

Opportunities and Challenges Managing Access in Rare Cancers: An Industry Perspective

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***CDDF Multi-stakeholder Workshop on Innovation
and Access in Rare Cancers***

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Content

- Terminology used in Early Access
- Regulatory landscape
- Examples
- RWD
- Awareness

Definition Regulators CU



EMA

EMA Article 83/2 (EC No726/2004): ... 'compassionate use' shall mean making a medicinal product belonging to the categories referred to in Article 3(1) and (2) available for compassionate reasons **to a group of patients with a chronically or seriously debilitating disease** or whose disease is considered to be **life-threatening**, and who can not be treated satisfactorily by an authorised medicinal product. The medicinal product concerned must either be the subject of an application for a marketing authorisation in accordance with Article 6 of this Regulation or must be undergoing clinical trials.

Article 5 of Directive 2001/83/EC provides a legal basis to MS to allow the **supply of unauthorised medicines to single patients**.

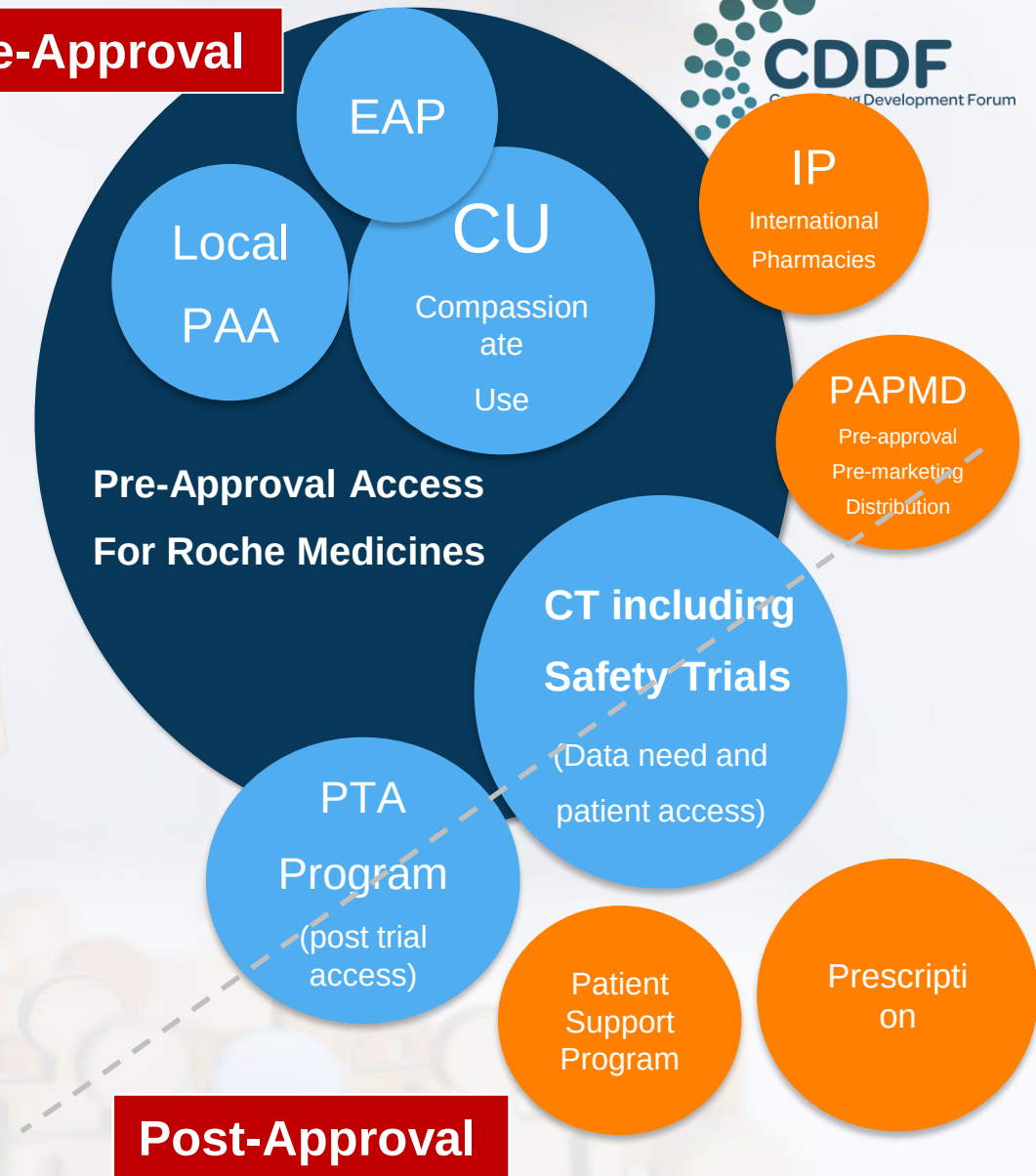
FDA

Sometimes called "compassionate use", **expanded access** is a potential pathway **for a patient with a serious or immediately life-threatening disease or condition** to gain access to an investigational medical product (drug, biologic, or medical device) for treatment outside of clinical trials when no comparable or satisfactory alternative therapy options are available.

Other terms

- Managed Access
- Extended access
- Early Access
- Named patient supply
- Special Access Scheme
- Personal Importation
- MNP in Belgium
- EAMS in UK
- Formerly ATU – AAP (early access authorization) and AAC (compassionate access authorization) in France

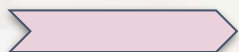
Pre-Approval



Regulatory challenges



Issue	Consequence
Compassionate Use Cohort v. individual patient requests: either in different regulations (like EMA) or not clarified at all.	Lack of clarity, country by country interpretation and respective diverse regulation.
Menu of different terminologies for compassionate use / pre-approval access, non existent for post trial access	Regulations use different terms - confusion for different actors in the healthcare system
Different Label requirement for unauthorized medicines cross EU (e.g. Special labels in France for cohort, Germany: statement for CU only; sometimes local language needed, sometimes English or French is fine e.g. Romania)	No harmonization, tailored labels required country by country, tedious and time consuming setup of CU programs
Free of charge versus paid compassionate use: some countries mandate a price, some require a symbolic price, some it is optional or not regulated (mostly free of charge)	Differences for patients depending on where patients live
Data collection in patient access programs - lack of guidance, not allowed in some countries	No consistency, poor data quality, missed opportunities for data collection in rare and pediatric settings leading to a delay in approval



Patient inequity, time to access varies depending on the location!

RWD

- RWD in compassionate use programs is being used more and more in rare diseases for Health Authority submissions for market approval*
- Regulations not clear, high variety (France most advanced in regulation)
- Data regarded in different ways by HA, e.g. pivotal data v. supportive

* RWD: [Expanded Access as a source of real-world data: An overview of FDA and EMA approvals - Polak - 2020 - British Journal of Clinical Pharmacology - Wiley Online Library](#)

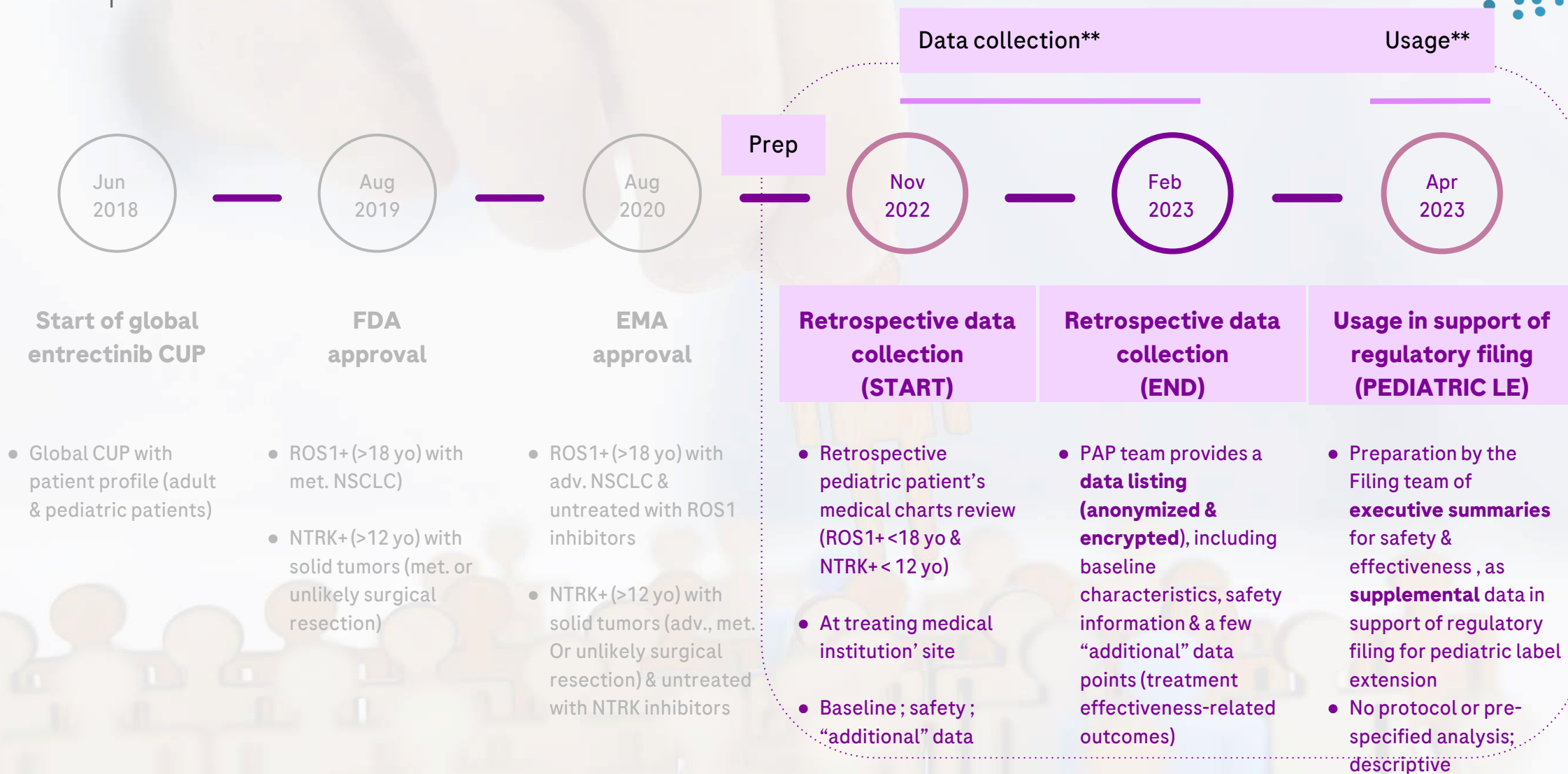
Industry case example

Data collection in pediatric patient with ROS1+ and NTRK+ solid tumors.

Data collection & usage_Entrectinib pediatric



Request & timelines



** ONLY IF permitted by country's laws & regulations AND with patient's specific consent (ascent) for data collection/usage

Data collection & usage_Entrectinib pediatric



Results

CLINICAL STUDIES

- **Pediatric patients** in entrectinib clinical studies:
- NTRK < 12 yo : N = 33 / 39* / 44**
- ROS1 < 18 yo : N = 16

*90 day update ** annual update

COMPASSIONATE USE PROGRAM

- **8 countries** with pediatric patients, treated (at least one dose)
- **3 countries** allowing data collection & usage
- **Pediatric patients** in entrectinib global CUP; treated (at least 1 dose) : N = 23
- Of whom, consent for data collection was granted : N = 16
- **NTRK < 12 yo : N = 13**
- **ROS1 < 18 yo : N = 3**

Anonymized CUP data provided as supplemental data to support regulatory pediatric label extension (FDA & EMA)*

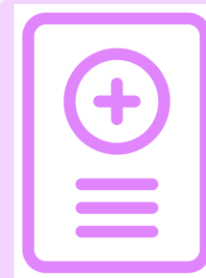


Safety

- Aggregate executive safety summary***
- All 16 pediatric patients (NTRK & ROS1)
- All patients < 12 yo
- Reported AEs consistent with safety profile observed in pediatric patients in clinical studies
- No discontinuation due to AEs

Effectiveness

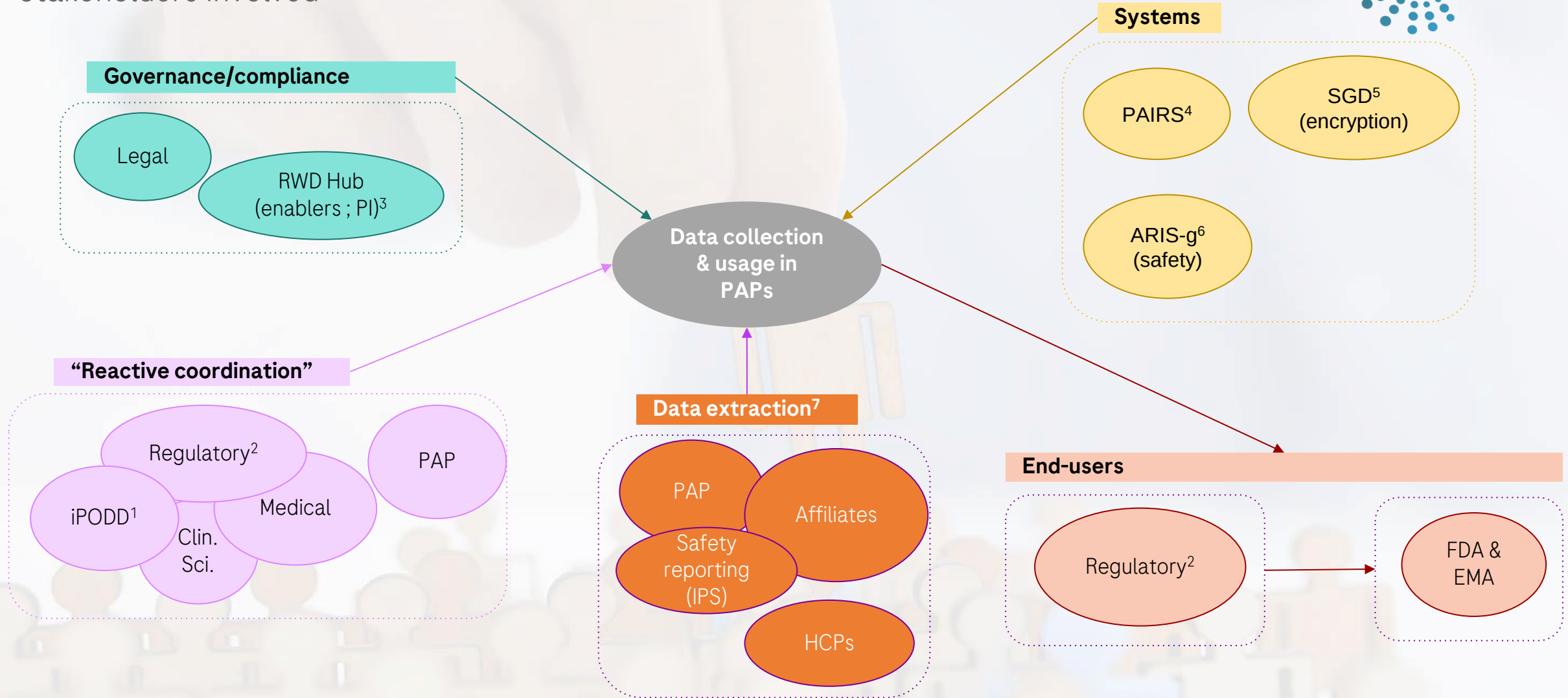
- Aggregate executive effectiveness summary*
- All 16 pediatric patients (ROS1 & NTRK for EU submission)
- Data points: patients' baseline characteristics, DoT, TTR, DoR, reason for discontinuation



***Clinical Overview Documents

Data collection & usage_Entrectinib pediatric

Stakeholders involved



¹iPODD: Investigative Pediatric Oncology Drug & Development ; ²Regulatory Filing Team for pediatric LE ; ³RWD Hub (enablers): giving guidance for classification of the RWD activity ; ⁴PAIRS: Patient Access Integrated Registry & Supply (PAP database)
⁵SGD: Shared Google Drive (files with encryption) ; ⁶Global Safety Database (was used to recheck the safety reporting against the safety information provided within the patients' narratives) ; ⁷Data extraction done via PAIRS & patient narratives completed retrospectively by HCPs based on patients medical charts (including effectiveness & safety)

FDA expands pediatric indication for entrectinib and approves new pellet formulation



On October 20, 2023, the Food and Drug Administration granted accelerated approval to entrectinib (Rozlytrek, Genentech Inc.) for pediatric patients older than 1 month with solid tumors that have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have progressed following treatment or have no satisfactory standard therapy. In August 2019, FDA granted accelerated approval to entrectinib for pediatric patients 12 years of age and older for this indication.

FDA also approved a new oral pellet formulation for entrectinib, and the prescribing information now includes instructions for making an oral suspension from the capsules.

<https://www.fda.gov/drugs/resources-information-approved-drugs/fda-expands-pediatric-indication-entrectinib-and-approves-new-pellet-formulation>

https://www.ema.europa.eu/en/documents/smop/chmp-post-authorisation-summary-positive-opinion-rozlytrek-x-17-g_en.pdf



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 April 2024
EMA/CHMP/169495/2024
Committee for Medicinal Products for Human Use (CHMP)

Summary of opinion¹ (post authorisation)

Rozlytrek

On 25 April 2024, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending a change to the terms of the marketing authorisation for the medicinal product Rozlytrek. The marketing authorisation holder for this medicinal product is Roche Registration GmbH.

The CHMP adopted a new pharmaceutical form, 50 mg film-coated granules, a new gastrointestinal route of administration for the 100 and 200 mg hard capsules, and an extension to an existing indication for film-coated granules and hard capsules, as follows:²

Neurotrophic tyrosine receptor kinase (NTRK) gene fusion

Rozlytrek as monotherapy is indicated for the treatment of adult and paediatric patients ~~12- years of age and older~~ **than 1 month** with solid tumours ~~expressing that have a neurotrophic-tyrosine receptor kinase (NTRK) gene fusion,~~

- who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and
- who have not received a prior *NTRK* inhibitor
- who have no satisfactory treatment options (see sections 4.4 and 5.1).

Awareness Early Access



- Currently no central registry for Compassionate Use
- Some companies publish their Compassionate Use programs on their websites
- Some online training for Compassionate Use available
- Some HA publish compassionate use programs
 - UK: <https://www.gov.uk/government/collections/early-access-to-medicines-scheme-eams-scientific-opinions>
 - France: All cohort programs are published on the website of the French Health Authority: <http://ansm.sante.fr/>.
 - US: Expanded Access Programs in the US on clinicaltrials.gov
 - EMA: only for programs for **which Member states requested CHMP opinion, 6 in the last 14 years**

What is ongoing at the moment?



- **EuropaBio** supports requesting more harmonization on CU in the context of the revision of the pharma legislation.
- Members of **Novartis, Merck, Roche** working with EFPIA – proposal (reactive) for EU pharma legislation
- Paper (above companies +**Sanofi**) to publish pain points based on industry data

Future Ideal State



- **Clarity & simplified process** on CU for patients, HCPs & industry
- **Harmonized Framework** for Compassionate Use in the Europe
- Increased Transparency e.g. compassionate use programs published in a **database/registry** (similar to FDA clinicaltrials.gov, France and UK mandate it)
- Revised **EMA guidance for CU** by outlining standardized technical requirements
- Vision: **One global** harmonized framework
- Foster **innovation**
 - Use RWD/RWE for approvals in rare cancers
 - External control arms
 - AI

Conclusion & Recommendation



- Agree and harmonize **definition** / terms globally
- Clear **roles & responsibilities** of all stakeholders
- **Harmonization** of regulatory **requirements**: consenting, product source of supply, labelling, QP release, importation, safety reporting requirements, individual & group CU
- **RWD/RWE** generated outside of CT should be used **consistently**
- Implement learnings from Covid-19 **pandemic**

Conclusion & Recommendation



- **Revised European guideline** on compassionate use covering single and cohort CU
- Appropriate change in the new **EU Pharma regulation** and directive might bring clarity
- More conversation and **harmonization** on CU across member states is needed
- **Same requirements** at a MS level for the overall CU request process / documentation
- Taking account of **any available opinions** on CU in the Member state to notify EMA - More reliance on CU

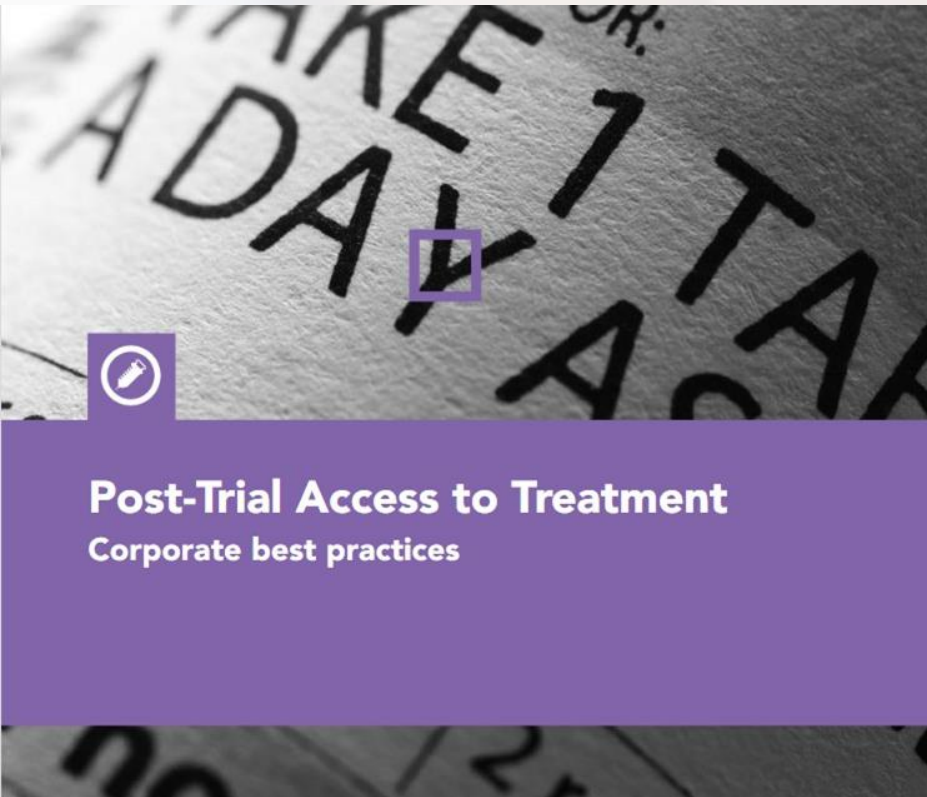


BKUP / ADDITIONAL SLIDES

Regulatory Challenges



Specific call out for Post Trial Access



*"In advance of a clinical trial, sponsors, researchers **and host country governments** should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process."*

- **Article 34**, Declaration of Helsinki 2013

Future Ideal State



Table. The 8-Factor Framework for CU Regulations

Regulatory robustness factor	Description
1. Roles of involved stakeholders	To eliminate unnecessary delays in patient access, robust CU regulations will define the roles of the various stakeholders involved (ie, HAs, EC/IRB, HCPs, pharmaceutical companies) throughout the life cycle of a CU request.
2. CU request process	A well-defined and publicly available application process can reduce uncertainties and enable HCPs to easily request CU. Scope and scenarios covered by the regulations, CU access criteria, pathways (ie, individual and cohort access) and duration of access should be outlined.
3. Involvement of HA in request evaluation	HA involvement in the evaluation of a CU request supports legitimation. HAs can act as facilitators of the process to enable patient access.
4. EC/IRB review	Approval by an EC/IRB should be a requirement for treatments via CU as it ensures that ethical and medical standards are being met and promotes consistent oversight.
5. Informed consent requirements	Obtaining patient informed consent prior to treatment via CU is the treating physician's responsibility. Informed consent ensures that patients understand all known risks and benefits.
6. Documentation requirements	The outline of the documentation required can help to eliminate delays and enable consistency in processing requests.
7. Drug importation/shipment process	Both geopolitical and logistical considerations play important roles during import and shipment. Well-defined, simplified, and pragmatic processes and requirements would prevent substantial delays and enable speedy product delivery to the patient.
8. AEs/safety reporting requirements	The reporting of AEs and other safety reporting responsibilities for HCPs and pharmaceutical companies is an important factor to be outlined in the regulatory framework. However, this factor should be limited to the reporting of key safety information only to reduce the burden on HCPs.

Abbreviations: AE, adverse event; CU, compassionate use; EC, ethics committee; HA, health authority; HCP, health care professionals; IRB, institutional review board.