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

**Phase I**
- Checking for safety
- Sample: 10-20 healthy volunteers
- Unexpected side effects may occur

**Phase II**
- Checking for efficacy
- Sample: about 200 patients
- Most research projects fail in Phase II due to product not being as effective as anticipated

**Phase III**
- Confirm findings in large patient population
- Sample: more than 1,000 people
- Likelihood to detect rare side effects increases with number of people involved

**Phase IV**
- Testing long-term safety in diverse patient population
- Sample: "real life patients" - testing being carried out outside of clinical environment (post-marketing studies)
- Previously untested groups may show adverse reactions

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

<table>
<thead>
<tr>
<th>Phase</th>
<th>Cost (in Million)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1</td>
<td>$1.6</td>
</tr>
<tr>
<td>Phase 2</td>
<td>$5.5</td>
</tr>
<tr>
<td>Phase 3a</td>
<td>$30.1</td>
</tr>
<tr>
<td>Phase 3b</td>
<td>$29.6</td>
</tr>
<tr>
<td>Phase 4</td>
<td>$4.8</td>
</tr>
</tbody>
</table>

Sample sizes: n=115, n=133, n=77, n=51, n=102
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

<table>
<thead>
<tr>
<th>Validated Surrogate Endpoint</th>
<th>Correlated Clinical Outcome</th>
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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:

<table>
<thead>
<tr>
<th>Biomarker or clinical trial end point</th>
<th>Item measured</th>
<th>Example from sitagliptin</th>
<th>Degree of confidence on efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>TE</td>
<td>Fraction of drug target bound by drug</td>
<td>Plasma DPP-4 activity</td>
<td>+*</td>
</tr>
<tr>
<td>Proximal PD biomarker</td>
<td>Substrate or other molecule immediately downstream of target</td>
<td>Plasma GLP-1 (substrate)</td>
<td>+*</td>
</tr>
<tr>
<td>Distal PD biomarker</td>
<td>Further downstream biological effect</td>
<td>Plasma glucose, insulin, glucagon</td>
<td>++</td>
</tr>
<tr>
<td>Surrogate end point</td>
<td>Biological effect intimately associated with clinical outcome</td>
<td>Hemoglobin A1c</td>
<td>++++</td>
</tr>
<tr>
<td>Clinical outcome</td>
<td>Mortality, morbidity, symptoms, quality of life</td>
<td>Myocardial infarction (MI), stroke, death from MI</td>
<td>++++</td>
</tr>
</tbody>
</table>

Biomarkers in Pharmaceutical Research
## PharmaPendium endpoint taxonomy

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

- Extracted pharmacokinetics data
- Extracted metabolizing enzymes and transporters protein data
- Extracted drug safety data
- Extracted efficacy data

PharmaPendium
>140,000 text searchable documents

>11 M FAERS Reports
DDI Risk calculator
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

1. Extract

• 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

2. Organize

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

3. Gain critical insights

• 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
Search using a wide range of Efficacy parameters

Extracted information lets you limit search to specific parameters including:

**Indication**
- In-house taxonomy
- Search by indication
- Filter results by indication type

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

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

**Treatment:**
- Dose
- Placebo
- Route of administration
- Dose frequency

**Demographics**
- Study population
- Gender
- Age

**Species**
- 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?
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?**

### Table: Validated Surrogate Endpoint vs Correlated Clinical Outcome

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[https://www.fda.gov/AboutFDA/Innovation/ucm512503.htm](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.

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

#### Search results

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

#### Refine search results:

<table>
<thead>
<tr>
<th>ID</th>
<th>Document with context</th>
<th>Drug name</th>
<th>Source</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Assessment Report EMEA/H/C/001243; EMEA/H/C/001243 PDF 756k</td>
<td>Fenofibrate; Pravastatin Sodium</td>
<td>EMA approval documents</td>
<td>2011</td>
</tr>
<tr>
<td>2</td>
<td>Briefing 4368 (Endocrinologic and Metabolic Drugs Advisory Committee) PDF 756k</td>
<td>N/A</td>
<td>FDA Advisory Committee Documents</td>
<td>2008</td>
</tr>
<tr>
<td>3</td>
<td>Background Part 65 (Endocrinologic and Metabolic Drugs Advisory Committee) PDF 641k</td>
<td>N/A</td>
<td>FDA Advisory Committee Documents</td>
<td>2012</td>
</tr>
<tr>
<td>4</td>
<td>Other documents (Endocrinologic and Metabolic Drugs Advisory Committee) PDF 3077k</td>
<td>N/A</td>
<td>FDA Advisory Committee Documents</td>
<td>2009</td>
</tr>
</tbody>
</table>
Need to text search ‘surrogate’
### Change to unvalidated surrogate search

**Advanced search**

**Find results**
- **with all the words**: surrogate unvalidated
- **within at least 5 words of one another**: 
- **with at least one of the words**: diabetes
- **without the words**: 

**Advanced Search Tips**
- Use the 1st field for proximity searching. Proximity terms are 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 20.
- Proximity Searches can also be done on the Quick Search.

**PharmaPendium**

**Search results**

12 records from Documents: [Surrogate.unvalidated=5] AND (diabetes) with synonyms

<table>
<thead>
<tr>
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<th>Drug name</th>
<th>Source</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Briefing 4355 Part 01 (Blood Products Advisory Committee) PDF 432k</td>
<td>N/A</td>
<td>FDA Advisory Committee Documents</td>
<td>2008</td>
</tr>
<tr>
<td>2</td>
<td>Briefing 4355 Part 02 (Blood Products Advisory Committee) PDF 466k</td>
<td>N/A</td>
<td>FDA Advisory Committee Documents</td>
<td>2008</td>
</tr>
<tr>
<td>3</td>
<td>Approval Package 0206045-040 PDF 2381k</td>
<td>Somatropin, Biosynthetic</td>
<td>FDA approval packages</td>
<td>2011</td>
</tr>
<tr>
<td>4</td>
<td>Background Part 17 (Cardiovascular and Renal Drugs Advisory Committee) PDF 2057k</td>
<td>N/A</td>
<td>FDA Advisory Committee Documents</td>
<td>2013</td>
</tr>
<tr>
<td>5</td>
<td>Transcript Part 01 (Peripheral and Central Nervous System Drugs Advisory Committee) PDF 2384k</td>
<td>N/A</td>
<td>FDA Advisory Committee Documents</td>
<td>2012</td>
</tr>
</tbody>
</table>
Again, need to search for ‘surrogate’ in the document
What values have been seen for a known endpoint?

Add endpoints

Search on:
Endpoints

- Diabetes
  - Clinical chemistry
    - Fasting plasma glucose (FPG) and Glycated hemoglobin (HbA1c)
    - % of 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%
One step – see all clinical data for an endpoint

<table>
<thead>
<tr>
<th>ID</th>
<th>Drug</th>
<th>Study Number</th>
<th>Phase</th>
<th>Mono/Combination</th>
<th>Study Design</th>
<th>Species</th>
<th>Sex</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Acarbose</td>
<td>626.0</td>
<td>Not specified</td>
<td>Monotherapy</td>
<td>four arm, double blind adjunct study</td>
<td>Human</td>
<td>Adult</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Acarbose</td>
<td>D91-006</td>
<td>Not specified</td>
<td>Monotherapy</td>
<td>randomized, double-blind, multi-center, placebo-controlled study</td>
<td>Human</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Acarbose</td>
<td>D96-004</td>
<td>Not specified</td>
<td>Combination</td>
<td>26 week, multi-center, randomized, double-blind, placebo controlled, two arm, parallel group comparison study</td>
<td>Human</td>
<td>Adult</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Acarbose</td>
<td>642.0</td>
<td>Not specified</td>
<td>Monotherapy</td>
<td>placebo controlled double blind study</td>
<td>Human</td>
<td>Adult</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Acarbose</td>
<td>619.0</td>
<td>Not specified</td>
<td>Monotherapy</td>
<td>double blind study</td>
<td>Human</td>
<td>Adult-aged</td>
<td></td>
</tr>
</tbody>
</table>
Apply a few filters and demo the rest

---

<table>
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<th>Phase</th>
<th>Mono/Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Albigitide</td>
<td>GLP114130</td>
<td>III</td>
<td>Monotherapy</td>
</tr>
<tr>
<td>2</td>
<td>Albigitide</td>
<td>GLP112757; GLP112753</td>
<td>III</td>
<td>Combination</td>
</tr>
<tr>
<td>3</td>
<td>Albigitide</td>
<td>GLP112757; GLP112753</td>
<td>III</td>
<td>Combination</td>
</tr>
</tbody>
</table>
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 glycosylated hemoglobin (HbA1c) endpoints 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.
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
   o 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

PharmaPendium®

Efficacy data search results

44970 records from Efficacy data: Oncology. Clinical response. Complete response (11385) OR Oncology. Clinical response. Comp...

Refine search results:

- Data provider
- Sources
- Study design
- Primary/Secondary
- Pathogens
- Dose Frequency
- Baseline

### Preclinical Data

<table>
<thead>
<tr>
<th>ID</th>
<th>Drug</th>
<th>Study Number</th>
<th>Phase</th>
<th>Mono/Combination</th>
<th>Study Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Abarelix</td>
<td>149-98-04</td>
<td>Not specified</td>
<td>Monotherapy</td>
<td>Open label, single arm, multicenter</td>
</tr>
<tr>
<td>2</td>
<td>Abarelix</td>
<td>149-98-04</td>
<td>Not specified</td>
<td>Monotherapy</td>
<td>Open label, single arm, multicenter</td>
</tr>
<tr>
<td>3</td>
<td>Abarelix</td>
<td>149-98-04</td>
<td>Not specified</td>
<td>Monotherapy</td>
<td>Open label, single arm, multicenter</td>
</tr>
<tr>
<td>4</td>
<td>Abarelix</td>
<td>149-98-04</td>
<td>Not specified</td>
<td>Monotherapy</td>
<td>Open label, single arm, multicenter</td>
</tr>
<tr>
<td>5</td>
<td>Abarelix</td>
<td>149-98-04</td>
<td>Not specified</td>
<td>Monotherapy</td>
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<tr>
<td>6</td>
<td>Abarelix</td>
<td>149-98-04</td>
<td>Not specified</td>
<td>Monotherapy</td>
<td>Open label, single arm, multicenter</td>
</tr>
</tbody>
</table>
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)
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 (59%) 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
Filter for placebo; sort by p-value

<table>
<thead>
<tr>
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<tr>
<td>ID</td>
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</tr>
<tr>
<td>1</td>
<td>Alatinib Dimulate</td>
</tr>
<tr>
<td>2</td>
<td>Alatinib Dimulate</td>
</tr>
<tr>
<td>3</td>
<td>Alatinib Dimulate</td>
</tr>
<tr>
<td>4</td>
<td>Alatinib Dimulate</td>
</tr>
<tr>
<td>5</td>
<td>Alatinib Dimulate</td>
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e.g., did not meet primary endpoint – would selection of a different patient population have helped?
Questions & suggestions