Meeting the expectation of patients with rare diseases: Regulatory pathways to facilitate access to medicine

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Medicines & Healthcare products Regulatory Agency

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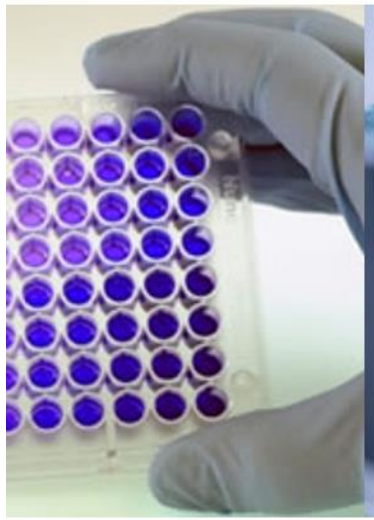




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Clinical Trials in Rare Disease – Challenges and opportunities

- Normally new drugs must demonstrate substantial evidence of clinical benefit in adequate, well-designed studies

- It is recognised that small number of patients presents challenges in the design, conduct, analysis and interpretation of clinical studies in rare diseases

- Granting of marketing authorisations (MA) on the basis of less complete data than is normally required may be feasible under some regulatory pathways

- Real-world-data (RWD) can be used pre-authorisation to inform study design and post-approval to address uncertainties at the time of licencing decision

- MHRA guidance on randomised controlled trials generating real-world evidence to support regulatory decisions will be published soon

Examples of disease areas with highly unmet medical need

Product name	Disease background	Approval Type
Luxturna (voretigene neparvovec)	➢ Leber's congenital amaurosis is an inherited retinal dystrophy estimated to affect about 1 in 80,000 individuals in the EU ➢ Patients develop progressive sight loss, starting early in life and progressing to total blindness	Full MA
BLENREP (belantamab mafodotin)	➢ Multiple myeloma (MM) is an incurable and devastating disease (incidence worldwide 1.7 per 100,000) ➢ Median OS 3-5 months	Conditional MA
Bylvay (odevixibat)	➢ PFIC is a rare disorder affecting young children that causes progressive, life-threatening liver disease with maximum life expectancy of around 20 years ➢ The prevalence of PFIC in Europe was estimated at 0.07/10,000 persons	Approval under exceptional circumstances

Example 1 - Luxturna (voretigene neparvovec)

Indication

Luxturna is indicated for the treatment of adult and paediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic RPE65 mutations and who have sufficient viable retinal cells.

Marketing authorization (MA)

Approved in the USA, **FDA Dec 2017**

Approved in the EU, **EMA Nov 2018**

https://www.ema.europa.eu/en/documents/assessment-report/luxturna-epar-public-assessment-report_en.pdf

Data

Main Studies

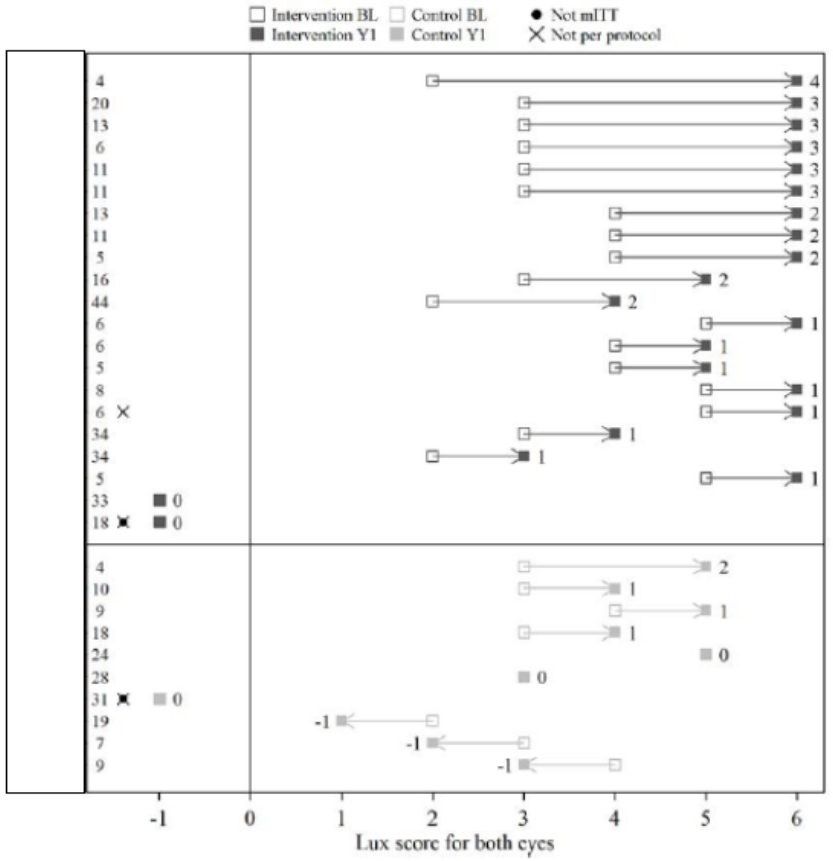
Randomised, open-label study with delayed entry design for subjects assigned first to Control (Study 301). After the first year of un-injected follow up, Control subjects were eligible to cross over to injection with AAV2-hRPE65v2 (study 302).

The primary endpoint for studies 301/302 was change from baseline to 1 year post exposure in score using the company's in-house mobility tool (MLMT). The tool returned ordinal scores between -1 and +6 (pass at 1 lux).

Supportive studies included: safety study (Study 101), follow-up study (Study 102), and a natural history study

Results (ITT population, n=31)

MLMT - Individual subject data



BL, Baseline. Age at Randomization displayed next to the Subject ID; change score displayed next to the Year 1 lux score.

Primary endpoint

Change in **MLMT** score 1 year after exposure and using binocular vision

1.6 (95% CI: 0.72, 2.41); p=0.001

Secondary endpoints:

- Full-field sensitivity threshold
- Monocular mobility testing change score
- Average change in visual acuity (averaged over both eyes) at Year 1 as compared to baseline

Supportive of primary analysis

Measures to address uncertainties

Description	Due date
SPKRPE-EUPASS: Non-interventional PASS: In order to further characterize the safety including long-term safety of Luxturna, the applicant should conduct and submit a study based on data from a disease registry in patients vision loss due to inherited retinal dystrophy caused by confirmed biallelic RPE65 mutations.	30 June 2030
AAV2-hRPE65v2-LTFU-01: In order to further evaluate the long-term efficacy and safety outcomes of Luxturna in adult and paediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic RPE65 mutations, the applicant should submit the long-term efficacy and safety follow-up of trial participants who received Luxturna in the clinical programme (15- year follow-up).	31 December 2031

Example 2 - BLENREP (belantamab mafodotin)

Indication

Blenrep is indicated as monotherapy for the treatment of multiple myeloma in adult patients, who have received at least four prior therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy.

Marketing authorisation

Accelerated approval in the USA, **FDA 5th August 2020**

Conditional MA in the EU, **EMA 25th August 2020**

https://www.ema.europa.eu/en/documents/assessment-report/blenrep-epar-public-assessment-report_en-0.pdf

Data

Six months primary results from the pivotal DREAMM-2 study (open label, randomised, two-arm, phase II study without active control arm), which enrolled patients with relapsed or refractory multiple myeloma (RRMM) who had actively progressing disease that had worsened despite current standard of care.

Primary endpoint was based on objective response rate (ORR) per IRC based on International Myeloma Working Group (IMWG) criteria

Key secondary endpoints: Duration of Response (DoR), Time to response (TTR) , Progression free survival (PFS) , and overall survival (OS)

Supportive studies included: DREAMM-1 (FIH in patients with RRMM)

Results (ITT, n=196)

- **2.5 mg/kg dose cohort:** ORR 32% (97.5% CI: 21.7, 43.6%) with a median duration of response of 11.0 months, median PFS of 2.8 months, and median OS of 13.7 months

- **3.4 mg/kg dose cohort :** ORR 35% (97.5% CI: 25%, 47%) with a median duration of response of 6.2 months, median PFS of 3.9 months

Measures to address uncertainties

Description	Due date
In order to confirm the efficacy and safety of BLENREP in relapsed/refractory multiple myeloma adult patients, who have received at least four prior therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy, the MAH should submit the results of the DREAMM-2 (205678) study investigating the efficacy of belantamab mafodotin in patients with multiple myeloma who had 3 or more prior lines of treatment, are refractory to a proteasome inhibitor and an immunomodulatory agent and have failed an anti-CD38 antibody	April 2021
In order to confirm the efficacy and safety of BLENREP in multiple myeloma adult patients, who have received at least four prior therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy, the MAH should submit the results of the DREAMM-3 (207495) study comparing the efficacy of belantamab mafodotin vs. pomalidomide plus low dose dexamethasone (pom/dex) in patients with relapsed/refractory multiple myeloma.	July 2024

Example 3 – Bylvay (odevixibat)

Indication

Bylvay is indicated for the treatment of progressive familial intrahepatic cholestasis (PFIC) in patients aged 6 months or older

Marketing authorisation

Approved under special circumstances (EMA, May 2021)

Approved in the USA (FDA, July 2021)

Approved in the UK (MHRA, Sept 2021)

https://www.ema.europa.eu/en/documents/assessment-report/bylvay-epar-public-assessment-report_en.pdf

Data

The Application was supported by a single pivotal study (**Study 005**) supported by one long-term open label follow-up study (**Study 008**) and one dose-finding study (**Study 003**).

Study 005 was a randomised double-blinded placebo-controlled study enrolling **62 paediatric patients.**

The primary efficacy endpoint was the proportion of patients experiencing at least a 70% reduction in serum bile acids (SBAs) concentration from baseline to the end of treatment or reaching a level ≤70 µmol/L (28.6 µg/mL) after 24 weeks of treatment.

Secondary endpoints included: The proportion of positive pruritus assessments at the patient level over the 24-week treatment period based on the Albireo ObsRO instrument.

Results (FAS=62)

Primary endpoint (Reduction in Serum Bile Acids Concentration from Baseline to End of Treatment)

STATISTIC	PLACEBO N=20	ODEVIXIBAT, ONCE DAILY DOSING		
		40 µG/KG N=23	120 µG/KG N=19	ALL DOSES N=42
Responders, n (%)	0	10 (43.5)	4 (21.1)	14 (33.3)
95% CI[a]	(0.00, 16.84)	(23.19, 65.51)	(6.05, 45.57)	(19.57, 49.55)

Secondary endpoint and exploratory endpoints are supportive.

Measures to address uncertainties

Description	Due date
Post-authorisation registry-based efficacy study: In order to investigate whether odevixibat treatment delays surgical biliary diversion (SBD) and/or liver transplantation (OLT), with matched comparison against untreated PFIC patients, the MAH should conduct and submit the results of a study based on data from a disease registry of patients aged 6 months or older with progressive familial intrahepatic cholestasis (PFIC) according to an agreed protocol.	Annual reports are to be submitted as part of the annual reassessment.

Other regulatory pathways at the MHRA

MHRA specific regulatory pathways to facilitate patients access to medicine and to speed up drug development in certain disease areas

- **Early Access to Medicines (EAMS)**

https://www.gov.uk/guidance/apply-for-the-early-access-to-medicines-scheme-eams

- **Innovative Licensing and Access Pathway (ILAP)**

https://www.gov.uk/guidance/innovative-licensing-and-access-pathway

Conclusion

- Convincing level of efficacy may be obtained with small number of subjects with appropriate trial design and large effect size
- Patient-centred trial designs are more likely to retain already limited numbers of patients and include outcome measures that are relevant to patients
- Regulatory pathways exist to recognise and allow some uncertainties that are inherent to trials in small populations
- Early engagement with regulator and collaborative partnerships are key to advancing drug development in rare diseases
- A positive benefit/risk balance is required for approval. Relevant and high quality RWD can support regulatory decision making

Acknowledgement

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Thank You

We can offer

- Scientific advice
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- Broader scope meetings
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