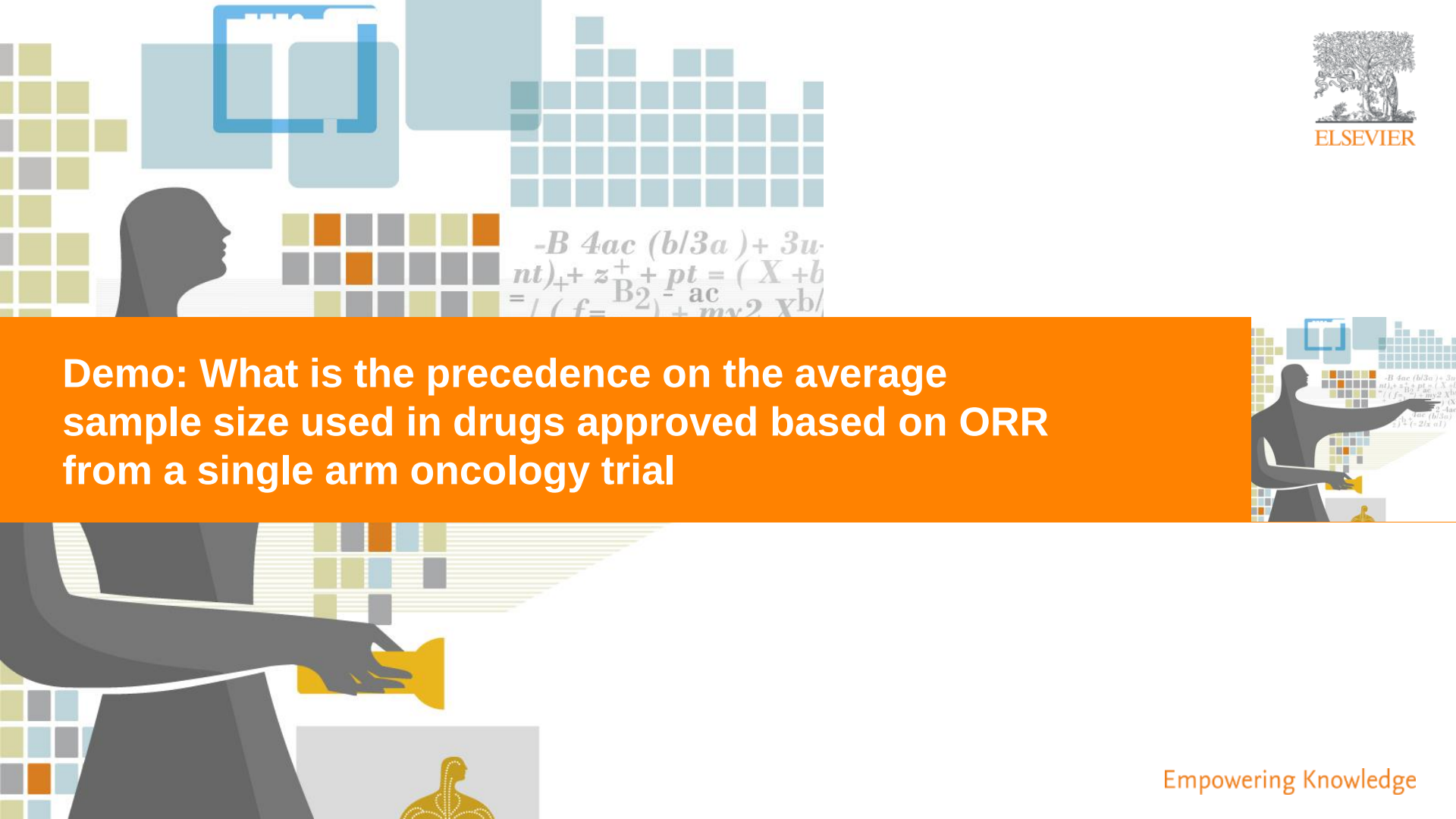
Apply a few filters and demo the rest



Search for ‘endpoint’



Demo: What is the precedence on the average sample size used in drugs approved based on ORR from a single arm oncology trial



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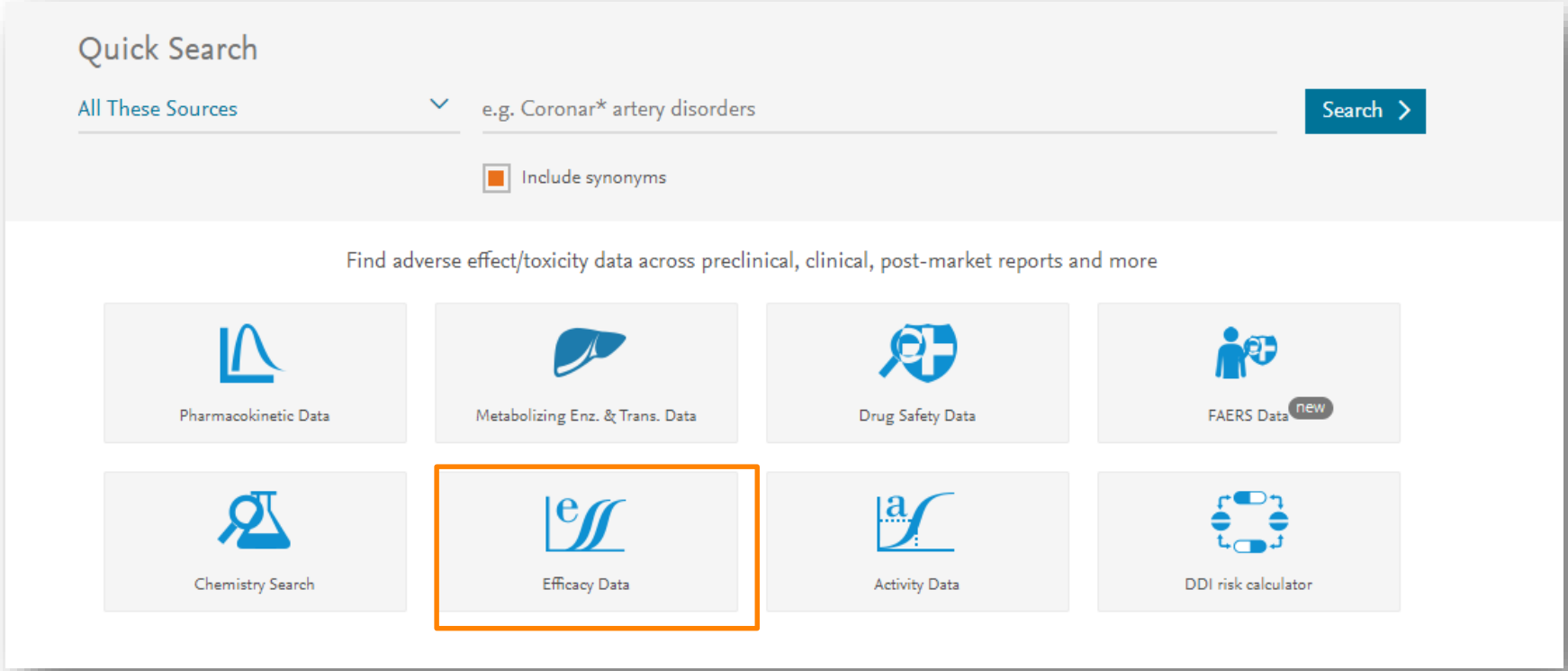
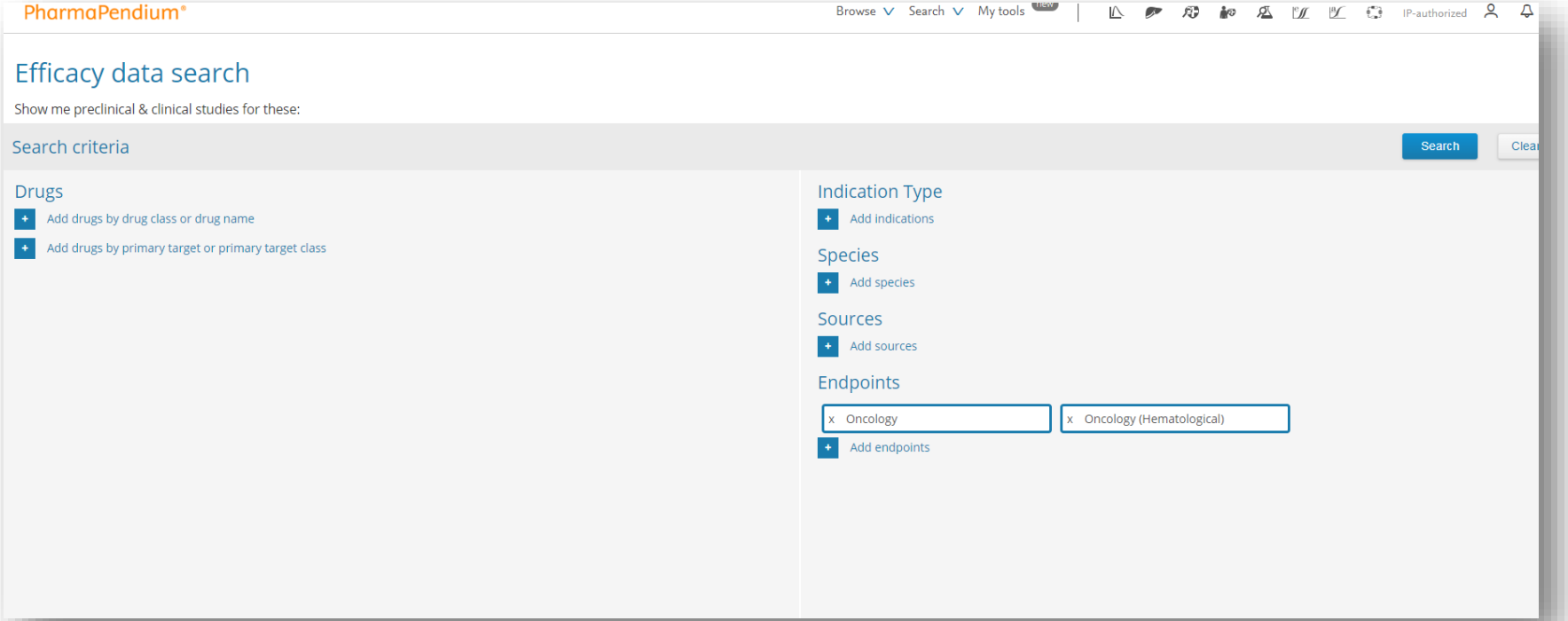
Workflow

1. Search efficacy module, open up the Endpoint limit, type in ORR into endpoint limit and select clinical, oncology-related endpoints). Click done and search
2. Filter results under primary/secondary – choose co-primary and primary
3. Export the results and now work in the Excel file
    1. In excel, replace all fields that mention single arm or single-arm with the same term but highlighted. Once the relevant cells are highlighted, it's easy to filter the coloured cells to the top of the page. Then filter by the appropriate p-value (I selected anything <0.05) and there are a small number of significant results
        - Eg. Carfilzomib - do a text search in the medical/clinical review of this approval document for ORR and immediately see this:

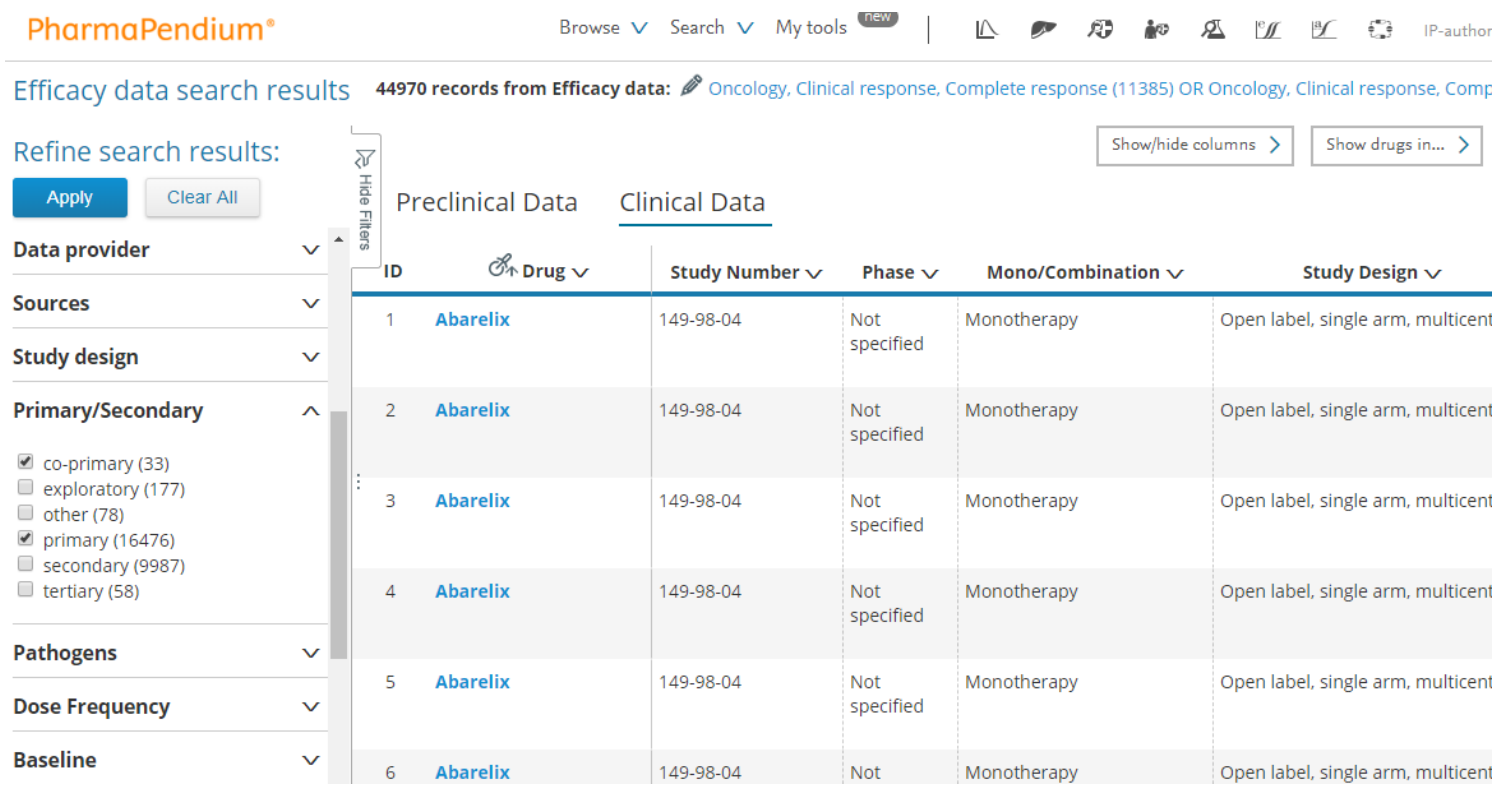
Click on Efficacy Data



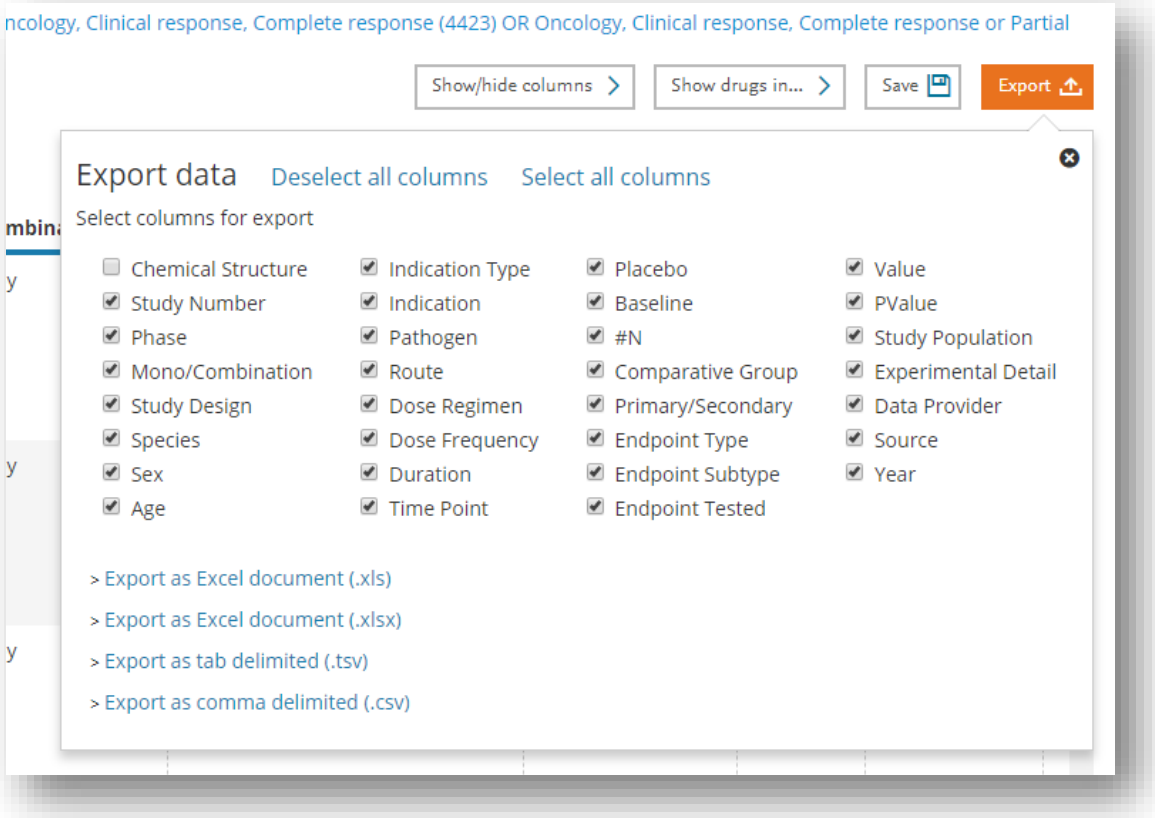
Select relevant endpoints (ORR – objective/overall response rate)



Filter for primary endpoints



Need to identify single-arm studies – Export results



Sort for relevant, significant results in export file

- Replace single arm and single-arm with highlighted cells
- Filter to get highlighted cells to the top and select significant p-values (e.g., <0.05)

1 Export date: 13-05-2018
2 Efficacy Data Search Results For: Endpoints: [Oncology, Clinical response, Complete response OR Oncology, Clinical response, Complete response or Partial response
3 Total results: 16509
4 Sort order: Drug (Ascending); Indication Type (Ascending); Endpoint Type (Ascending);
5

6	Drug	Study Number	Phase	Mono/Combinati	Study Design	Specie	Se	Age	
499	Atezolizumab	IMvigor 210 (GO29293)	II	Monotherapy	single-arm open-label Phase II study	Human	Both	Adult-aged	Urothelial car
500	Carfilzomib	PX-171-003 A1	II	Monotherapy	Phase 2, open-label, single-arm, multicenter clin	Human		Adult-aged	Myeloma mul
501	Carfilzomib	PX-171-003 A1	II	Monotherapy	Phase 2, open-label, single-arm, multicenter clin	Human		Adult-aged	Myeloma mul
502	Carfilzomib	PX-171-003 A1	II	Monotherapy	Phase 2, open-label, single-arm, multicenter clin	Human		Adult-aged	Myeloma mul
503	Carfilzomib	PX-171-003 A1	II	Monotherapy	Phase 2, open-label, single-arm, multicenter clin	Human		Adult-aged	Myeloma mul
504	Vismodegib	SHH4476g	II	Monotherapy	Phase 2, pivotal, international, single-arm, multi-	Human		Adult-aged	Carcinoma ba
505	Vismodegib	SHH4476g	II	Monotherapy	Phase 2, pivotal, international, single-arm, multi-	Human		Adult-aged	Carcinoma ba
506	Vismodegib	SHH4476g	II	Monotherapy	Phase 2, pivotal, international, single-arm, multi-	Human		Adult-aged	Carcinoma ba
507	Vismodegib	SHH4476g	II	Monotherapy	Phase 2, pivotal, international, single-arm, multi-	Human		Adult-aged	Carcinoma ba
508	Vismodegib	SHH4476g	II	Monotherapy	Phase 2, pivotal, international, single-arm, multi-	Human		Adult-aged	Carcinoma ba
509	Vismodegib	SHH4476g	II	Monotherapy	Phase 2, pivotal, international, single-arm, multi-	Human		Adult-aged	Carcinoma ba
510	Vismodegib	SHH4476g	II	Monotherapy	Phase 2, pivotal, international, single-arm, multi-	Human		Adult-aged	Carcinoma ba
511	Aminolevulinic Acid Hydrochloride	ALA-BCC-CT008	III	Combination	randomized, observer blind, multinational phase	Human	Both	Adult-aged	Carcinoma ba
512	Aminolevulinic Acid Hydrochloride	ALA-BCC-CT008	III	Combination	randomized, observer blind, multinational phase	Human	Both	Adult-aged	Carcinoma ba
513	Bevacizumab	AVF3708g	II	Combination	pivotal, randomized, open-label, multicenter, Pha	Human	Both	Adult-aged	Glioblastoma
514	Bevacizumab	AVF3708g	II	Monotherapy	pivotal, randomized, open-label, multicenter, Pha	Human	Both	Adult-aged	Glioblastoma
515	Bevacizumab	AVF3708g	II	Monotherapy	pivotal, randomized, open-label, multicenter, Pha	Human	Both	Adult-aged	Glioblastoma

PharmaPendium® Browse Search My tools new IP-authorized

FDA Approval Package

Search this FDA Package

- + Administrative documents
- + Approval Letter
- + Chemistry Review
- + Clinical Pharmacology and Bi...
- + Label
- + Letter
- + Medical/Clinical Review
- + Microbiology Review
- + Other Important Informatio...
- + Pharmacology Review
- + Review
- − Statistical Review
  - 2011-11-02 PDF(2148k) **Statistical Review 2027...**
- + Summary Review

FDA Approval Package - Carfilzomib > Statistical Review

Statistical Review 202714/S-000

115% Go

5.1 Statistical Issues and Collective Evidence

The exact sample size required was 243. The Sponsor mentioned it to be 250 and recruited 266 subjects. There were 5 responders among the 16 who last entered the study. Sample proportions for n = 250 and for n = 266 were 0.224 and 0.229, respectively. Standard errors under null hypothesis were 0.019 and 0.0184 when n = 250 and when n = 266, respectively.

5.2 Conclusions and Recommendations

The key efficacy findings based on all subjects from study PX-171-003- Part 2 (A1) are:

- The overall response rate (ORR) was 30% [95% CI: (18%, 28%)]. The ORR was significantly greater than 10% (p-value < 0.0001).
- IRC assessed median duration of response was 7.8 months [95% CI: (5.6, 9.2)].
- The clinical benefit rate (CBR) was 36% [95% CI: (30%, 41%)].
- One-hundred and thirty (50%) patients died during the study. The median overall survival was 15.4 months [95% CI: (12.4, 19.0)].
- IRC assessed median PFS was 3.7 months [95% CI: (2.8, 4.6)]

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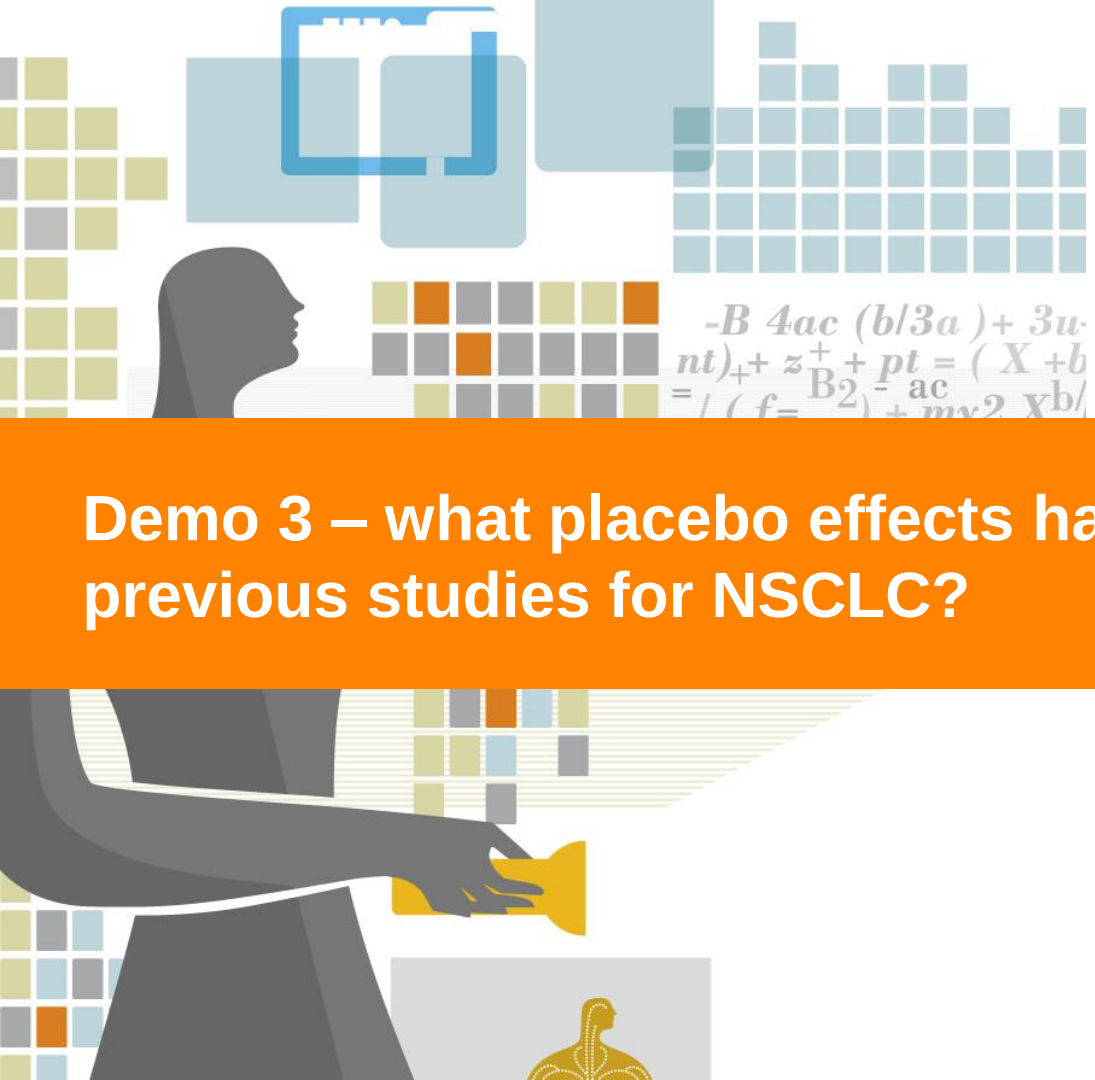
Demo 3 – what placebo effects have been seen in previous studies for NSCLC?



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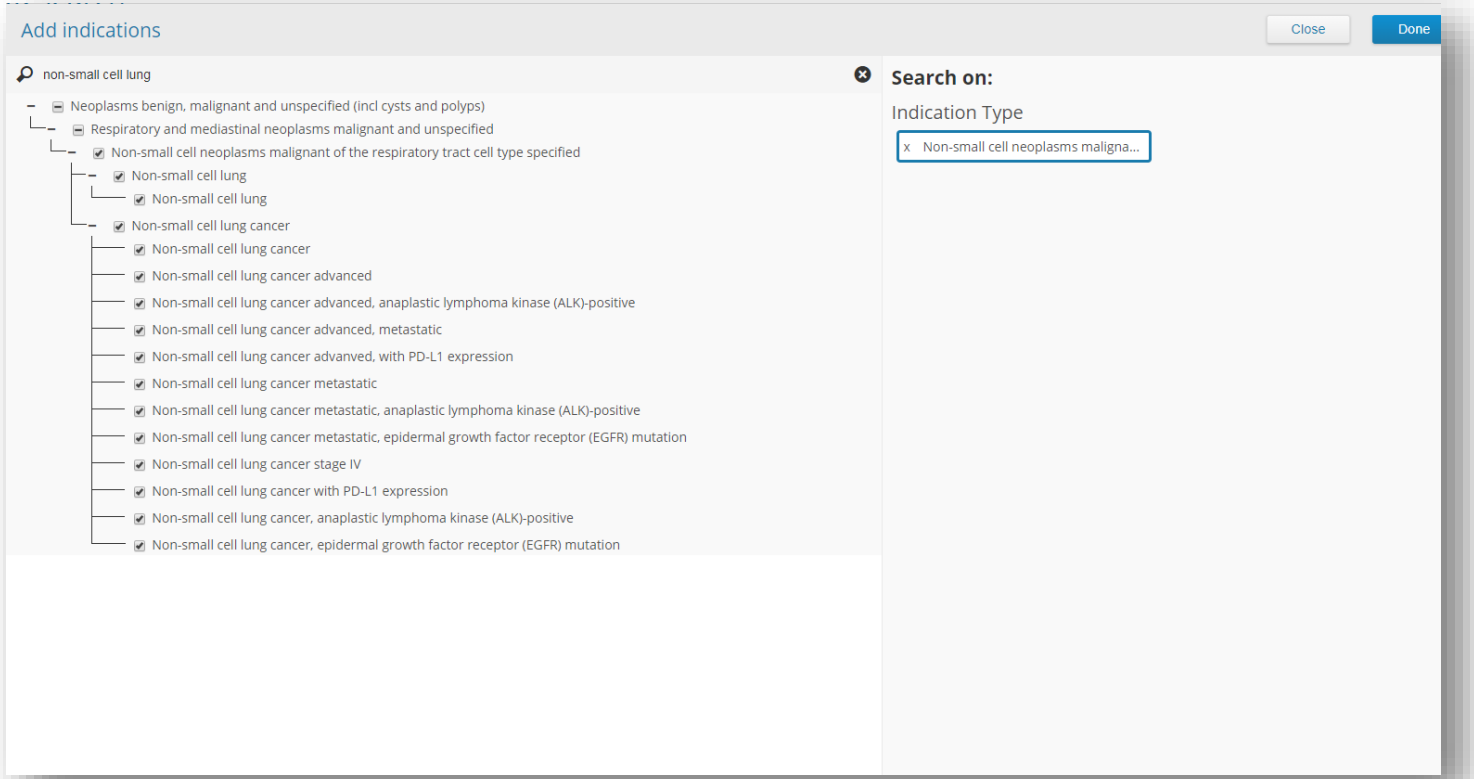
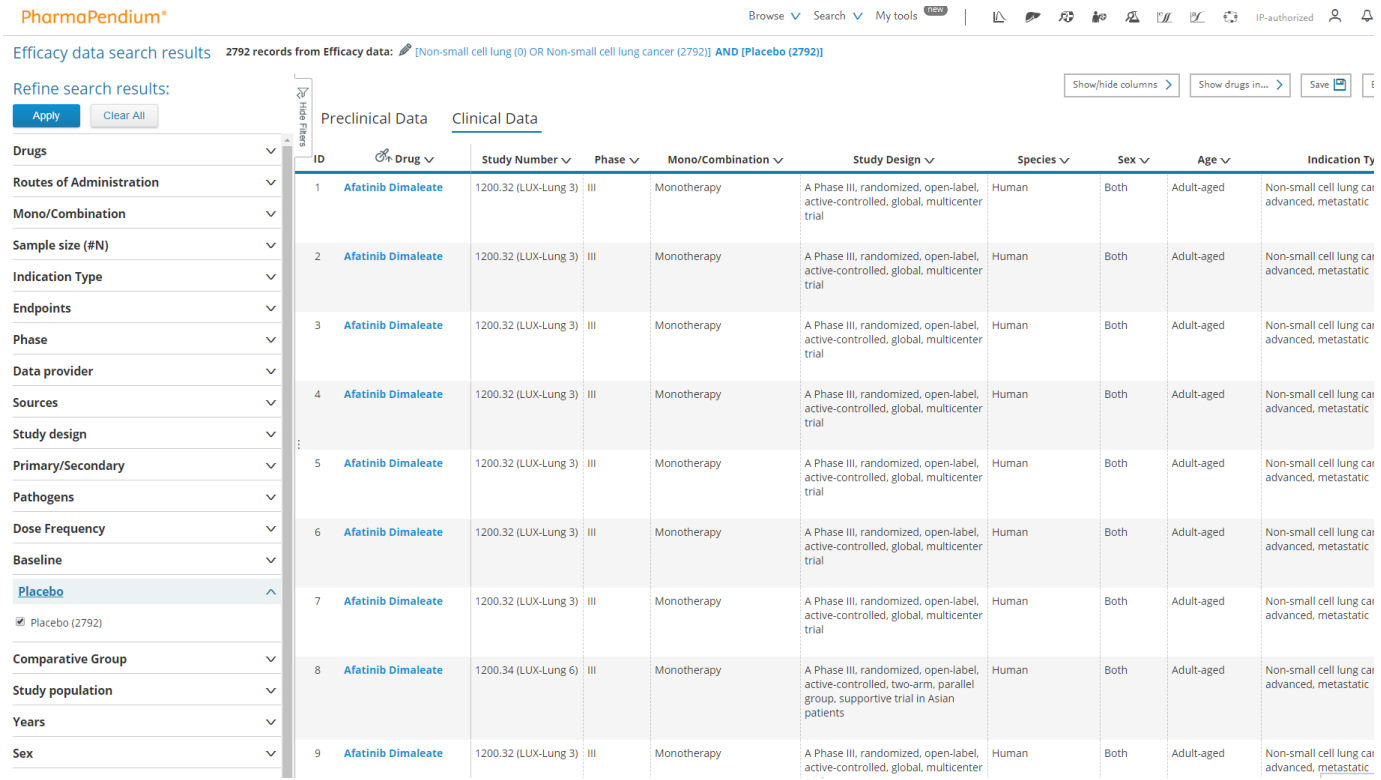
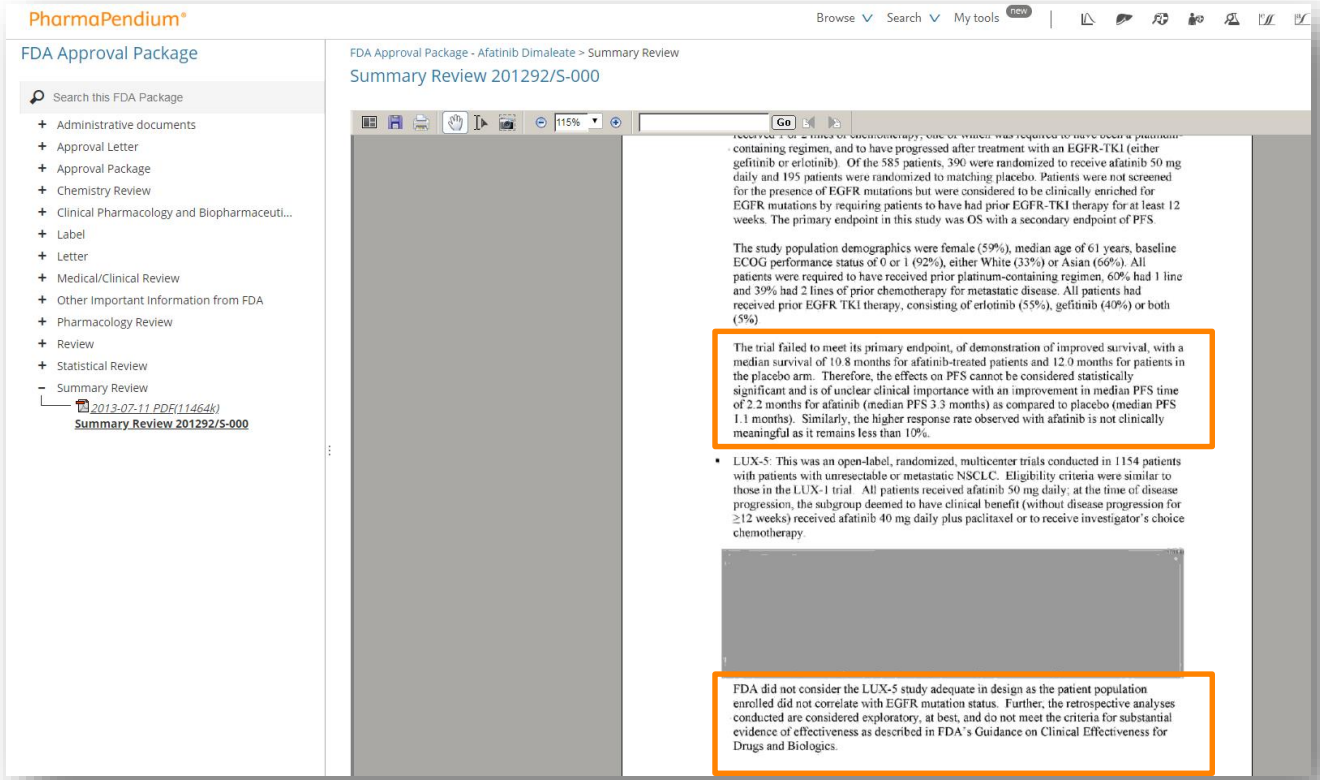
Search for the indication



Filter for placebo; sort by p-value



e.g., did not meet primary endpoint – would selection of a different patient population have helped?



Questions & suggestions

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