

R&D Solutions

Reducing efficacy-related failures with PharmaPendium



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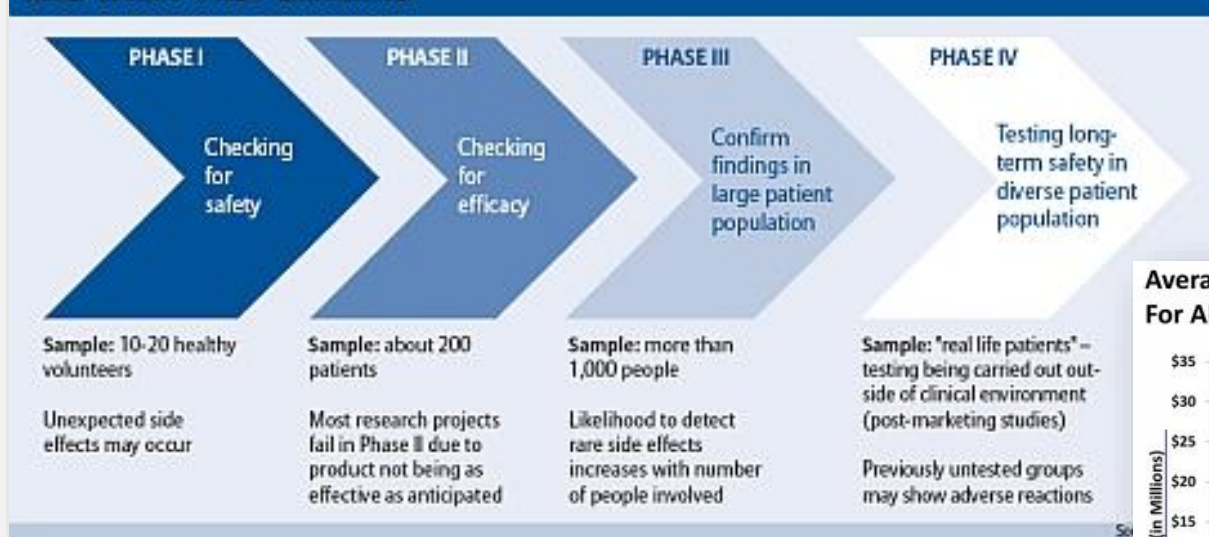
Agenda – focus on efficacy

- 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?

Stages, costs and challenges of clinical development

WATCHING YOUR STEP – THE DIFFERENT STAGES OF CLINICAL DEVELOPMENT AND WHAT THEY EXAMINE



Average Clinical Trial Operations Cost By Phase For All Therapeutic Areas in 2013



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

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).



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) <i>The amount of air that a person can blow out of his or her lungs in 1 second</i>	Improved breathing after taking medication for chronic lung diseases such as asthma
Human immunodeficiency virus (HIV) viral load <i>The amount of the human immunodeficiency virus that is present in the blood</i>	Development of an acquired immunodeficiency syndrome (AIDS) diagnosis

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	+
Proximal PD biomarker	Substrate or other molecule immediately downstream of target	Plasma GLP-1 (substrate)	+
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	++++

PharmaPendium endpoint taxonomy

Endpoint Types	Endpoint Subtypes	Endpoint Tested (Descriptions are heterogeneous)
Physical Measurements	Change in Body Weight	<ul style="list-style-type: none">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	<ul style="list-style-type: none">Number of patients at risk of discontinuation
Markers	Anti-drug Antibodies	<ul style="list-style-type: none">Subjects who had low antibody titersSubjects who tested positive for anti-albiglutide antibodiesSubjects with positive pre-existing antibodies tested weakly positive for neutralizing antibodies
Clinical Response	Response	<ul style="list-style-type: none">Number of patients tested positive during the first 2 years of treatment when receiving Process 2Treatment Difference

$$\frac{-B \pm \sqrt{B^2 - 4ac}}{2a} = \frac{(b/3a) \pm \sqrt{(b/3a)^2 - 4ac}}{2}$$

Finding efficacy information in PharmaPendium

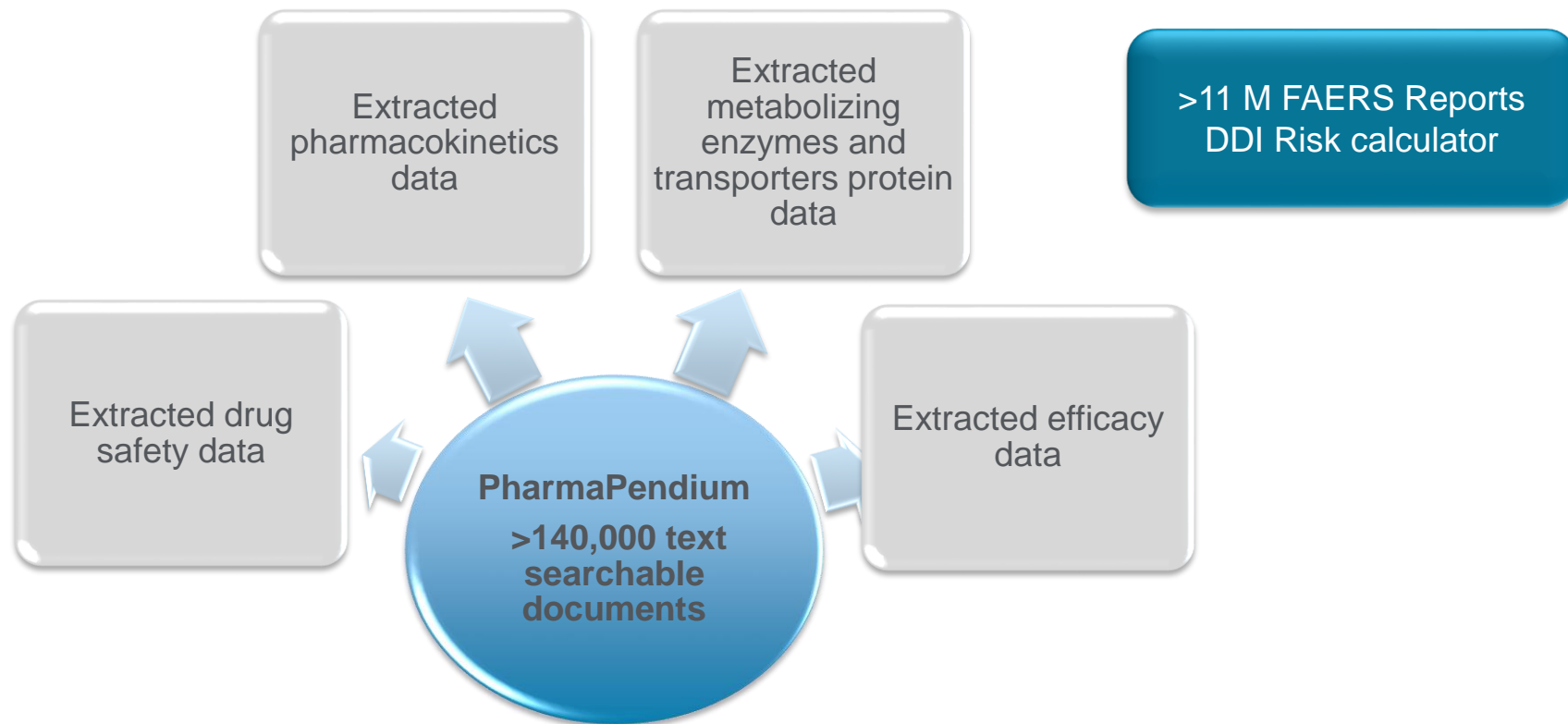
Critical decision-support



- ✓ 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

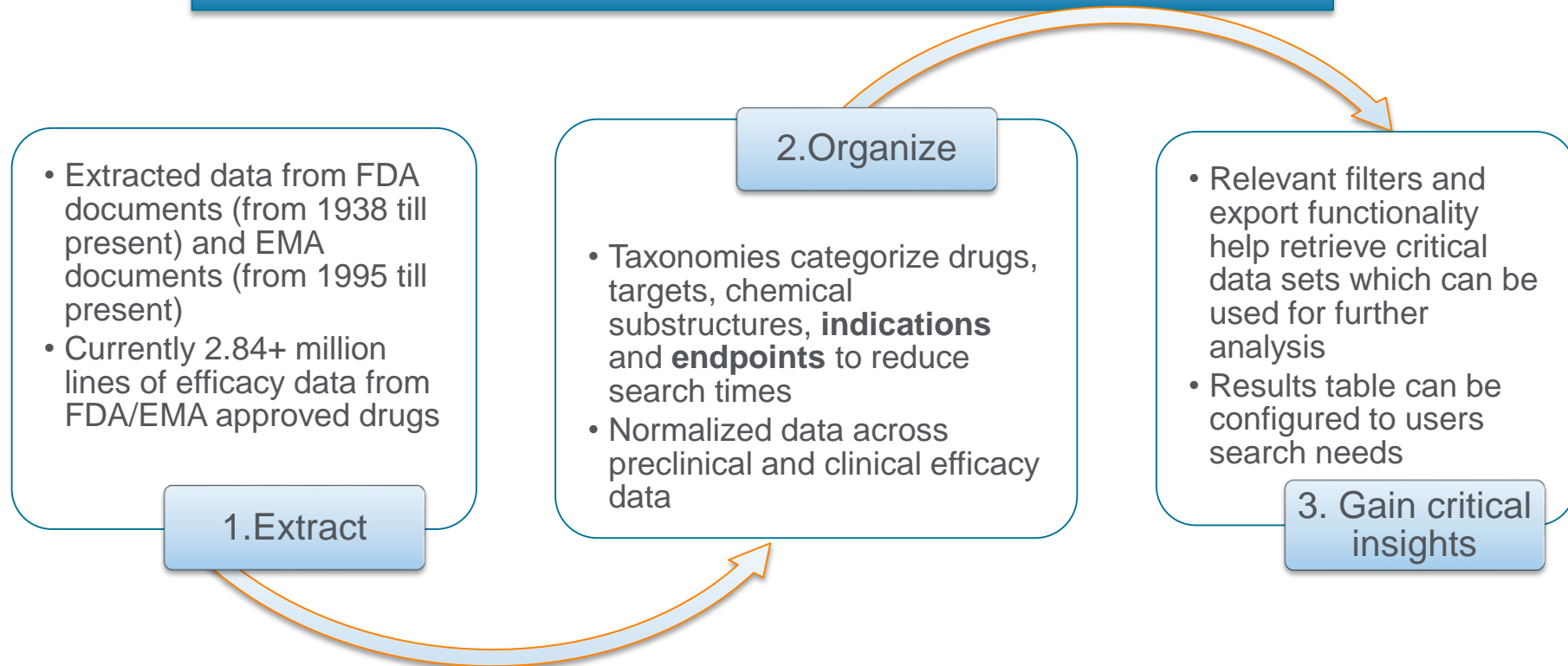
119K

activity data lines

* as of May 2018

Simplified data structure to quickly find relevant efficacy data

Efficacy Module data structure



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:

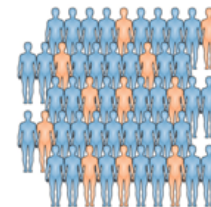
- In-house taxonomy
- Filter by primary, secondary or other



Study design:

Includes:

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



Treatment:

Includes:

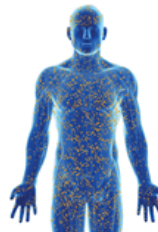
- Dose
- Placebo
- Route of administration.
- Dose frequency



Demographics

Includes:

- Study population
- Gender
- Age



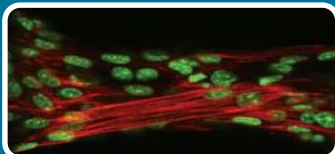
Species

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?

$$\frac{-B \pm \sqrt{B^2 - 4ac}}{2a} = \frac{-(b/3a) \pm \sqrt{(b/3a)^2 - 4ac}}{2}$$

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

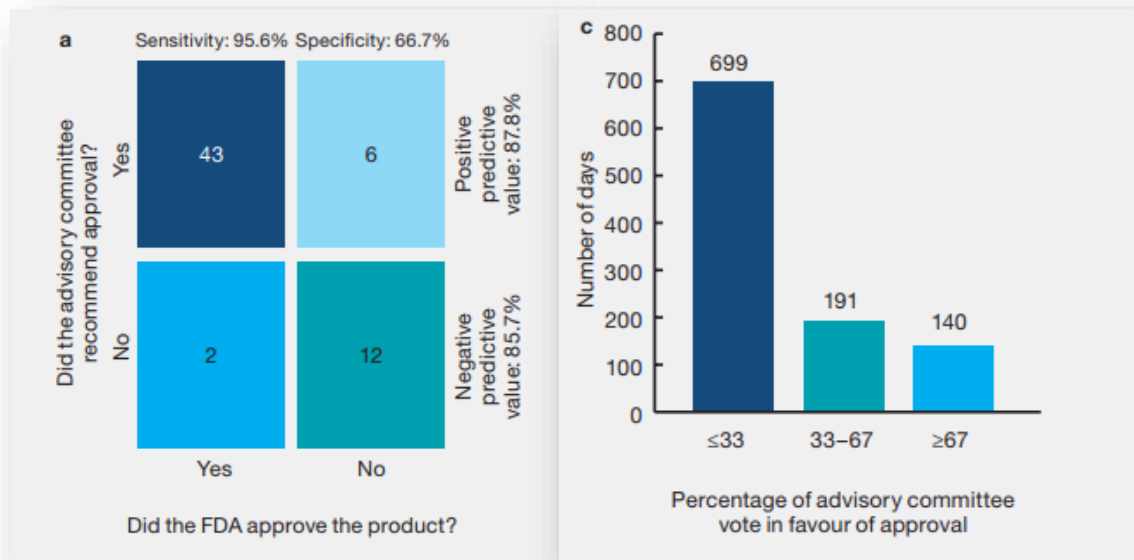
Reminder - types of endpoints

- 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) <i>The amount of air that a person can blow out of his or her lungs in 1 second</i>	Improved breathing after taking medication for chronic lung diseases such as asthma
Human immunodeficiency virus (HIV) viral load <i>The amount of the human immunodeficiency virus that is present in the blood</i>	Development of an acquired immunodeficiency syndrome (AIDS) diagnosis

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

PharmaPendium®

Browse ▾ Search ▾ My tools

Advanced search

Search criteria

Find results

... with **all** the words: ... within at least words of one another... with **at least** one of the words: ... **without** the words: ☒ Include synonyms

Advanced Search Tips

- Use the 1st field for proximity searching. Proximity term NEAR operator.
The proximity search does NOT search for synonyms
Wildcards (* or ?) can be used here.
The number at the end (distance) is how close in the document the phrases to be. The maximum distance for this search is 1000.
Proximity Searches can also be done on the Quick Search.
... termN = Distance

PharmaPendium®

Browse ▾ Search ▾ My tools NEW

IP-authorized

Search results 126 records from Documents: [surrogate.validated=5] AND (diabetes) with synonyms [\[QUERY DETAILS\]](#)

Refine search results:

Jump to: [Show/hide columns](#)[Show drugs in...](#)[Save](#)[Export](#)[Search in EMBASE](#)[Apply](#)[Clear All](#)

Drugs ▾

Sources ▾

Years ▾

ID

Document with context

Drug name ▾












Source ▾


Year ▾

1	Assessment Report EMEA/H/C/001243; EMEA/H/C/001243 PDF 756k ... (Important potential risk: Diabetes mellitus aggravated, diabetes mellitus exacerbated, worsening of ...	Fenofibrate; Pravastatin Sodium	EMA approval documents	2011
2	Briefing 4368 (Endocrinologic and Metabolic Drugs Advisory Committee) PDF 756k ... diabetes mellitus ; N Engl J Med. 1999;341:1127-33. 4. Frank RN. Diabetes retinopathy. N Engl J Med ...	N/A	FDA Advisory Committee Documents	2008
3	Background Part 05 (Endocrinologic and Metabolic Drugs Advisory Committee) PDF 641k ... (CDER) February 2008 Clinical/Medical 1\7630dft.doc 02/13/08 Guidance for Industry Diabetes Mellitus ...	N/A	FDA Advisory Committee Documents	2012
4	Other documents (Endocrinologic and Metabolic Drugs Advisory Committee) PDF 3077k ... = 0.0431 MedDRA preferred term Any diabetes AE Diabetes Mellitus Blood glucose	N/A	FDA Advisory Committee Documents	2009




Explore AC documents

PharmaPendium®

Browse ▾ Search ▾ My tools ^{new} |         IP-authorized   


Search results 126 records from Documents:  [surrogate,validated=5] AND (diabetes) with synonyms [\[QUERY DETAILS\]](#)

Refine search results:

Jump to: Show/hide columns > Show drugs in... > Save  Export  Search in  EMBASE

Apply Clear All

Hide Filters

	ID	 Document with context	Drug name ▾	Source ▾	Year ▾
Drugs ▾	1	Assessment Report EMEA/H/C/001243; EMEA/H/C/001243 PDF 756k ... (Important potential risk): Diabetes mellitus aggravated diabetes mellitus exacerbated, worsening of ...	Fenofibrate; Pravastatin Sodium	EMA approval documents	2011
Sources ▾	2	Briefing 4368 (Endocrinologic and Metabolic Drugs Advisory Committee) PDF 756k ... diabetes mellitus ; N Engl J Med. 1999;341:1127-33. 4. Frank RN. Diabetic retinopathy. N Engl J Med ...	N/A	FDA Advisory Committee Documents	2008
Years ▾	3	Background Part 05 (Endocrinologic and Metabolic Drugs Advisory Committee) PDF 641k ... (CDER) February 2008 Clinical/Medical I:7630dft.doc 02/13/08 Guidance for Industry Diabetes Mellitus ...	N/A	FDA Advisory Committee Documents	2012
	4	Other documents (Endocrinologic and Metabolic Drugs Advisory Committee) PDF 3077k ... = 0.0431 MedDRA preferred term Any diabetic AE Diabetes mellitus Blood glucose	N/A	FDA Advisory Committee Documents	2009

Need to text search 'surrogate'

The screenshot displays the PharmaPendium website interface. On the left, a sidebar titled 'EMA Approval Package' contains a search bar and a list of links: '+ All Authorized Presentations', '+ ANNEX I', '- Assessment Report' (which is expanded to show a PDF link for '2011-01-01 PDF(756k) Assessment Report EM...'), '+ Marketing Authorization Steps', '+ Other Information from EMA', and '+ Public Assessment Report'. The main content area shows the breadcrumb 'EMA Approval Package - Fenofibrate; Pravastatin Sodium > Assessment Report' and the title 'Assessment Report EMEA/H/C/001243; EMEA/H/C/001243'. Below this is a toolbar with icons for document, save, print, and navigation, along with a zoom level of 115%. A search bar in the toolbar contains the word 'surrogate' and a 'Go' button. The text of the assessment report is visible, with the word 'surrogate' highlighted in yellow. The text discusses the benefit-risk balance of the combination therapy for dyslipidaemic high CV risk patients with type 2 diabetes. A section titled '2.8.1. Discussion on the benefit-risk balance' is also visible, discussing the rationale for the combination therapy.

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Browse ▾ Search ▾ My tools ^{new}

EMA Approval Package

Search this EMA Package

- + All Authorized Presentations
- + ANNEX I
- Assessment Report
 - 2011-01-01 PDF(756k)
Assessment Report EM...
- + Marketing Authorization Steps
- + Other Information from EMA
- + Public Assessment Report

EMA Approval Package - Fenofibrate; Pravastatin Sodium > Assessment Report

Assessment Report EMEA/H/C/001243; EMEA/H/C/001243

115% surrogate 2/2 Go

fenofibrate/simvastatin combination therapy to reduce cardiovascular events in the majority of dyslipidaemic high CV risk patients with type 2 diabetic patients. Indeed, only beneficial effects on cardiovascular endpoints were observed in patients with high TG and low HDL-C values. This has also been extensively discussed during Article 31 referral on fenofibrate. Thus, finally, only an indication that will be limited to this specific population subgroup can be granted by the CHMP.

Benefit-risk balance

Based on the provided data, benefits on lipid parameters (surrogate endpoints) were effectively demonstrated in the subgroup of patients with mixed dyslipidaemia defined by TG >204mg/dl and HDL-C <34mg/dL levels. Results are however insufficient to recommend an extensive use in patients with high TG or low HDL-C levels as originally claimed. Nevertheless, the importance whether these biological effects could translate into benefits on cardiovascular endpoints was considered by the CHMP during the first step of the Pravafenix procedure in the context of the long term use of the statin/fenofibrate combination. After reviewing data from the ACCORD study, it would appear that there is a detrimental effect of the long term use of a statin/fenofibrate combination on women. This gender issue has been extensively discussed during referral on fibrates. Overall, the biological benefit expressed in the newly worded and approved indication can be recognised for the pravastatin/fenofibrate combination.

2.8.1. Discussion on the benefit-risk balance

Based on the provided data and the rationale above, Pravafenix is aimed to offer an alternative to a specifically targeted population; i.e. high CHD-risk adult patients with mixed dyslipidaemia characterised by high TG and low HDL-C whose LDL-C are adequately controlled while on a treatment with pravastatin 40mg monotherapy.

Change to unvalidated surrogate search

Advanced search

Search criteria

Find results

... with **all** the words:

... within at least: words of one another

... with **at least** one of the words:

... **without** the words:

☒ Include synonyms

Advanced Search Tips

- Use the 1st field for proximity searching. Proximity terms (NEAR operator). The proximity search does NOT search for synonyms. Wildcards (* or ?) can be used here. The number at the end (distance) is how close in the document phrases to be. The maximum distance for this search is 20. Proximity Searches can also be done on the Quick Search

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Browse ▾ Search ▾ My tools new



Search results 12 records from Documents: [QUERY DETAILS]

Jump to:

Show/hide columns >

Show drugs in... >

Save

ID	Document with context	Drug name ▾	Source ▾	Year ▾
1	Briefing 4355 Part 01 (Blood Products Advisory Committee) PDF 432k ... unvalidated surrogate endpoint at this time. For the secondary endpoints attack severity and attack duration ...	N/A	FDA Advisory Committee Documents	2008
2	Briefing 4355 Part 02 (Blood Products Advisory Committee) PDF 466k ... addition, the secondary endpoint of C1INH levels must be considered an unvalidated surrogate endpoint at ...	N/A	FDA Advisory Committee Documents	2008
3	Approval Package 020604/S-040 PDF 2381k ... -related events including new onset diabetes mellitus and diabetic ketoacidosis led to a language upgrade ...	Somatropin, Biosynthetic	FDA approval packages	2011
4	Background Part 17 (Cardiovascular and Renal Drugs Advisory Committee) PDF 2057k ... of 224 Tolvaptan (OPC-41061) NDA 204441 that TKV is an unvalidated surrogate TKV was chosen as the ...	N/A	FDA Advisory Committee Documents	2013
5	Transcript Part 01 (Peripheral and Central Nervous System Drugs Advisory Committee) PDF 2384k ... , to understand 16 that concluding that an effect on an unvalidated surrogate will	N/A	FDA Advisory Committee Documents	2012

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

The screenshot displays the PharmaPendium website interface. On the left, a sidebar titled "FDA Advisory Committee" contains a search bar and a list of documents. The main content area shows the "Background Part 17" of a document from the "FDA Advisory Committee - Cardiovascular and Renal Drugs Advisory Committee > 2013-Aug-05". A search bar at the top of the document content area shows the word "surrogate" entered, with a "Go" button next to it. The search results show the word "surrogate" highlighted in yellow in the text. The text discusses the progression of a disease and the use of TKV as a surrogate endpoint. The page number "Page 77 of 224" is visible. At the bottom, a footer indicates "11 of 39" pages.

PharmaPendium™

Browse Search My tools IP-authorized

FDA Advisory Committee

Search this FDA Advisory Committee

- 2013-08-05 PDF(2057k) Background Part 17
- 2013-08-05 PDF(2581k) Background Part 18
- 2013-08-05 PDF(1603k) Background Part 19
- 2013-08-05 PDF(471k) Background Part 20
- 2013-08-05 PDF(3399k) Background Part 21
- 2013-08-05 PDF(644k) Background Part 22
- 2013-08-05 PDF(315k) Minutes
- 2013-08-05 PDF(202k) Other documents
- 2013-08-05 PDF(249k) Questions Part 01
- 2013-08-05 PDF(235k)

FDA Advisory Committee - Cardiovascular and Renal Drugs Advisory Committee > 2013-Aug-05

Background Part 17

progression. Its ability to detect changes over a relatively short (3-year) period of the disease's slow course of progression permitted estimation of power for what would be a clinically relevant degree of change (20% reduction). While the sponsor acknowledges

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This document shows original U.S. government data provided by the U.S. Food & Drug Administration and is available in the public domain. It has been processed to facilitate searching and data extraction and may be viewed at www.pharmapendium.com

Tolvaptan (OPC-41061) NDA 204441

that TKV is an unvalidated surrogate, TKV was chosen as the primary endpoint for this trial because if no effect were seen in TKV, it was believed no other clinical benefits would be conveyed to patients.

The TKV endpoint methodology established in the NIH CRISP program was adapted for the pivotal study and validated.⁵ Total kidney volume also served as a mechanism for prognostic enrichment: data available during protocol design supported an association of

11 of 39

What values have been seen for a known endpoint?

Add endpoints

Close

Done

hba1c

- ☐ Estimated treatment difference in HbA1c
- ☐ Estimated treatment ratio in HbA1c
- ☐ Mean change from baseline in HbA1c
- ☐ Mean HbA1c
- ☐ Mean Ratio to baseline in HbA1c

- Diabetes

- ☐ Clinical chemistry
 - ☐ Fasting plasma glucose (FPG) and Glycated hemoglobin (HbA1c)
 - ☐ %patients achieved and maintained control of blood glucose and Hb...
- ☒ Glycated hemoglobin (HbA1c)
 - ☒ % of patients who had a fall in glycated hemoglobin A1c (HbA1c) of 1.0
 - ☒ % of subjects achieving an HbA1c level < 7.0%
 - ☒ % of subjects who achieved target HbA1c levels of <7.0%
 - ☒ % of subjects with HbA1c level 7.0% to 7.5%
 - ☒ % of subjects with HbA1c level 7.5% to 8%

Search on:

Endpoints



x Diabetes, Clinical chemistry, Glycat...

One step – see all clinical data for an endpoint

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Browse ▾ Search ▾ My tools ^{new}

Efficacy data search results 39299 records from Efficacy data: Diabetes, Clinical chemistry, Glycated hemoglobin (HbA1c)

Show/hide columns > Show drugs in... > Save  Export 

Preclinical Data Clinical Data

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
2	Acarbose	D91-006	Not specified	Monotherapy	randomized, double-blind, multi-center, placebo-controlled study	Human		
3	Acarbose	D96-004	Not specified	Combination	26 week, multi-center, randomized, double-blind, placebo controlled, two arm, parallel group comparison study	Human		Adult
4	Acarbose	642.0	Not specified	Monotherapy	placebo controlled double blind study	Human		Adult
5	Acarbose	619.0	Not specified	Monotherapy	double blind study	Human		Adult-aged

Feedback 

Apply a few filters and demo the rest

Efficacy data search results 5057 records from Efficacy data: [\[Diabetes, Clinical chemistry, Glycated hemoglobin \(HbA1c\)\]](#)

Refine search results:

[Apply](#) [Clear All](#)

Phase

- ☒ III (4745)
- ☒ IIIa (7)
- ☒ IIIb (305)

Data provider

- ☒ Reviewer (1482)
- ☐ Sponsor (2573)
- ☐ Unreported (1002)

Sources

Study design

Primary/Secondary

- ☒ co-primary (83)
- ☒ primary (4974)

Preclinical Data **Clinical Data**

ID	Drug	Study Number	Phase	Mono/Combination
1	Albiglutide	GLP114130	III	Monotherapy
2	Albiglutide	GLP112757; GLP112753	III	Combination
3	Albiglutide	GLP112757; GLP112753	III	Combination

Search for 'endpoint'

The screenshot displays the PharmaPendium website interface. At the top, the PharmaPendium logo is on the left, and navigation links for 'Browse', 'Search', and 'My tools' are in the center. On the right, there are icons for various functions and a user profile indicator labeled 'IP-authorized'.

The main content area is titled 'FDA Approval Package - Canagliflozin > Summary Review' and 'Summary Review 204042/S-000'. A search bar is visible with the text 'endpoint' entered, and a 'Go' button next to it. The search results show a document titled '2013-03-25 PDF(3600k) Summary Review 2040...'.

The document content is displayed in a large text area. It includes the following text:

Dr. Guettier has concisely summarized the effect of canagliflozin on several secondary efficacy endpoints. Pre-specified sequential testing procedures were in place to assess the treatment differences of the primary and secondary endpoints. The effect of canagliflozin on glycemic secondary endpoints of fasting plasma glucose (FPG), postprandial glucose (PPG) and proportion meeting HbA1c goals were significantly different from placebo and supported the effect of drug on the primary glycemic endpoint of HbA1c reduction.

Non-glycemic secondary endpoints included weight loss, systolic blood pressure changes, and lipid changes. Canagliflozin 100 and 300 mg resulted in an average 0.4 to 3.3% placebo-subtracted weight reduction across multiple trials. DXA assessments in a subgroup of patients revealed greater loss in fat mass than lean body mass. Average reductions of 0.1 to 7.9 mmHg in systolic blood pressure relative to placebo were also observed across trials.

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Reference ID: 3281940 has been processed to facilitate searching and data extraction and may be viewed at www.pharmapendium.com

Division Director Review

$$\frac{-B \pm \sqrt{B^2 - 4ac}}{2a} = \frac{-(b/3a) \pm \sqrt{(b/3a)^2 - 4ac}}{2}$$

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

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

Quick Search

All These Sources



e.g. Coronar* artery disorders

Search >



Include synonyms

Find adverse effect/toxicity data across preclinical, clinical, post-market reports and more



Pharmacokinetic Data



Metabolizing Enz. & Trans. Data



Drug Safety Data



FAERS Data new



Chemistry Search



Efficacy Data




Activity Data













DDI risk calculator

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

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Browse ▾ Search ▾ My tools 

        IP-authorized  

Efficacy data search

Show me preclinical & clinical studies for these:

Search criteria

Drugs

- + Add drugs by drug class or drug name
- + Add drugs by primary target or primary target class

Indication Type

- + Add indications

Species

- + Add species

Sources

- + Add sources

Endpoints

x Oncology x Oncology (Hematological)

- + Add endpoints

Search Clear

Filter for primary endpoints

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Browse ▾ Search ▾ My tools ^{new}        IP-authorEfficacy data search results 44970 records from Efficacy data:  Oncology, Clinical response, Complete response (11385) OR Oncology, Clinical response, Comp

Refine search results:

Apply

Clear All

Show/hide columns >

Show drugs in... >

Data provider ▾

Sources ▾

Study design ▾

Primary/Secondary ^

- ☒ co-primary (33)
- ☐ exploratory (177)
- ☐ other (78)
- ☒ primary (16476)
- ☐ secondary (9987)
- ☐ tertiary (58)

Pathogens ▾


Dose Frequency ▾

Baseline ▾

Hide Filters



Preclinical Data

Clinical Data

ID	 Drug ▾	Study Number ▾	Phase ▾	Mono/Combination ▾	Study Design ▾
1	Abarelix	149-98-04	Not specified	Monotherapy	Open label, single arm, multicent
2	Abarelix	149-98-04	Not specified	Monotherapy	Open label, single arm, multicent
3	Abarelix	149-98-04	Not specified	Monotherapy	Open label, single arm, multicent
4	Abarelix	149-98-04	Not specified	Monotherapy	Open label, single arm, multicent
5	Abarelix	149-98-04	Not specified	Monotherapy	Open label, single arm, multicent
6	Abarelix	149-98-04	Not	Monotherapy	Open label, single arm, multicent

Need to identify single-arm studies – Export results

Oncology, Clinical response, Complete response (4423) OR Oncology, Clinical response, Complete response or Partial

Show/hide columns > Show drugs in... > Save  Export 

Export data

[Deselect all columns](#) [Select all columns](#)

Select columns for export

<input type="checkbox"/> Chemical Structure	<input checked="" type="checkbox"/> Indication Type	<input checked="" type="checkbox"/> Placebo	<input checked="" type="checkbox"/> Value
<input checked="" type="checkbox"/> Study Number	<input checked="" type="checkbox"/> Indication	<input checked="" type="checkbox"/> Baseline	<input checked="" type="checkbox"/> PValue
<input checked="" type="checkbox"/> Phase	<input checked="" type="checkbox"/> Pathogen	<input checked="" type="checkbox"/> #N	<input checked="" type="checkbox"/> Study Population
<input checked="" type="checkbox"/> Mono/Combination	<input checked="" type="checkbox"/> Route	<input checked="" type="checkbox"/> Comparative Group	<input checked="" type="checkbox"/> Experimental Detail
<input checked="" type="checkbox"/> Study Design	<input checked="" type="checkbox"/> Dose Regimen	<input checked="" type="checkbox"/> Primary/Secondary	<input checked="" type="checkbox"/> Data Provider
<input checked="" type="checkbox"/> Species	<input checked="" type="checkbox"/> Dose Frequency	<input checked="" type="checkbox"/> Endpoint Type	<input checked="" type="checkbox"/> Source
<input checked="" type="checkbox"/> Sex	<input checked="" type="checkbox"/> Duration	<input checked="" type="checkbox"/> Endpoint Subtype	<input checked="" type="checkbox"/> Year
<input checked="" type="checkbox"/> Age	<input checked="" type="checkbox"/> Time Point	<input checked="" type="checkbox"/> Endpoint Tested	

> Export as Excel document (.xls)

> Export as Excel document (.xlsx)

> Export as tab delimited (.tsv)

> Export as comma delimited (.csv)

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/Combination	Study Design	Species	Sex	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, Ph	Human	Both	Adult-aged	Glioblastoma
514	Bevacizumab	AVF3708g	II	Monotherapy	pivotal, randomized, open-label, multicenter, Ph	Human	Both	Adult-aged	Glioblastoma
515	Bevacizumab	AVF3708g	II	Monotherapy	pivotal, randomized, open-label, multicenter, Ph	Human	Both	Adult-aged	Glioblastoma

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- + Summary Review

FDA Approval Package - Carfilzomib > Statistical Review

Statistical Review 202714/S-000

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)].

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

Search for the indication

Add indications

non-small cell lung

Neoplasms benign, malignant and unspecified (incl cysts and polyps)

Respiratory and mediastinal neoplasms malignant and unspecified

Non-small cell neoplasms malignant of the respiratory tract cell type specified

Non-small cell lung

Non-small cell lung

Non-small cell lung cancer

Non-small cell lung cancer

Non-small cell lung cancer advanced

Non-small cell lung cancer advanced, anaplastic lymphoma kinase (ALK)-positive

Non-small cell lung cancer advanced, metastatic

Non-small cell lung cancer advanced, with PD-L1 expression

Non-small cell lung cancer metastatic

Non-small cell lung cancer metastatic, anaplastic lymphoma kinase (ALK)-positive

Non-small cell lung cancer metastatic, epidermal growth factor receptor (EGFR) mutation

Non-small cell lung cancer stage IV

Non-small cell lung cancer with PD-L1 expression

Non-small cell lung cancer, anaplastic lymphoma kinase (ALK)-positive

Non-small cell lung cancer, epidermal growth factor receptor (EGFR) mutation

Search on:

Indication Type

x

Non-small cell neoplasms maligna...

Filter for placebo; sort by p-value

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Efficacy data search results

2792 records from Efficacy data:
[Non-small cell lung (0) OR Non-small cell lung cancer (2792)]
AND [Placebo (2792)]

Refine search results:

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Routes of Administration

Mono/Combination

Sample size (#N)

Indication Type

Endpoints

Phase

Data provider

Sources

Study design

Primary/Secondary

Pathogens

Dose Frequency

Baseline

Placebo

Comparative Group

Study population

Years

Sex

Preclinical Data

Clinical Data

ID	Drug	Study Number	Phase	Mono/Combination	Study Design	Species	Sex	Age	Indication
1	Afatinib Dimaleate	1200.32 (LUX-Lung 3)	III	Monotherapy	A Phase III, randomized, open-label, active-controlled, global, multicenter trial	Human	Both	Adult-aged	Non-small cell lung cancer, advanced, metastatic
2	Afatinib Dimaleate	1200.32 (LUX-Lung 3)	III	Monotherapy	A Phase III, randomized, open-label, active-controlled, global, multicenter trial	Human	Both	Adult-aged	Non-small cell lung cancer, advanced, metastatic
3	Afatinib Dimaleate	1200.32 (LUX-Lung 3)	III	Monotherapy	A Phase III, randomized, open-label, active-controlled, global, multicenter trial	Human	Both	Adult-aged	Non-small cell lung cancer, advanced, metastatic
4	Afatinib Dimaleate	1200.32 (LUX-Lung 3)	III	Monotherapy	A Phase III, randomized, open-label, active-controlled, global, multicenter trial	Human	Both	Adult-aged	Non-small cell lung cancer, advanced, metastatic
5	Afatinib Dimaleate	1200.32 (LUX-Lung 3)	III	Monotherapy	A Phase III, randomized, open-label, active-controlled, global, multicenter trial	Human	Both	Adult-aged	Non-small cell lung cancer, advanced, metastatic
6	Afatinib Dimaleate	1200.32 (LUX-Lung 3)	III	Monotherapy	A Phase III, randomized, open-label, active-controlled, global, multicenter trial	Human	Both	Adult-aged	Non-small cell lung cancer, advanced, metastatic
7	Afatinib Dimaleate	1200.32 (LUX-Lung 3)	III	Monotherapy	A Phase III, randomized, open-label, active-controlled, global, multicenter trial	Human	Both	Adult-aged	Non-small cell lung cancer, advanced, metastatic
8	Afatinib Dimaleate	1200.34 (LUX-Lung 6)	III	Monotherapy	A Phase III, randomized, open-label, active-controlled, two-arm, parallel group, supportive trial in Asian patients	Human	Both	Adult-aged	Non-small cell lung cancer, advanced, metastatic
9	Afatinib Dimaleate	1200.32 (LUX-Lung 3)	III	Monotherapy	A Phase III, randomized, open-label, active-controlled, global, multicenter trial	Human	Both	Adult-aged	Non-small cell lung cancer, advanced, metastatic

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

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FDA Approval Package - Afatinib Dimaleate > Summary Review
Summary Review 201292/S-000

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The trial failed to meet its primary endpoint, of demonstration of improved survival, with a median survival of 10.8 months for afatinib-treated patients and 12.0 months for patients in the placebo arm. Therefore, the effects on PFS cannot be considered statistically significant and is of unclear clinical importance with an improvement in median PFS time of 2.2 months for afatinib (median PFS 3.3 months) as compared to placebo (median PFS 1.1 months). Similarly, the higher response rate observed with afatinib is not clinically meaningful as it remains less than 10%.

LUX-5: This was an open-label, randomized, multicenter trials conducted in 1154 patients with patients with unresectable or metastatic NSCLC. Eligibility criteria were similar to those in the LUX-1 trial. All patients received afatinib 50 mg daily; at the time of disease progression, the subgroup deemed to have clinical benefit (without disease progression for ≥ 12 weeks) received afatinib 40 mg daily plus paclitaxel or to receive investigator's choice chemotherapy.

FDA did not consider the LUX-5 study adequate in design as the patient population enrolled did not correlate with EGFR mutation status. Further, the retrospective analyses conducted are considered exploratory, at best, and do not meet the criteria for substantial evidence of effectiveness as described in FDA's Guidance on Clinical Effectiveness for Drugs and Biologics.

$$\frac{-B \pm \sqrt{B^2 - 4ac}}{2a} = \frac{-(b/3a) \pm \sqrt{(b/3a)^2 - 4ac}}{2}$$

Questions & suggestions