Use of Single Study plus Confirmatory Evidence Pathway

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Regulatory Standards for Effectiveness

- FDA may consider a **single AWC study** with clinically meaningful and statistically robust and very persuasive effects

- Under certain circumstances, FDA can also conclude that **one AWC clinical investigation plus confirmatory evidence** is sufficient to establish effectiveness
  - "If [FDA] determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, [FDA] may consider such data and evidence to constitute substantial evidence." (21 U.S.C. §355(d))

Source: 2019 Draft Guidance: *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* https://www.fda.gov/media/133660/download

2023 Draft CE Guidance

- Issued September 2023
- CE is defined as data drawn from one or more sources to substantiate results of one adequate and well-controlled clinical investigation
- 7 categories described in the guidance
  - Clinical Evidence from a Related Indication
  - Mechanistic or Pharmacodynamic Evidence
  - Evidence from a Relevant Animal Model
  - Evidence from Other Members of the Same Pharmacological Class
  - Natural History Evidence
  - Real-World Data/Evidence
  - Evidence from Expanded Access Use of an Investigational Drug

Source: 2023 Draft Guidance: *Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* https://www.fda.gov/media/172166/download

2023 Draft CE Guidance

- Strength of the single study and the confirmatory evidence are evaluated together
  - Considerations
    - Strength of the single study
    - Multiple sources of data available as CE
    - Disease population
    - Unmet need
    - Feasibility of conducting another study

Examples of CE in Neurology

- Omaveloxolone (Skyclarys)
- Givinostat (Duvyzat)

Specific Examples in DN1

- **Givinostat (Duvyzat)**
  - First nonsteroidal treatment for DMD approved for all patients regardless of mutation (6 years and older)
  - One adequate and well-controlled study:
    - 179 male patients on background stable doses of steroids (2:1 randomization)
    - Primary endpoint was 4 stair climb time at 18 months
    - Statistically significant less decline in time to climb 4 stairs (- 1.78 sec diff, p = 0.037)
    - Nominally significant less decline on North Star Ambulatory Assessment (p = 0.021)
  - Confirmatory evidence:
    - Pharmacodynamic effect on muscle, with nominally significant smaller mean increase in muscle fat fraction in vastus lateralis compared to placebo
    - Post hoc exploratory analysis comparing patients in open-label extension study with natural history cohorts of patients with DMD showing a benefit in the time to loss of function (including ambulation)

Specific Examples in DN1

- **Omaveloxolone (Skyclarys)**
  - First approved treatment for Friedreich's ataxia (FA)
  - One adequate and well-controlled study:
    - Primary endpoint was the modified Friedreich's Ataxia Rating Scale (mFARS) , improved at 48 weeks compared to placebo (-2.41 points, p = 0.0138)
    - Key secondary endpoints did not reach statistical significance
    - Nominal improvement in the Activities of Daily Living scale (p = 0.04)
  - Confirmatory Evidence:
    - Post hoc exploratory analysis comparing patients in the Open-Label extension for up to 3 years to a propensity-matched cohort of patients from the natural history study, nominally significant difference in mFARs at 3 years (p = 0.0002)
    - Dose-dependent increases in ferritin, a pharmacodynamic marker of Nrf2 activation
    - Supports biologic plausibility of a treatment effect


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