Strengthening Confidence in Drug Approval – The Role of Evidence, Openness and Digital Tools

Maximilian Siebert, PhD
Postdoctoral Fellow
Harvard Medical School
November 11, 2025

Structure

- Transparency in Marketing Authorization (EMA)
- Postmarketing Requirements (FDA)
- Cell and Gene Therapy
- What needs to be done
- Outlook

Reminder of the importance of Clinical Trial Transparency & Drug Approval

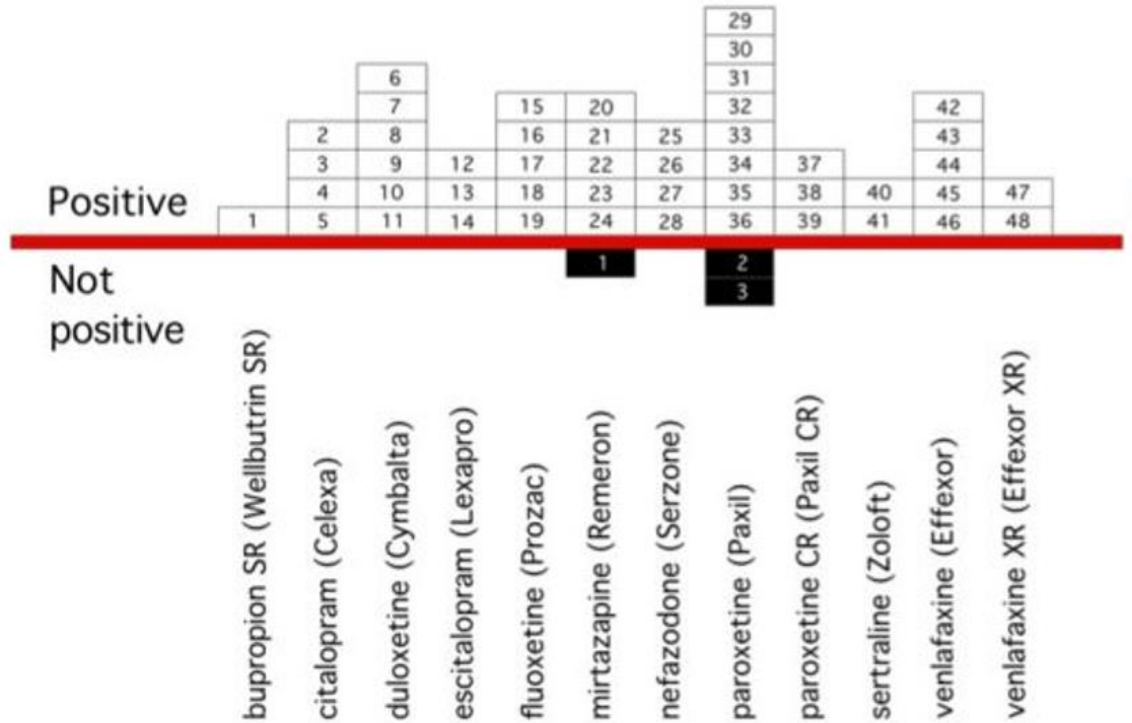
The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

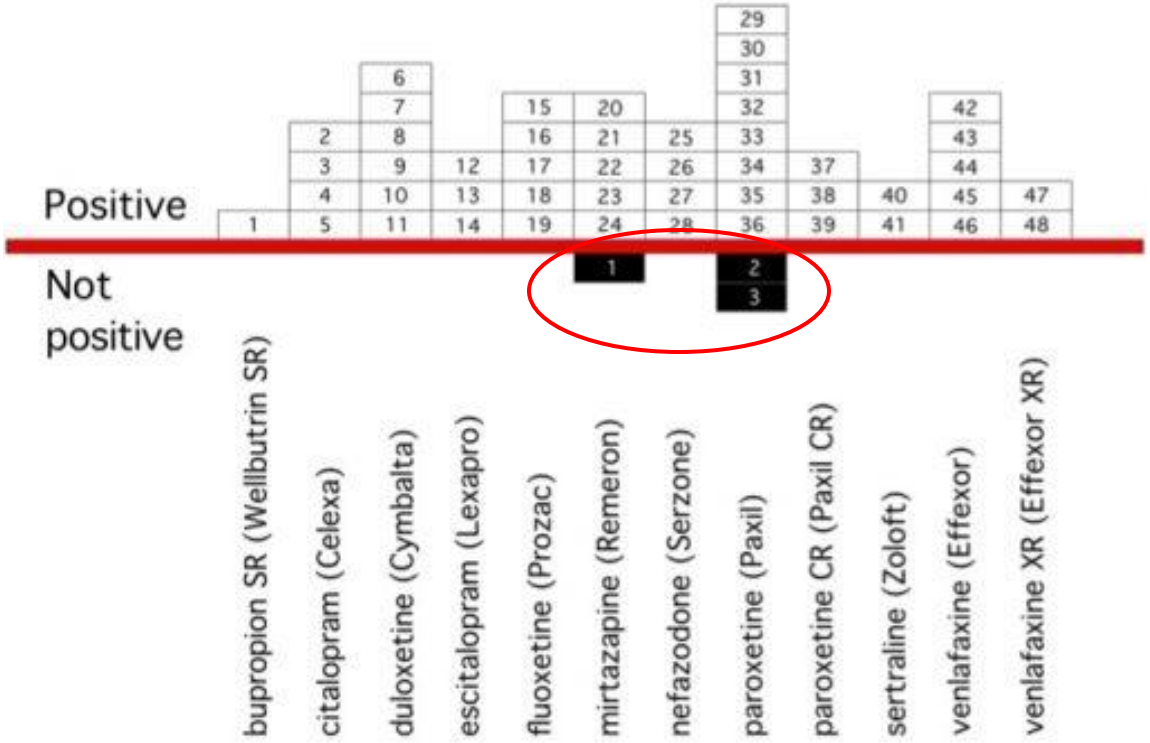
Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy

Erick H. Turner, M.D., Annette M. Matthews, M.D., Eftihia Linardatos, B.S., Robert A. Tell, L.C.S.W., and Robert Rosenthal, Ph.D.

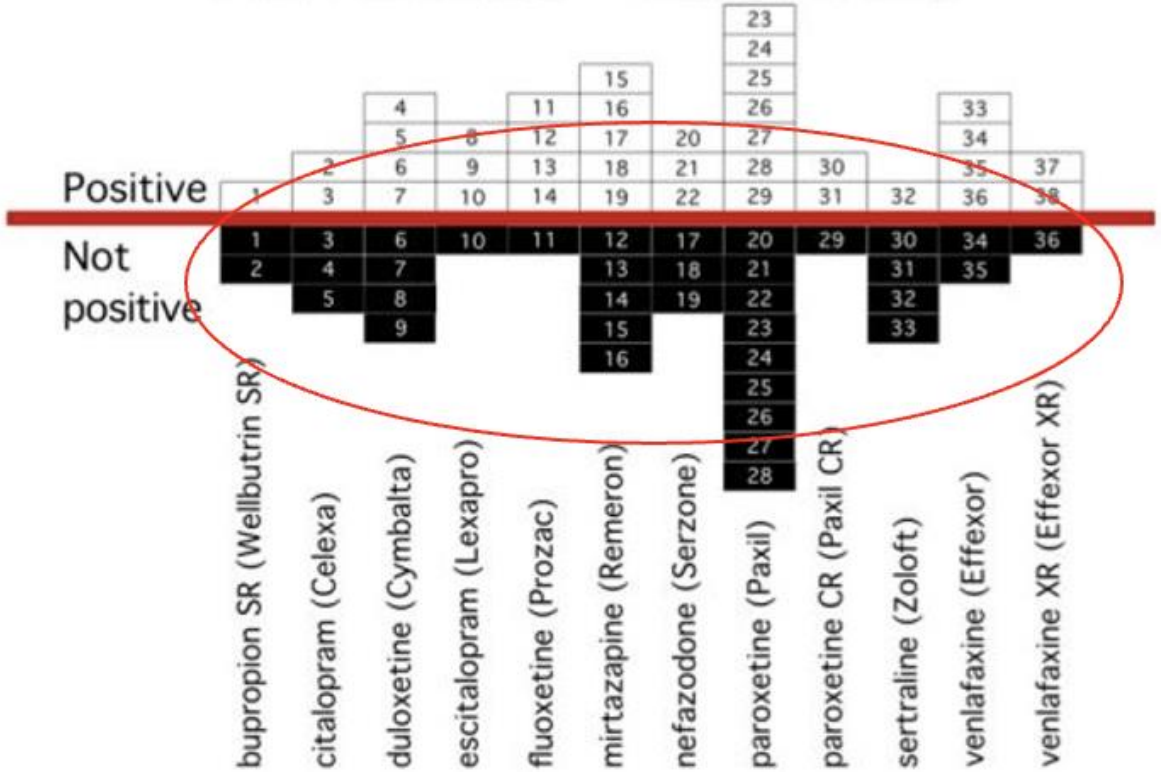
Journal version of antidepressant trials



Journal version of antidepressant trials



FDA version – same trials



Implications

- More awareness for Publication Bias
- Shedding Light on Regulatory Uncertainty

Structure

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- Outlook

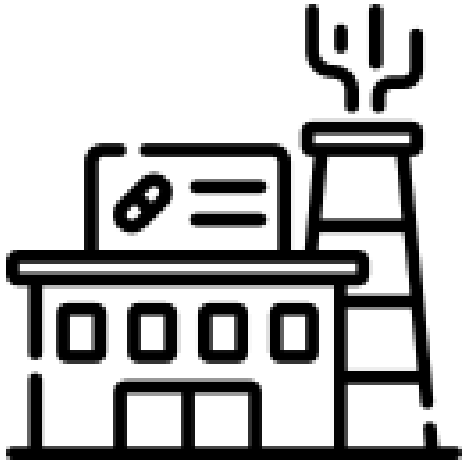
Siebert *et al. BMC Medicine* (2022) 20:177
https://doi.org/10.1186/s12916-022-02377-2

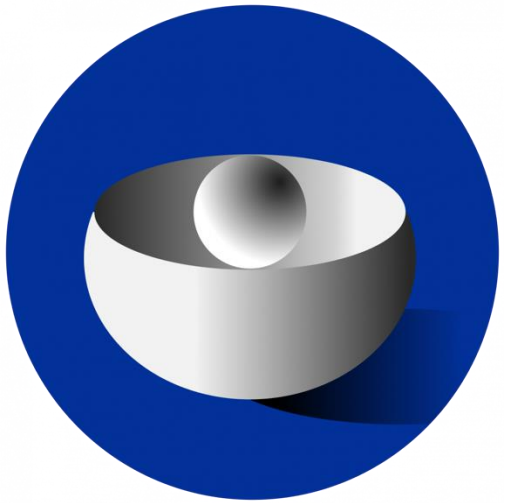
BMC Medicine

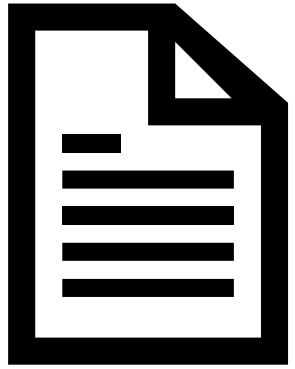
REGISTERED REPORT Open Access

Data-sharing and re-analysis for main studies assessed by the European Medicines Agency—a cross-sectional study on European Public Assessment Reports

Maximilian Siebert[1,2], Jeanne Gaba[1,2], Alain Renault[1,2], Bruno Laviolle[1,2], Clara Locher[1,2], David Moher[3] and Florian Naudet[1,2,4*]







Pharmaceutical Company demands authorization

EMA checks evidence and (dis)approves

European Public Assessment Reports (EPAR)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 November 2019
EMA/614876/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Spravato

International non-proprietary name: esketamine

Procedure No. EMEA/H/C/004535/0000

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How many of those main studies are reproduced when re-analyzed by independent researchers?

The European Medicines Agency (EMA) is currently, in general, not directly re-analysing clinical trial data from marketing authorisation applications. The EMA structures their assessments on subsequent rounds of questions and answers (detailed here: [https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/evaluation-medicines-step-step]) whereby - among other things - the details of the re-analyses to be performed are communicated to the applicant which responds with the results of such re-analyses.

Email Communication with EMA Staff October 2021

Our approach

- Main studies in EMA Approvals from 2017 – 2019

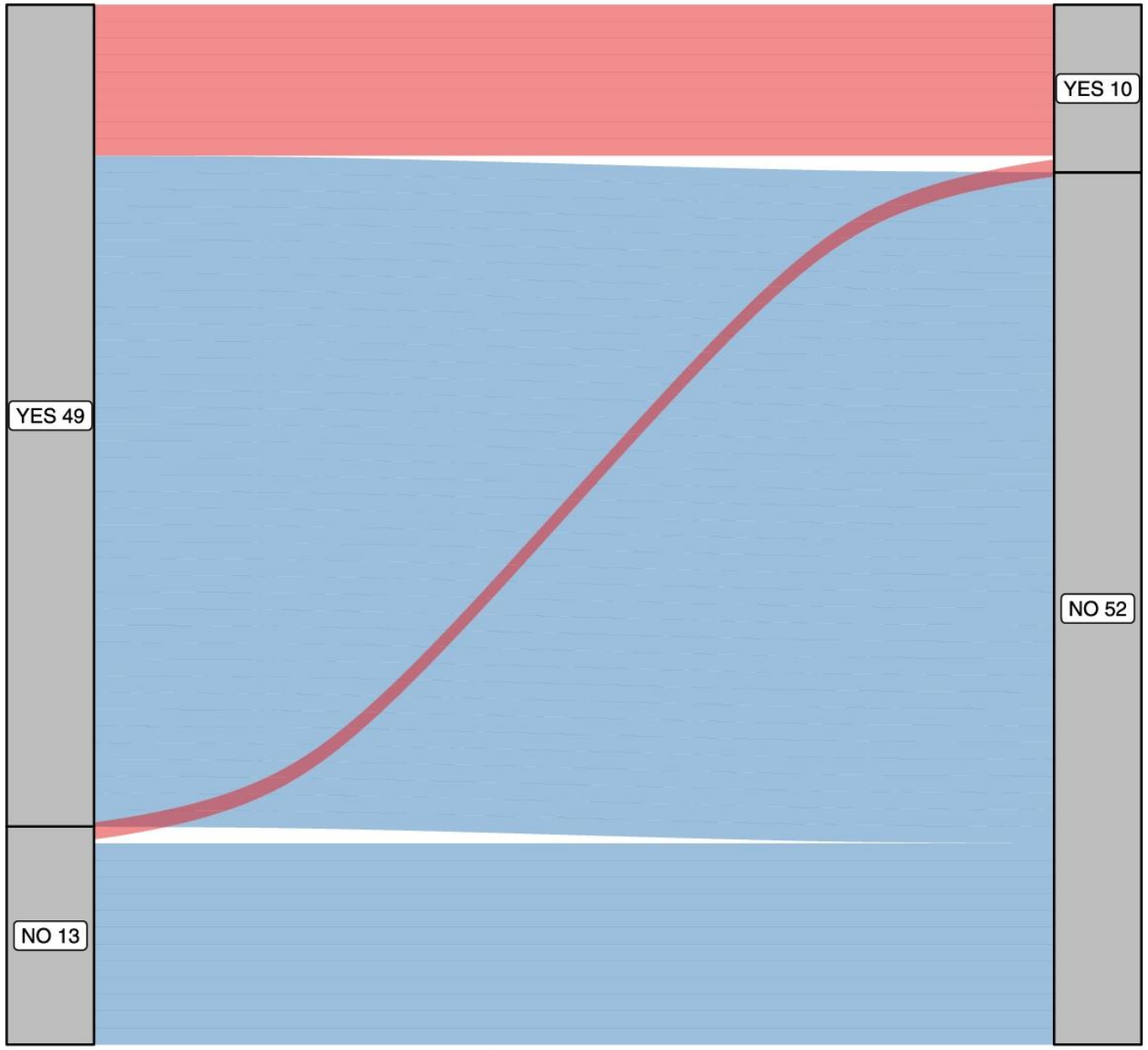
- Asked for 62 trial datasets

Our approach

- Pivotal Trials in EMA Approvals from 2017 – 2019
- Asked for 62 trial datasets
- All endpoints in trials were reproduced

BUT

we received only 10 out of the 62 datasets requested by the pharmaceutical sponsors



Reasons for not sharing (n = 52)

- Restriction due to study status (n = 13)
- Confidentiality (n = 9)
- **Doubt of scientific merit (n = 9)**
- **No explicit reason (n = 5)**
- **No response (n = 4)**
- **Complexity of the original study (n = 3)**
- No data sharing initiative (n = 3)
- Data Sharing policy does not extent to data sharing (n = 2)
- Inability to request data (n = 2)
- Patient informed consent (n = 1)
- Risk of re-identification of patients (n = 1)

What did we learn?

- Data sharing & Clinical Trial Transparency was low
- Scientific merit should not be determined by Pharmaceutical companies
- Independent verification of strength of evidence behind approvals complicated

What was my biggest takeaway from this study ?

- Main Studies with unmet primary endpoints

- Observational Studies serve as Main Studies

Research Letter | Health Care Policy and Law

FREE

February 13, 2023

US Food and Drug Administration Approval of Drugs Not Meeting Pivotal Trial Primary End Points, 2018-2021

James L. Johnston, MD[1]; Joseph S. Ross, MD, MHS[2,3,4,5]; Reshma Ramachandran, MD, MPP, MHS[2,4,5]

» Author Affiliations | Article Information

JAMA Intern Med. 2023;183(4):376-380. doi:10.1001/jamainternmed.2022.6444

1 in 10 drug approvals contained a trial with a failed primary endpoint

EMA Approvals from 2020-2023

- Main goals:

1/ Strength of Evidence of Approvals

2/ Clinical Trial Failure

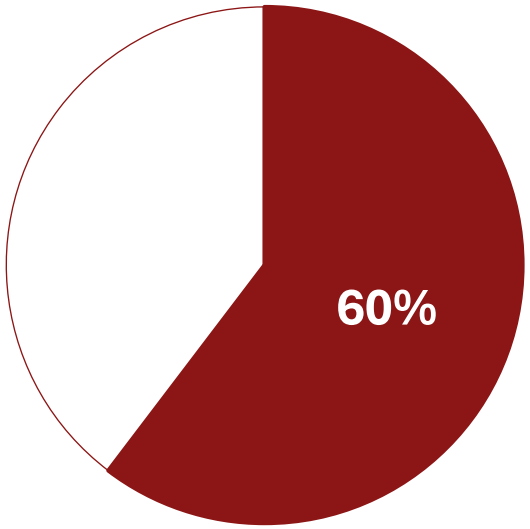
Under Review

EMA Approvals from 2020-2023

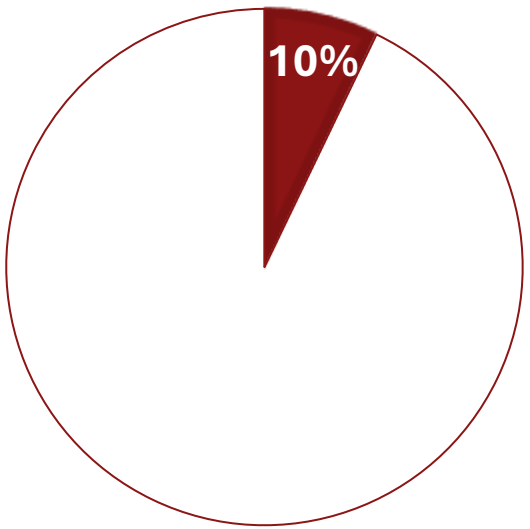
- 232 drugs were approved by the EMA for 281 indications

- 46 products (19.8%) were approved via a special regulatory program, most commonly Conditional Approval

EMA Approvals from 2020-2023



- 60% (140/232) of approvals were based on one single pivotal trial



- 22 approvals (10%) were supported by at least one main study in which one primary endpoint has not been met
- For 7 of these (31.8%), the failed trial was the sole main study

Implications

- Substantial variability in the design and evidentiary strength of main studies supporting EMA approvals
- A failed clinical trial does not necessarily mean the drug itself has failed
- Unmet clinical need remains an important consideration

Structure

- Transparency in Marketing Authorization (EMA)
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- What needs to be done
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How to overcome these uncertainties

1. Actions by the Regulatory Agency

Postmarketing Requirements

The FDA has been granted authority to require postmarketing studies under four statutes:

1. Accelerated Approval pathway (1992)
2. Animal Efficacy Rule (2002)
3. Pediatric Research Equity Act (2003)
4. FDA Amendments Act (2007)

FDAAA PMRs

Section 505(o)(3) of the Act authorizes FDA to require postmarketing studies or clinical trials at the time of approval or after approval if FDA becomes **aware of new safety information**

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GLP-1 agonists have been associated with thyroid tumors

FDAAA PMRs

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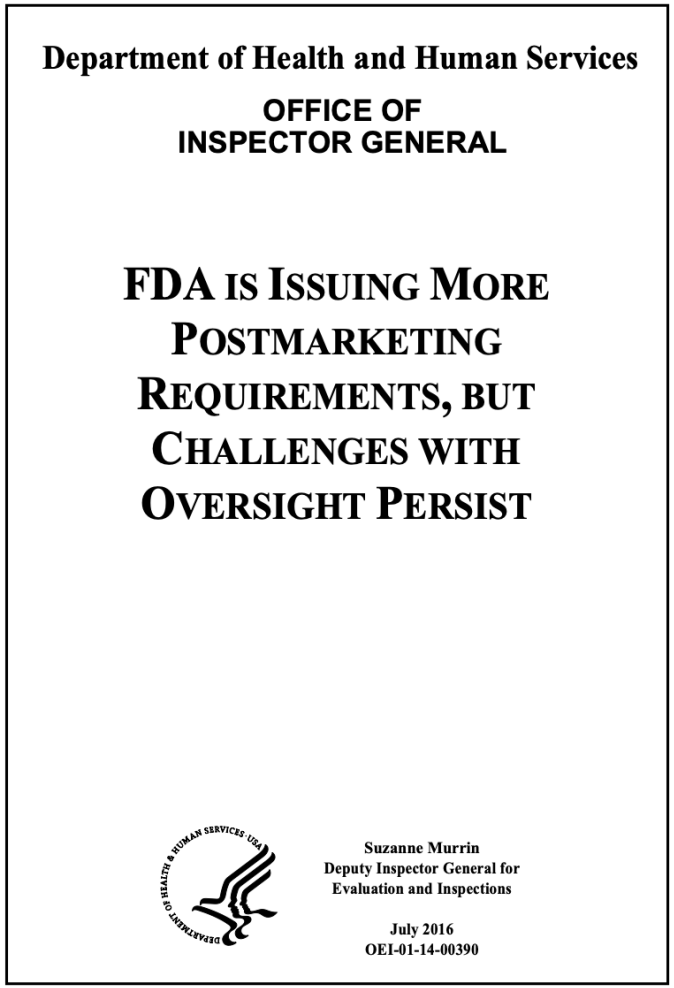
GLP-1 agonists have been associated with thyroid tumors

Registry-based case series of at least 15 years duration to systematically monitor the annual incidence of thyroid carcinoma in the United States

2016 HHS Office of Inspector General Report



Department of Health and Human Services

OFFICE OF
INSPECTOR GENERAL

FDA IS ISSUING MORE POSTMARKETING REQUIREMENTS, BUT CHALLENGES WITH OVERSIGHT PERSIST

Suzanne Murrin
Deputy Inspector General for
Evaluation and Inspections

July 2016
OEI-01-14-00390

Despite governmental oversight, issues with compliance

Objective

- Focusing on postmarketing requirements issued under FDAAA 505(o)(3)

- Main goals:
  - Tracking status of fulfillment
  - Timeliness of completion

Under Review

Completion status

Sample of 420 drugs approved by the FDA 2016-2024

Requirements due by Dec 31, 2024	Requirements completed	
470	345 (73.4%)	

Completion status

Sample of 420 drugs approved by the FDA 2016-2024

Requirements due by Dec 31, 2024	Requirements completed	Requirements completed on time
470	345 (73.4%)	157 (33.4%)

Implications

- Postmarketing Requirements are critical to ensure continued efficacy and safety evaluation

- Delays are common, underscoring the need for stronger oversight and timely study conduct and reporting

Structure

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Cell and Gene Therapy

- Approvals in the U.S.: 38

- Approvals in Europe: 19

(on the market, November 2025)

- Costly : up to $3.5 million, e.g. Hemgenix

(genetic blood-clotting disorder haemophilia B)

Cell and Gene Therapy

- High risk, high gain therapeutics
  - Uncertainty at time of approval
  - Many single arm trials
  - Open label trials
  - Come at high cost
- **However:** potential to transform conditions once fatal into manageable or resolved ones

Conclusion

- Cell and Gene Therapies promise transformative, often one-time treatments
- Clinical relevance of results reported up to 20 years post-approval is uncertain
- Each therapy can cost several million dollars per patient, yet long-term benefit–risk profiles are still being defined

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How to overcome these uncertainties

1. Actions by the Regulatory Agency

2. Self initiated actions /Web tools/Policy work

Why is this important?

- Overlapping research efforts
- Recurring issues but few solutions
- No innovation and no incentives in regulatory science

Dashboard for clinical trial transparency

This dashboard displays the performance of University Medical Centers (UMCs) in Germany on established registration and reporting practices for clinical trial transparency. The dashboard displays data for interventional clinical trials conducted at German UMCs, registered in ClinicalTrials.gov or the German Clinical Trials Register (DRKS), and considered as complete between 2009 - 2017 per the registry. For summary results reporting, we additionally included trials conducted at German UMCs and registered in the EU Clinical Trials Register (EUCTR). The dashboard was developed as part of a scientific research project with the overall aim to support the adoption of responsible research practices at UMCs. More metrics may be added in the future.

The *Start page* displays data across all included UMCs. The *All UMCs* page displays the data of all UMCs side-by-side. The *One UMC* page allows you to focus on any given UMC by selecting it in the drop-down menu. The data for this UMC is then contextualized to that across all included UMCs. Besides each plot, you can find an overview of the methods and limitations by clicking on the associated widgets. For more detailed information on the methods and underlying datasets used to assess the practices displayed in this dashboard, visit the *Methods* and *Datasets* pages. The *Trial Characteristics* page provides an overview of the characteristics of trials included in the dashboard. The *FAQ* and *Why these practices?* pages provide more general information about this dashboard and our selection of practices.

More information on the overall aim and methodology can be found in the associated publication.

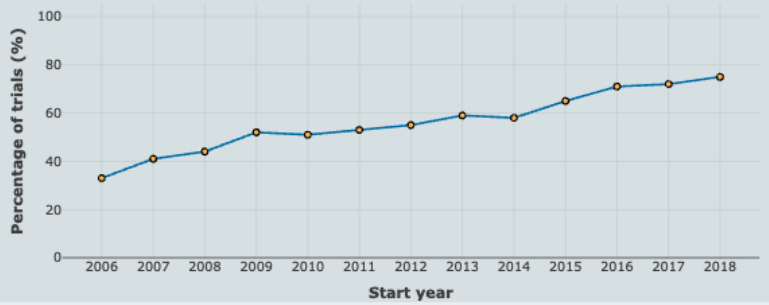
See one UMC | See all UMCs | See methods | See datasets

Trial Registration

Prospective registration

75%

of registered clinical trials started in 2018 (n=193) were prospectively registered



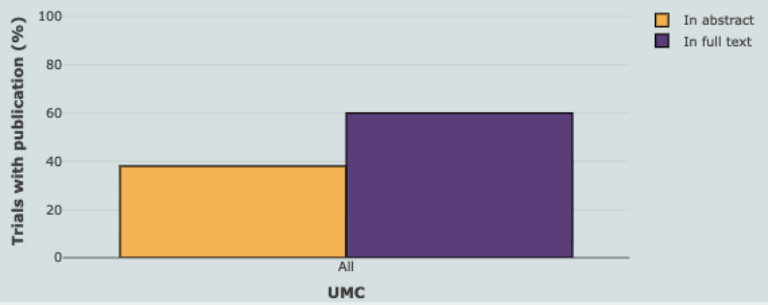
Trial registry

ClinicalTrials.gov

Reporting of Trial Registration Number in publications

38%

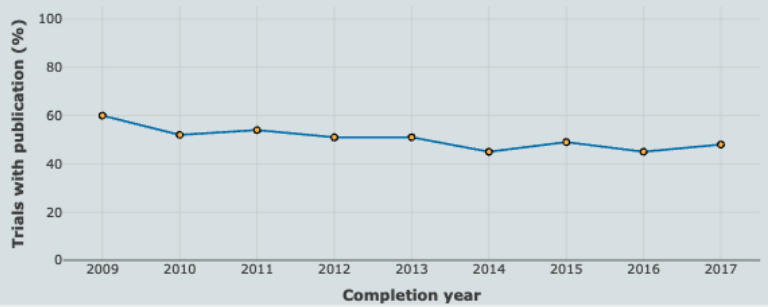
of trials with a publication (n=1895) reported a trial registration number in the abstract



Publication link in registry

48%

of trials completed in 2017 with a publication (n=252) provide a link to this publication in the registry entry



Trial registry

All

Charité Dashboard on Responsible Research

Charité has committed itself to establish, promote and maintain a research environment which enhances the robustness of research and the reproducibility of results (Rethinking Health – Charité 2030).

This dashboard gives an overview of several metrics of open and responsible research at the Charité (including the Berlin Institute of Health). For a detailed discussion about monitoring core Open Science practices see (Cobey et al. 2023). For more detailed information on the methods used to calculate those metrics, the dataset underlying the metrics, or resources to improve your own research practices, click one of the following buttons on the right.

For more detailed open access metrics you can visit the Charité Open Access Dashboard developed by the Charité Medical Library.

See methods | See resources | See dataset

Latest Update: April 2025

Cite us:

APA

BIH QUEST Center for Responsible Research. (n. d.). *Charité Dashboard on Responsible Research*. Retrieved 08 November, 2025, from https://quest-dashboard.charite.de/

Open Science

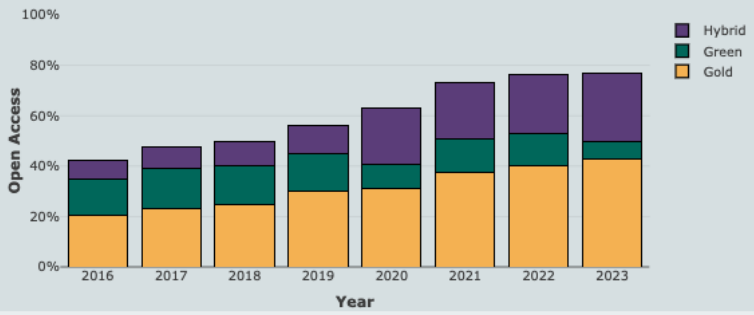
☐ Show absolute numbers

Double-click or select rectangular area inside any panel to zoom in

Open Access

77 %

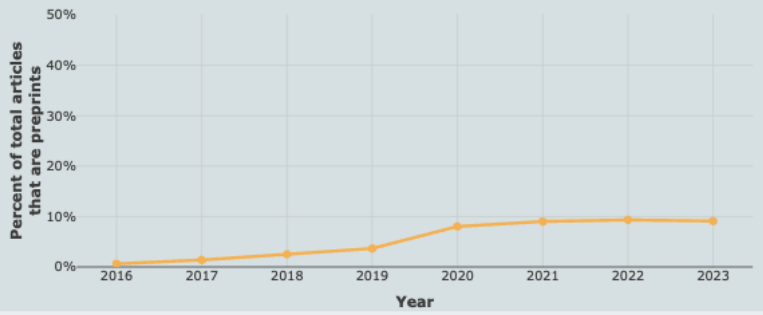
of publications were open access in 2023



Preprints and journal publications

553

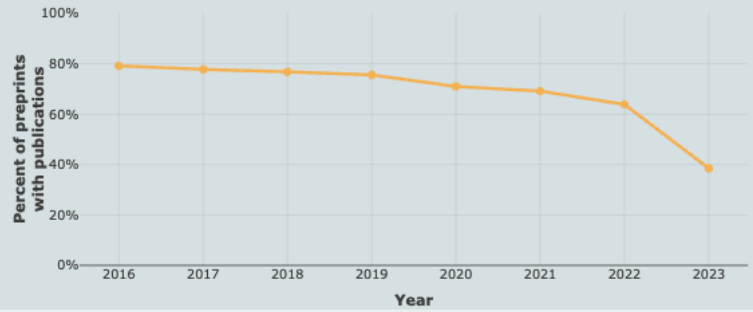
preprints published in 2023



Any preprints with journal publications

39 %

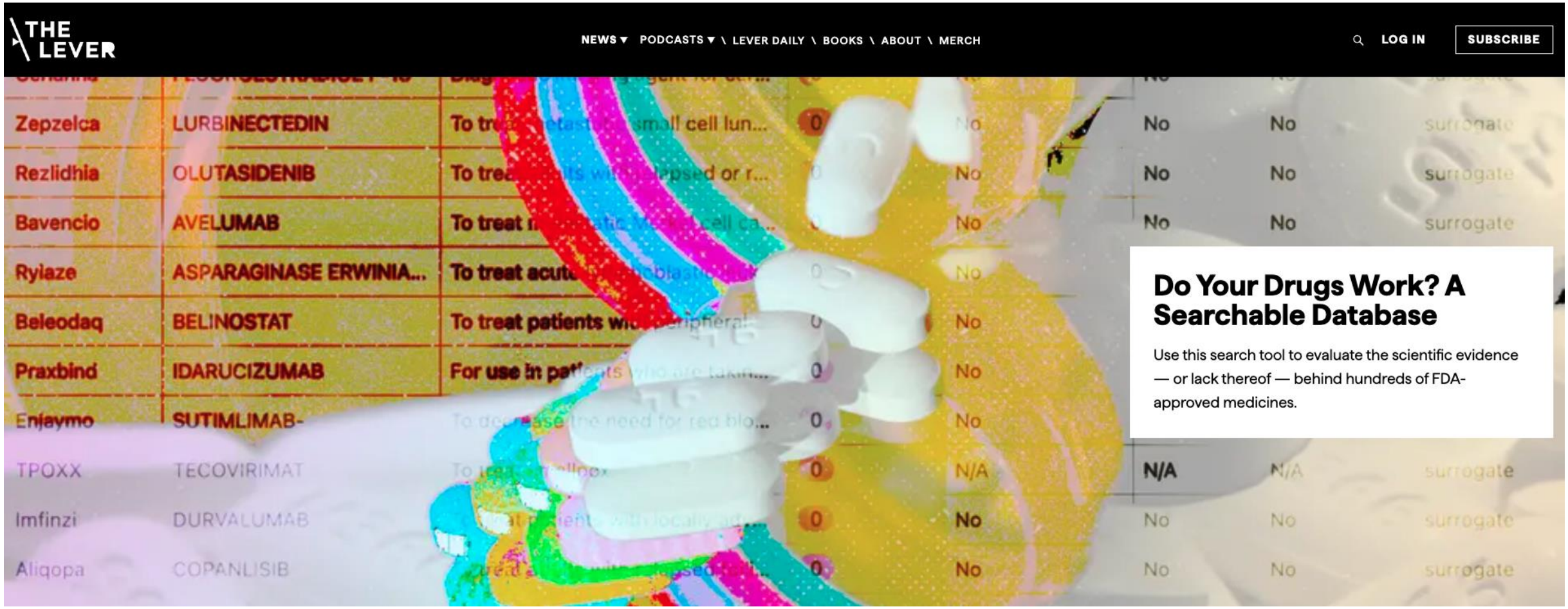
of preprints published in 2023 were also published in peer-reviewed journals as of December 2024



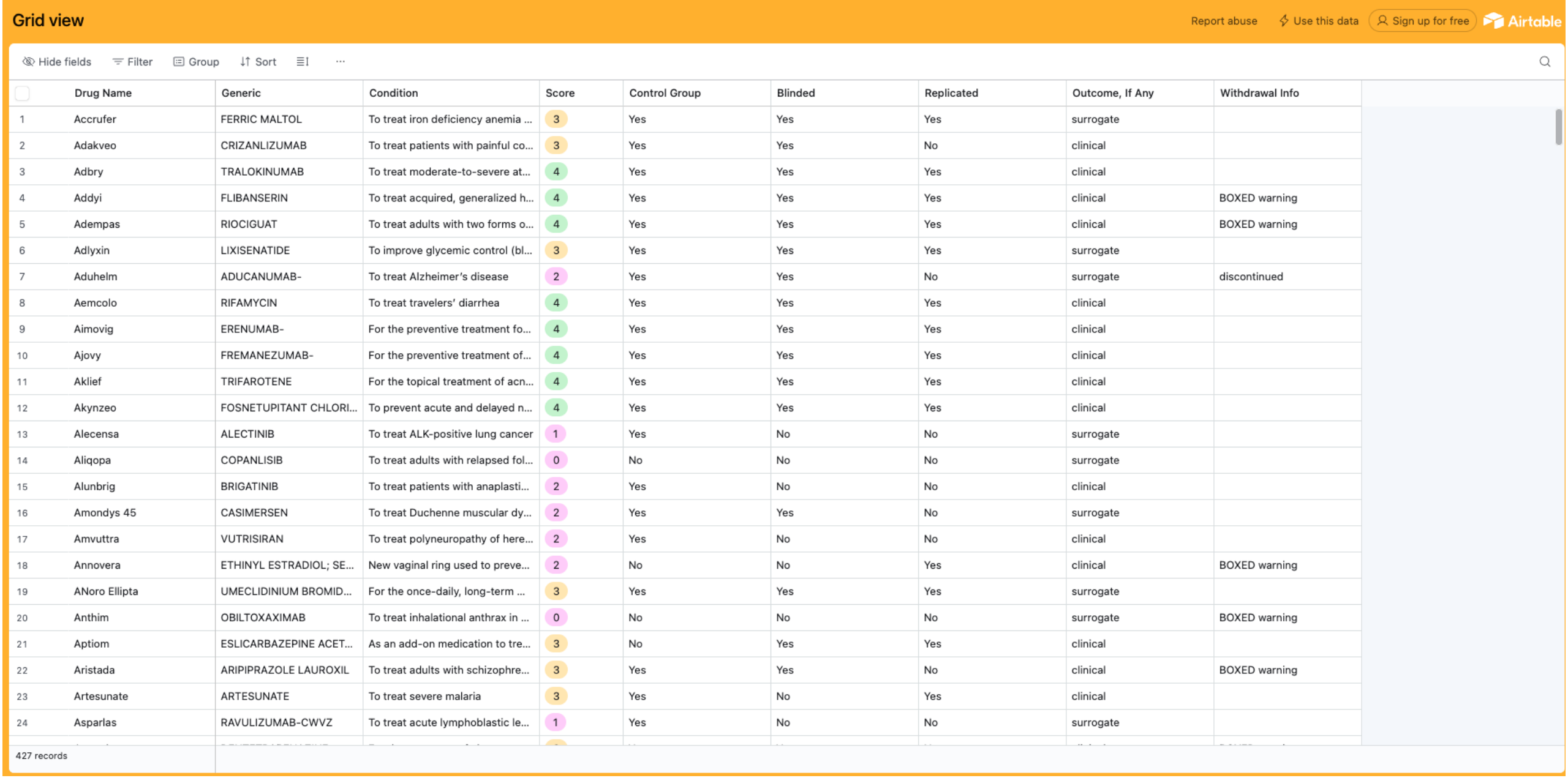
Any Data (DAS) or Code Availability Statement (CAS)

Any Open Data

Any Open Code



The Lever June 5 , 2025



	Drug Name	Generic	Condition	Score	Control Group	Blinded	Replicated	Outcome, If Any	Withdrawal Info
1	Accrufer	FERRIC MALTOL	To treat iron deficiency anemia ...	3	Yes	Yes	Yes	surrogate	
2	Adakveo	CRIZANLIZUMAB	To treat patients with painful co...	3	Yes	Yes	No	clinical	
3	Adbry	TRALOKINUMAB	To treat moderate-to-severe at...	4	Yes	Yes	Yes	clinical	
4	Addyi	FLIBANSERIN	To treat acquired, generalized h...	4	Yes	Yes	Yes	clinical	BOXED warning
5	Adempas	RIOCIGUAT	To treat adults with two forms o...	4	Yes	Yes	Yes	clinical	BOXED warning
6	Adlyxin	LIXISENATIDE	To improve glycemic control (bl...	3	Yes	Yes	Yes	surrogate	
7	Aduhelm	ADUCANUMAB-	To treat Alzheimer's disease	2	Yes	Yes	No	surrogate	discontinued
8	Aemcolo	RIFAMYCIN	To treat travelers' diarrhea	4	Yes	Yes	Yes	clinical	
9	Aimovig	ERENUMAB-	For the preventive treatment fo...	4	Yes	Yes	Yes	clinical	
10	Ajovy	FREMANEZUMAB-	For the preventive treatment of...	4	Yes	Yes	Yes	clinical	
11	Aklief	TRIFAROTENE	For the topical treatment of acn...	4	Yes	Yes	Yes	clinical	
12	Akynzeo	FOSNETUPITANT CHLORI...	To prevent acute and delayed n...	4	Yes	Yes	Yes	clinical	
13	Alecensa	ALECTINIB	To treat ALK-positive lung cancer	1	Yes	No	No	surrogate	
14	Aliqopa	COPANLISIB	To treat adults with relapsed fol...	0	No	No	No	surrogate	
15	Alunbrig	BRIGATINIB	To treat patients with anaplasti...	2	Yes	No	No	clinical	
16	Amondys 45	CASIMERSEN	To treat Duchenne muscular dy...	2	Yes	Yes	No	surrogate	
17	Amvuttra	VUTRISIRAN	To treat polyneuropathy of here...	2	Yes	No	No	clinical	
18	Annovera	ETHINYL ESTRADIOL; SE...	New vaginal ring used to preve...	2	No	No	Yes	clinical	BOXED warning
19	ANoro Ellipta	UMECLIDINIUM BROMID...	For the once-daily, long-term ...	3	Yes	Yes	Yes	surrogate	
20	Anthim	OBILTOXAXIMAB	To treat inhalational anthrax in ...	0	No	No	No	surrogate	BOXED warning
21	Aptiom	ESLICARBAZEPINE ACET...	As an add-on medication to tre...	3	No	Yes	Yes	clinical	
22	Aristada	ARIPIPRAZOLE LAUROXIL	To treat adults with schizophre...	3	Yes	Yes	No	clinical	BOXED warning
23	Artesunate	ARTESUNATE	To treat severe malaria	3	Yes	No	Yes	clinical	
24	Asparlas	RAVULIZUMAB-CWVZ	To treat acute lymphoblastic le...	1	Yes	No	No	surrogate	

https://www.levernews.com/do-your-drugs-work-a-searchable-database/

Importance of web tools

- Awareness of regulatory and evidentiary issues, not only the scientific community but also for patients and the public
- Greater commitment to Open Science, also to avoid redundancy
- Discussions should remain science-driven, not driven by sensation or hype

Structure

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Conclusion

- The strength of evidence supporting drug approval varies considerably
- Regulatory oversight and compliance are not always assured
- Greater awareness and public accountability are essential

What we need!

More and better research in Germany

(going beyond US Focus)

Bigger focus on innovative and next-generation therapeutics

Active Monitoring of Therapeutics and Postapproval Requirements via Dashboards

Thank You

Maximilian_siebert@hms.harvard.edu