EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Mini-COMP and mini-SAWP

Background, Questions **and Answers** (for presentation)

EURODIS Open Academy
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PART 1

Application for orphan designation (OD)

Orphan designation (OD)

What?

OD is an **special status** granted to medicinal products which provides companies with certain **benefits.**

It is optional for Sponsors, not mandatory.

Why?

- **Encourages Development**: It incentivizes companies to develop treatments for rare diseases that might otherwise be neglected due to limited market potential.

What are the benefits?

- **Fee Reductions for regulatory activities**: Making the development process more affordable.
- **Market Exclusivity**: a period of about 10 years in which the medicinal products are protected against the authorization of similar competitor products, encouraging investment in research and development.

Application for orphan designation

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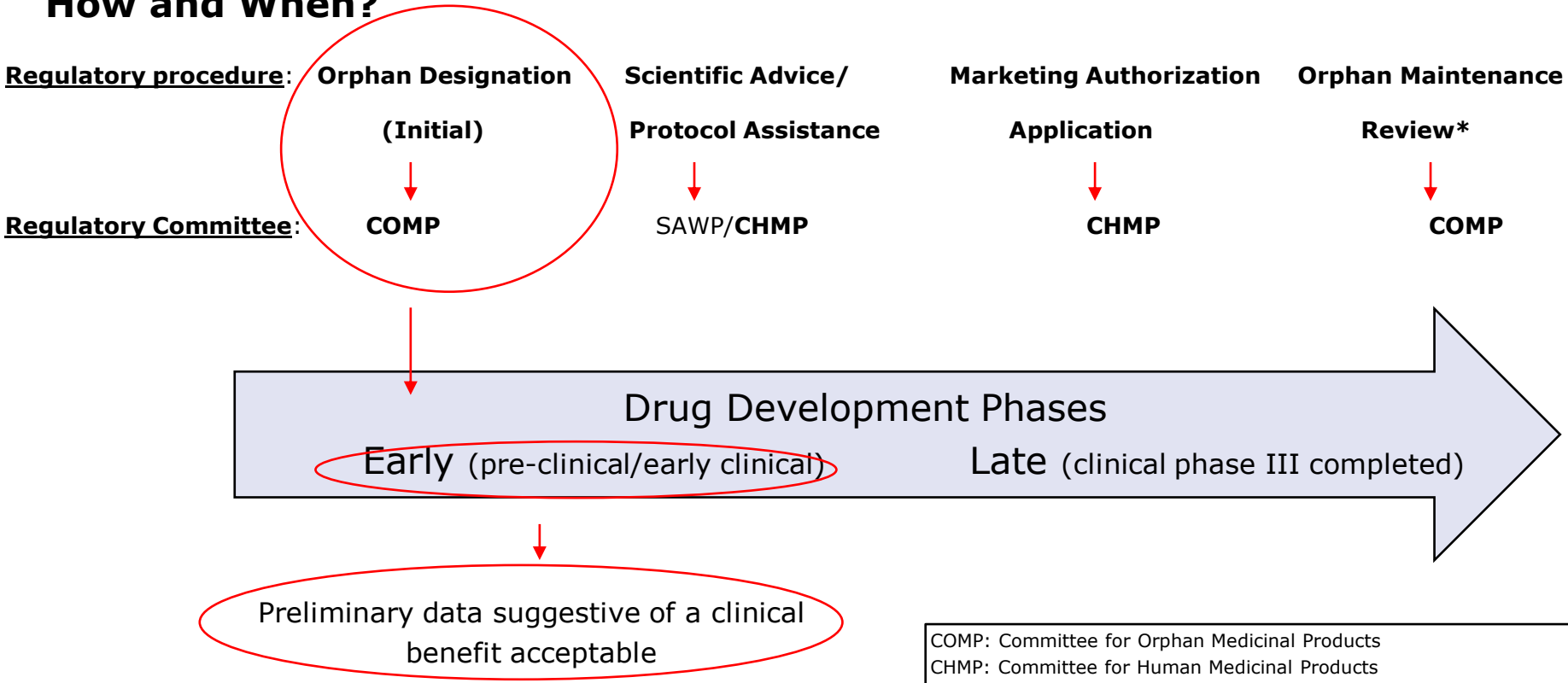
How and When?



COMP: Committee for Orphan Medicinal Products
CHMP: Committee for Human Medicinal Products
SAWP: Scientific Advice Working Party (linked to CHMP)
*Orphan Maintenance Review around the time of Marketing Authorization

Orphan designation (OD) criteria (EU)

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1.Orphan Condition:

- The medicine must be intended for **treatment, prevention, or diagnosis** of a condition that is 1) a **broad distinct disease entity** (not disease subset), and 2) is **life-threatening and/or chronically debilitating**.

2.Prevalence:

- The **prevalence** of the condition in the EU must **not** be **more** than **5 in 10,000** individuals (~ below 250.000)

3.Medical Plausibility:

- Is there a **biologic rationale** for the proposed drug to improve the condition? What is the **pre-clinical or clinical data to show the (potential) benefits** -> as minimum pre-clinical data in a valid animal model is required showing a benefit of the drug (i.e. functional/symptomatic improvement)

4. Significant Benefit:

- Only applicable if authorized products for condition exist in the EU -> if yes, new drug must demonstrate **significant benefit** over these **authorized drugs** by means of showing 1) **improved efficacy or safety** or 2) a **major contribution to patient care** (MCPC) -> note: MCPC requires demonstration of at least equivalent efficacy and safety as compared to the authorized products (MCPC could be derived through change in formulation or route of administration which leads to a decrease in patient burden

Application for orphan designation (OD)

Your Task:

You are the Committee for Orphan Medicinal Products (COMP) and need to review the following hypothetical application for OD and decide if product can be designated:

Sponsor: Gaudipharm

Condition: Cystic fibrosis

Medicinal Product: Antonicaftor, tablet (2 cm length), oral administration 2 times per week

Mechanism of action: drug acts as a so called “potentiator” of the defective chloride channel (CFTR) and helps increasing the “channel-open” probability (or gating) and thereby enhancing chloride transport across cell membranes in various organs, incl lung.

Background information on proposed condition

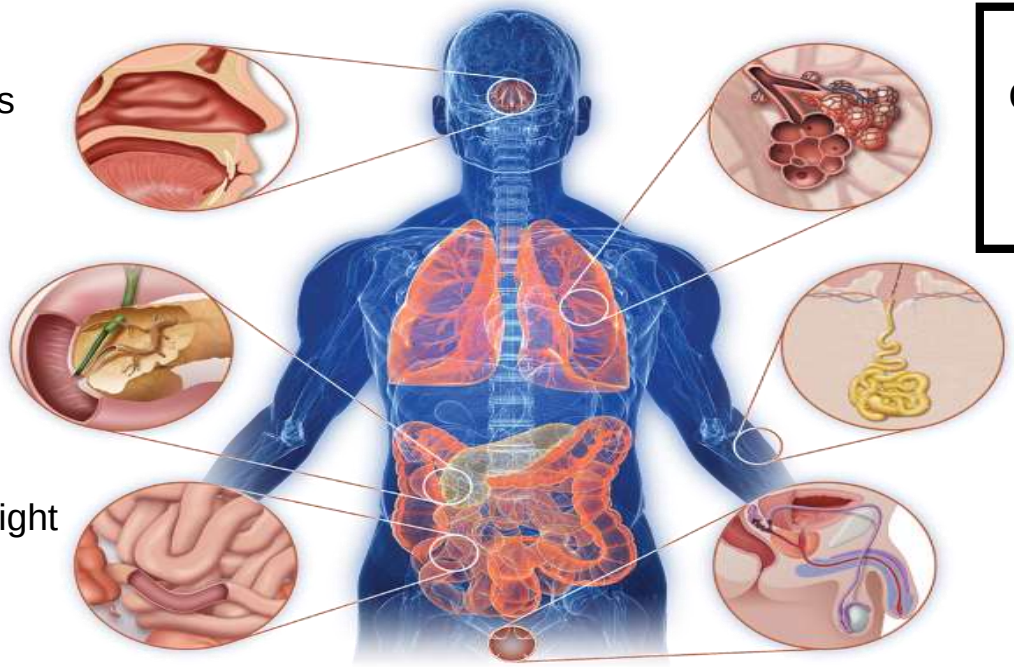
Cystic fibrosis (CF)

O'Sullivan BP, Freedman SD. *Lancet.* 2009;373:1891-1904.

Sinusitis
Nasal polyps

Pancreatic insufficiency leading to malnutrition
CF-related diabetes
Liver disease

Failure to thrive/gain weight
Digestive problems
Intestinal blockages



Reduced lung function
Chronic lung infections
Lung inflammation
Damaged Airways

Salty sweat

Reduced fertility
Infertility

Frequent hospitalizations and medical appointments, emotional and psychological strain due to chronic illness.

Reduced life expectancy compared to general population (~40 years).

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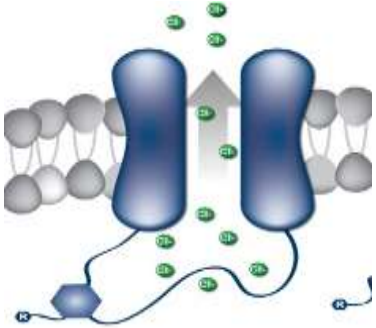
Pathophysiology of CF Lung Disease

Genetic mutations in the chloride ion channel called CFTR -> defective ion transport

CFTR is widely expressed in body, particularly the lung, pancreas and skin

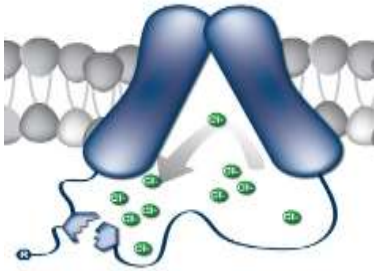
Lung: Thickened secretions and mucus accumulation -> lung infection and inflammation

Normal



CF

and/or



Is the condition life-threatening and/or seriously debilitating?

- ❑ Yes
- ❑ No

Is the condition a distinct medical entity, suitable for orphan designation?

- ❑ Yes
- ❑ No

Is the condition life-threatening and/or seriously debilitating?

- ❑ **Yes**
- ~~❑ No~~

Is the condition a distinct medical entity, suitable for orphan designation?

- ❑ **Yes**
- ~~❑ No~~

What is the estimated number of patients affected by the condition in the EU?

Sponsor conducted a comprehensive review of publications reporting epidemiologic data from the EU on the proposed condition CF (incl from recent years).

Only yearly incidence data was available which was on average ~ 0.025 per 10,000 persons.

In order to derive the prevalence from incidence data, one can use the formula of:

Prevalence per 10,000 = Incidence per 10,000 X Disease Duration or Life Expectancy for this condition

(tip: the information on approx. life expectancy in CF can also be found in the slide set ☺)

What is the prevalence of the Condition and is it acceptable according to the criteria?

- ❑ Yes
- ❑ No

What is the prevalence of the Condition and is it acceptable according to the criteria?

- ❑ **Yes**
- ~~❑ No~~

Prevalence per 10,000 = Incidence per 10,000 X Disease Duration or Life Expectancy for this condition

1 = 0,025 X 40 (years)

Conclusion adopted is that cystic fibrosis affects approximately 1 in 10,000 people in the European Union (EU). This was equivalent to a total of around 50,000 people (assuming an EU population of 500 million).

Medical Plausibility

Mechanism of action:

Antonicaftor has disease modifying intent by restoring the function of the defective chloride-ion channel, so chloride ions can be efficiently transported again into and out of cells. This is intended to help maintain the proper level of salt and water on airway surfaces, reducing the formation and accumulation of mucus in the lung, and thus improving the symptoms of the disease.

Data to support the medical plausibility:

Non-clinical data from a valid rat model of the condition has been provided.

Results demonstrate 1) improved chloride channel (CFTR) function in lung tissue (extracted from previously treated vs untreated animals) -> Ussing Chamber Assay, measuring ion transport across the lung epithelium, and 2) improved lung function -> Negative Pressure-Driven Forced Expiratory (NPFE) testing which assesses expiratory flow and volume.

Has the Company shown Medical Plausibility for the claimed activity of their product (mechanism of action & efficacy)?

- ❑ Yes
- ❑ No

Has the Company shown Medical Plausibility for the claimed activity of their product (mechanism of action & efficacy)?

- ❑ **Yes**
- ~~❑ No~~

Medical plausibility can be justified due to:

- ➔ Strong biologic rationale
- ➔ Data demonstrating functional improvement (improved chloride channel function & improved lung function in an in vivo disease model)

Existing Methods

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For the purpose of our example (old days), standard of care authorized pharmacologic treatments for CF exist in EU, incl:

Antibiotics, anti-inflammatory drugs, and mucus thinners.

Note: no disease modifying therapies are available at this time (i.e. drugs that correct the underlying defect of CF)

Is significant benefit applicable here and why/why not?

- ❑ Yes
- ❑ No

Is significant benefit applicable here and why/why not?

- ❑ **Yes, because authorized pharmacologic treatments for CF exist in EU**
- ❑ ~~No~~

Significant benefit

The sponsor refers to the same data as submitted in support of medical plausibility, see described in earlier slide above (i.e. non-clinical data from a valid rat model of the condition).

Would this data be sufficient to support the significant benefit over existing authorized medicines for CF?....and why yes or why no?

- ❑ Yes
- ❑ No

Significant benefit

Would this data be sufficient to support the significant benefit over existing authorized medicines for CF?....and why yes or why no?

- ❑ **Yes**
- ❑ **No**

➔ In principle it could be either of the two!

➔ On the negative side: the sponsor has not shown how the described benefits of the drug compare to the ones achieved with the authorized drugs.

➔ On the positive side: the new drug brings a possible fundamental improvement due to its disease modifying mechanism of action (MoA), which cannot be expected from currently authorized symptomatic therapies; also, the sponsor has demonstrated that this novel MoA translates into functional benefits. Also, the new drug could be used in combination with the existing drugs, due to complementary MoAs.

➔ Personally: I would be positive for this application, also acknowledging the early stage of development (only non-clinical efficacy data available) but I would recommend Scientific Advice/Protocol Assistance

PART 2

Application for Scientific Advice /Protocol Assistance

Scientific Advice/Protocol Assistance

Regulatory procedure:	**Orphan Designation (Initial)**	**Scientific Advice/ Protocol Assistance**	**Marketing Authorization Application (MAA)**	**Orphan Maintenance Review**
Regulatory Committee:	**COMP**	SAWP/CHMP	**CHMP**	**COMP**

COMP: Committee for Orphan Medicinal Products
CHMP: Committee for Human Medicinal Products
SAWP: Scientific Advice Working Party (linked to CHMP)

Scientific Advice (SA)/Protocol Assistance (PA)

-> general information

Terminology:

- It's **SA** if there is no Orphan Designation for this product in the applied for condition -> full fees
- It's **PA** if there is Orphan Designation for this product in the applied for condition -> reduced fees

It is **optional** for Sponsors, not mandatory (even though it was strongly recommended by COMP).

It can be requested from EMA **at any time** throughout the drug development, on **any aspects** (incl Quality, Non-clinical, Clinical development and Regulatory aspects) and **as often as needed**

Advice is given by the Scientific Advice Working Party (SAWP) and is always **endorsed by** the licensing Committee (**CHMP**) -> so it will be considered a CHMP advice

If there is a question related to the **Significant Benefit** it will be referred to **COMP**

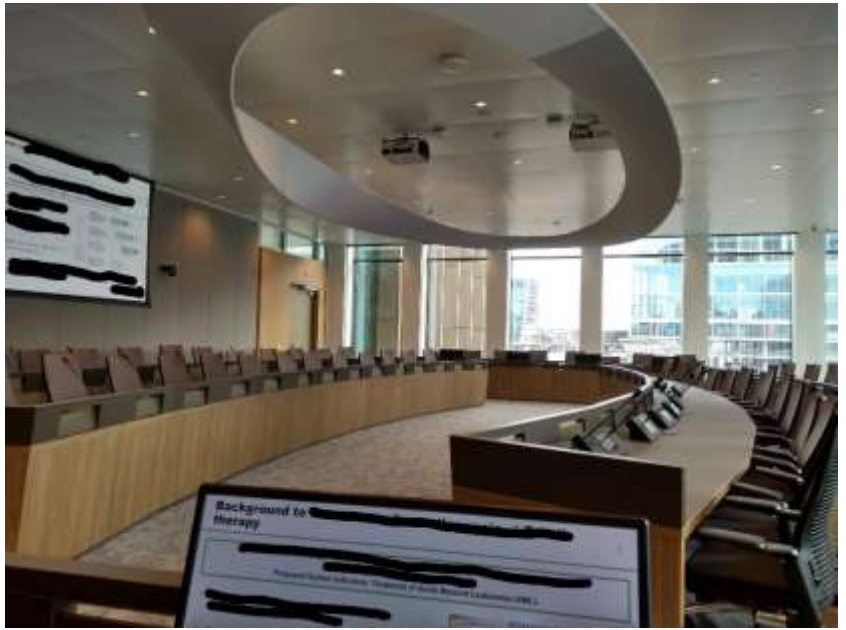
It is **strictly** a **Question (Sponsor) – Answer (SAWP/CHMP) based principle** where advice is limited to the questions asked by the Sponsor

The advice given by SAWP/CHMP is **not binding** on the Sponsor (but if not followed should be justified)

Application for Protocol Assistance

Your Task:

You are the SAWP/CHMP and need to answer the specific questions asked by the same Sponsor (Gaudipharm), for the same product and formulation (Antonicaftor) and the same condition (Cystic fibrosis), refer also to information on previous slides, as needed



Purpose of Advice

1. Discussion of key aspects of the clinical development program to support a marketing authorisation for the therapeutic indication:

- ***"Antonicaftor is indicated for the treatment of patients with cystic fibrosis from 2 years of age and older"***

2. Obtain feedback on the significant benefit in relation to the Orphan Maintenance review by the COMP, at time of MAA

Background information

Stage of drug development: Sponsor completed Non-clinical (NC) development and is about to start their clinical development

Data:

Safety and efficacy profile of antonicaftor has been well characterized in adult animals

- NC efficacy data: see in previous slides for Medical Plausibility;
- NC safety data: no adverse safety pharmacology effects (cardiovascular, central nervous system, gastrointestinal, and respiratory models), not genotoxic but teratogenic, well tolerated in acute toxicity studies up to highest doses tested, same for Repeat-dose toxicity studies up to 3 months duration in adult mice, rats but in adult dogs adverse effects on the bone were observed.

Planned pivotal licensing study:

will be a phase II study which will be single-arm, uncontrolled (Note: a pivotal licensing study is the most important study to support the marketing authorization, it should be robust and large study to allow informed conclusions on the products safety and efficacy)

Background information (ff)

Planned endpoints for pivotal phase II study:

- Primary endpoint chosen: Absolute change from baseline in percent predicted Forced Expiratory Volume in one second (FEV1) through Week 24 (*Note: it is considered the most relevant efficacy endpoint among experts to determine lung function and can be performed by adults and children from school age onwards*)
- Secondary endpoints include: body weight, number of episodes of disease worsening and a health-related quality of life (HRQoL) instrument, i.e. the Cystic Fibrosis Questionnaire-Revised (CFQ-R) through Week 24

Note: the CFQ-R includes various domains related to symptoms, physical functioning, emotional well-being, social functioning, there are 3 age specific questionnaires available, depending on patient age:

- **CFQ-R Teen/Adult**: 50 questions.
- **CFQ-R Parent**: 44 questions.
- **CFQ-R Child**: 35 questions.

Question: Does the SAWP agree that data from the nonclinical studies is sufficient for initiation of the proposed pivotal clinical phase II study in CF patients from 2 years of age?

- ❑ Yes -> Why?
- ❑ No -> Why?

Question: Does the SAWP agree that data from the nonclinical studies is sufficient for initiation of the proposed pivotal clinical phase II study in CF patients from 2 years of age?

~~❑ Yes -> Why?~~

❑ **No**

Concerns include the following:

➔ Inclusion of children from 2y of age

- Bone toxicity observed in dogs -> such effects may be exacerbated in children and might impact longitudinal growth or bone structure) -> suggestion: age staggered development (adults first) and also conduct of juvenile toxicology study to see impact of bone tox in developing organism, specific safety endpoints should be included in the clinical study to specifically monitor adverse effects on the bone/growth
- Primary endpoint cannot be measured in children below 6 years of age -> suggest age-appropriate endpoints
- A 2 cm tablet is too big for children -> suggest an age appropriate formulation

Question: Does the SAWP agree with the selected endpoints selected for evaluation in the study?

- ❑ Yes -> Why?
- ❑ No -> Why?

Question: Does the SAWP agree with the selected endpoints selected for evaluation in the study?

- ❑ **Yes** -> BUT….
- ❑ No -> Why?

Comments:

The efficacy endpoints are in principle acceptable, as they are relevant and validated for the disease BUT adjustment is recommended as regards the age appropriateness and also for the limited duration for measuring episodes of disease worsening and body weight, this should be followed up for longer; bone specific age-appropriate safety endpoints should be added (see previous comment) and followed up for longer

Health-related quality of life (HRQoL) instrument i.e. the *Cystic Fibrosis Questionnaire-Revised (CFQ-R)*, is one of the most frequently used HRQoL instruments in clinical trials in CF. It captures the impact of CF on patients' physical, emotional, and social well-being. In addition, it also captures domains like treatment burden and patient's own health perception.

Question: Does the COMP agree that this development programme and survey will support significant benefit at marketing authorisation?

The company plans conduct a phase II, single arm, open label study with Antonicaftor and compare FEV1 change from baseline.

As there are several products authorised for treatment of cystic fibrosis, we would like to question patients for their preferences using a survey.

- ❑ Yes -> Why?
- ❑ No -> Why?

Question: Does the COMP agree that this development programme and Patient Preference survey will support significant benefit at marketing authorisation?

- ~~Yes -> Why?~~
- **No** -> Why?

Likely no -> a single arm study is unlikely to justify a benefit over the authorized products due to lack of any comparator arm. Is there good natural history data and would this be enough to establish the safety and efficacy? Suggest randomized controlled study.

Patient Preference data can be meaningful but a robust methodology is important. If it remains purely hypothetical and not based on (concomitant) counter experience from a group receiving a comparator drug, it is difficult to establish a significant benefit. Also, patient preference should ideally translate into a measurable decrease in patient burden, reflected in the QoL data. Also here, just the QoL data without putting it into context of a comparator arm makes interpretation of such data very difficult.

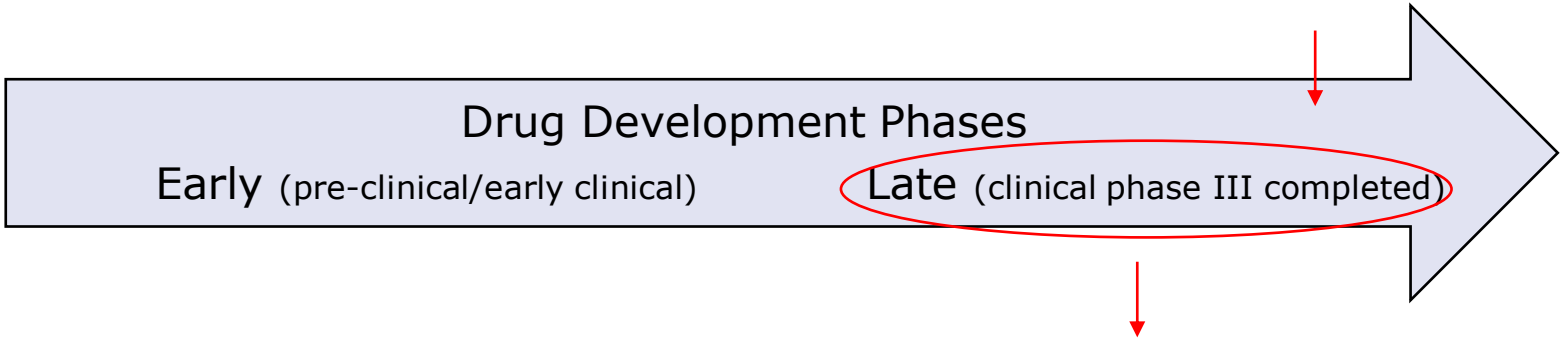
PART 3

Application for Orphan Maintenance

Application for Orphan Maintenance

How and When?

Regulatory procedure:	**Orphan Designation (Initial)**	**Scientific Advice/ Protocol Assistance**	**Marketing Authorization Application**	**Orphan Maintenance Review**
Regulatory Committee:	**COMP**	SAWP/CHMP	**CHMP**	**COMP**



Orphan designation (OD) criteria (EU)

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1.Orphan Condition:

- The medicine must be intended for **treatment, prevention, or diagnosis** of a condition that is 1) a **broad distinct disease entity** (not disease subset), and 2) is **life-threatening and/or chronically debilitating**.

2.Prevalence:

- The **prevalence** of the condition in the EU must **not** be **more** than **5 in 10,000** individuals (~ below 250.000)

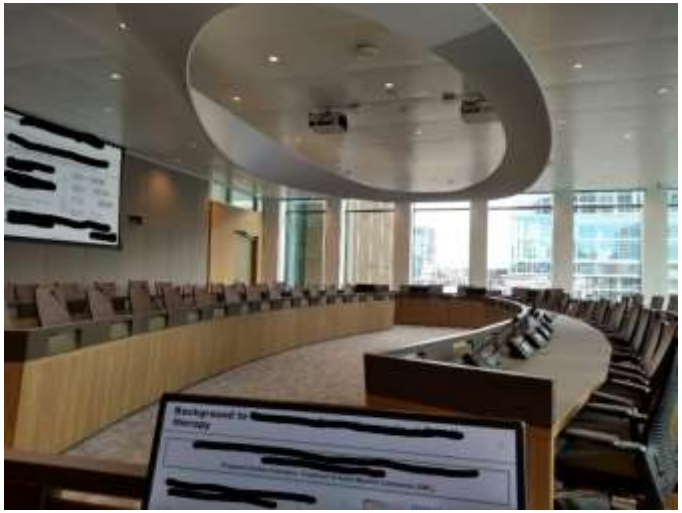
3.Medical Plausibility:

- **If the Benefit/Risk balance is positive according to the CHMP evaluation, the COMP automatically accept that the Medical Plausibility is confirmed and will not re-assess it themselves again.**

4. Significant Benefit:

- Only applicable if authorized products for condition exist in the EU -> if yes, new drug must demonstrate **significant benefit** over these **authorized drugs** by means of showing 1) **improved efficacy or safety** or 2) a **major contribution to patient care** (MCPC) -> note: MCPC requires demonstration of at least equivalent efficacy and safety as compared to the authorized products (MCPC could be derived through change in formulation or route of administration which leads to a decrease in patient burden e.g. ease of self-administration, or improved treatment adherence)

Application for Orphan Maintenance



Your Task:

You are the Committee for Orphan Medicinal Products (COMP) and need to review the following hypothetical application for OD and decide if product can **maintain its Orphan Designation** and receive the 10-year Market Exclusivity.

Stage of development: pivotal clinical study data is available, CHMP review complete and drug considered approvable (positive Benefit/Risk balance), Prevalence remains below 5 per 10,000 and the condition is still debilitating and life-threatening, BUT….

Application for Orphan Maintenance

BUT….meanwhile a new medicinal product has been authorized from different company in the EU. This new drug (Segradacaftor) has a very similar mechanism of action, is intended for the same patients (CF from 2 year of age) and has shown similar safety and efficacy based on a similar pivotal clinical study

→ As the sponsor can no longer claim improved efficacy or safety, "Major Contribution to Patient Care" (MCPC) is claimed:

- Segradacaftor is a **tablet** for once **daily** administration vs
  Antonicaftor is a **tablet** for administration **twice per week**

Application for Orphan Maintenance

Sponsor supports their Major Contribution to Patient Care (MCPC) claim for Antonicaftor with Patient Preference data (using non-validated questionnaire) from the single arm phase II study, showing that 77% of patients prefer Antonicaftor as compared to "previous experience" with current standard of care treatments, as they believe Antonicaftor has improved tolerability and needs to be taken less frequently.

Type of study	Population	Number	Variable	Outcome
Survey (non-validated questionnaire)	Patients	135	Preference of current drug in terms of tolerability compared to previous experience	77% rate current treatment as better; 23% no change
Phase II open label	Mild CF with mutation delta F508 deletion	135	FEV1	FEV1 clinically relevant improvement compared to baseline in 73% patients

Is the data presented for Antonicaftor sufficient to establish a of significant benefit over the currently authorized drugs, incl Segradacaftor?

- Yes -> Why?
- No -> Why?

Is the data presented for Antonicaftor sufficient to establish a of significant benefit over the currently authorized drugs, incl Segradacaftor?

- ~~Yes -> Why?~~
- **No** -> most likely not; the study was a single-arm study which generally makes interpretation of indirect comparisons very difficult; a non-validated questionnaire was used so concerns over methodological limitations are even higher; it is not clear which of the several authorized drugs are included in the "Previous Patient experience"; the MoA of Segradacaftor and Antonicaftor are very similar and so is the safety and efficacy data, plus these drugs are both tablets for oral administration, making it difficult to establish a significant benefit of Antonicaftor

Note: if the COMP outcome is negative, this changes nothing on the positive CHMP opinion and Antonicaftor will still be authorized and available to patients.

Thank you!