ATMP, Are we there yet?

Lessons from the first 22 ATMP submitted to the EMA 2001 - 2018

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INTRODUCTION
Background

- As of June 2019;
  - 25 ATMP have been submitted to the EMA since 2001
  - We took a cut-off of completion by end of 2018
  - = 22 submitted and reached a conclusion
- One will be unfamiliar to most;
  - Apligraf (manufactured by Organogenesis)
  - Submitted April 2001 by Novartis
  - Precedes Directive 2003/63/EC – first definition of ATMP
  - Today would likely be defined as somatic cell therapy.

AIMS

What can we learn from these?

- Use of scientific advice/protocol assistance
  - Are applicants using this effectively?
- Length of MAA procedure
  - The time taken for ATMP seemed to be longer than other medicines
  - Why is this?
- What other factors affect approval success?

SCIENTIFIC ADVICE

Come early, come often?

- Data from 17 Submissions (no information for others)
  - 100% of these sought advice at some point.
    - Average 2.6 requests (range 1 to 5)
    - Failed, 1.2 advices (range 1 to 2)
    - Approved, 3.1 advices (range 1 to 5)

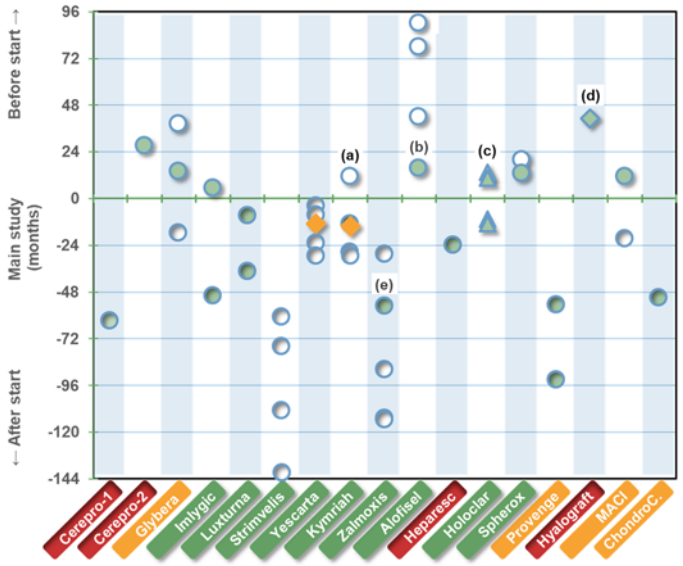
☑ Come often

- Of all medicines submitted to the EMA
  - 2000 – 2013* - Only 42% sought advice
  - 2004 – 2007** - Only 37% sought advice
  - 2008-2012*** - 62% sought advice; by 2012 this is 70%

*Hofer et al (2018) 10.1016/j.drudis.2017.10.012
**Regnstrom (2010) 10.1007/s00228-009-0756-y
***Hofer (2015) 10.1038/nrd4621

SCIENTIFIC ADVICE

Timing of advice – relative to start of the main clinical study (n=17).



- Prime
- Scientific advice
- Confirmed clinical Q's

Come early

(a) 2 main studies started within 1 month.
(b) Earlier advice was for an autologous equivalent.
(c) Retrospective analysis; date of protocol used as main trial date.
(d) No main study submitted, but advice relates to an intended main trial.

SCIENTIFIC ADVICE

But does it improve your chances of success?

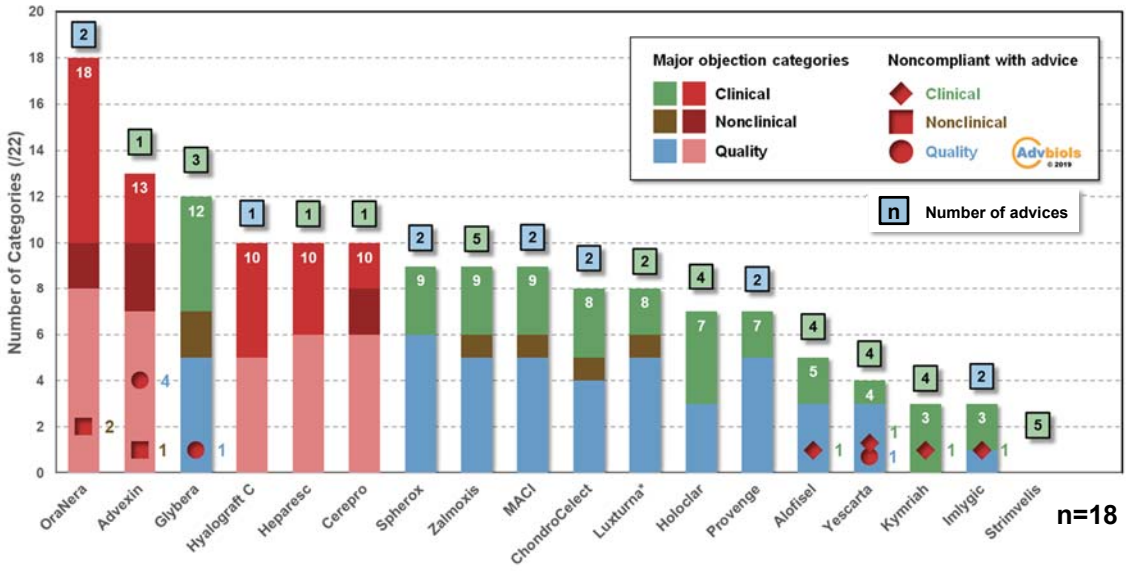
- Analysis of all EMA submissions consistently shows no difference between the chance of success between those that sought advice and those that did not.
- What matters is if you follow that advice;
  - e.g. 2008-2012*;
    - Compliant with advice – 86% approved
    - Non-compliant with advice – 41% approved

*Hofer (2015) 10.1038/nrd4621

SCIENTIFIC ADVICE

But does it improve your chances of success?

Major objections from:
Barkholt (2018) 10.1038/nrd.2018.200



SCIENTIFIC ADVICE

But does it improve your chances of success?

- All ATMP for which we have data sought ≥1 advice
  - Approved ATMP – 0.5 non-compliances (range 0 to 2; n=13)
  - Failed ATMP – 1.4 non-compliances (range 0 to 5; n=5)

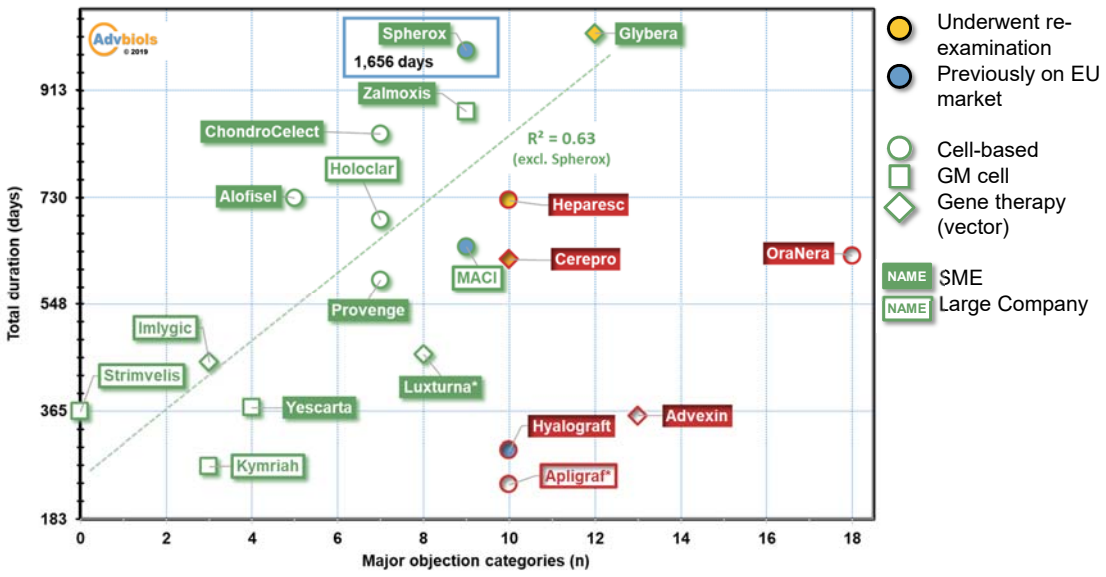
- But if you look at the impact on success;
  - Compliant with advice – 73% approved (n=11)
  - Non-compliant with advice – 71% approved (n=7)

MAJOR OBJECTIONS
What impact do these have?

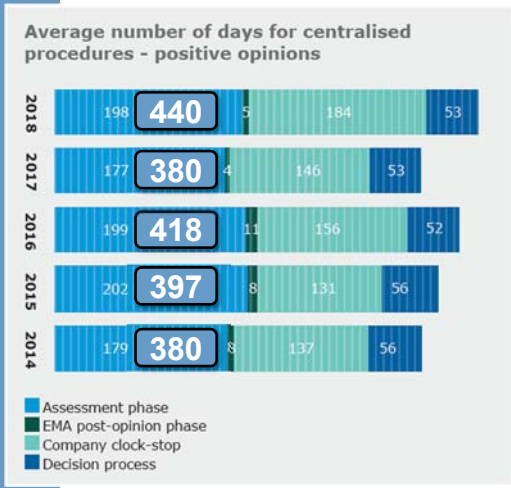
Major objections from:
Barkholt (2018) 10.1038/nrd.2018.200

- Barkholt et al defined 22 major objection categories
- 11 quality, 3 nonclinical and 8 clinical.
- ATMP average 8 major objections;
  - Approved 6.4 (0 to 12; n=13)
    - only one product had no major objections.
  - Failed 11.8 (10 to 18; n=6)

MAJOR OBJECTIONS
Impact on timelines

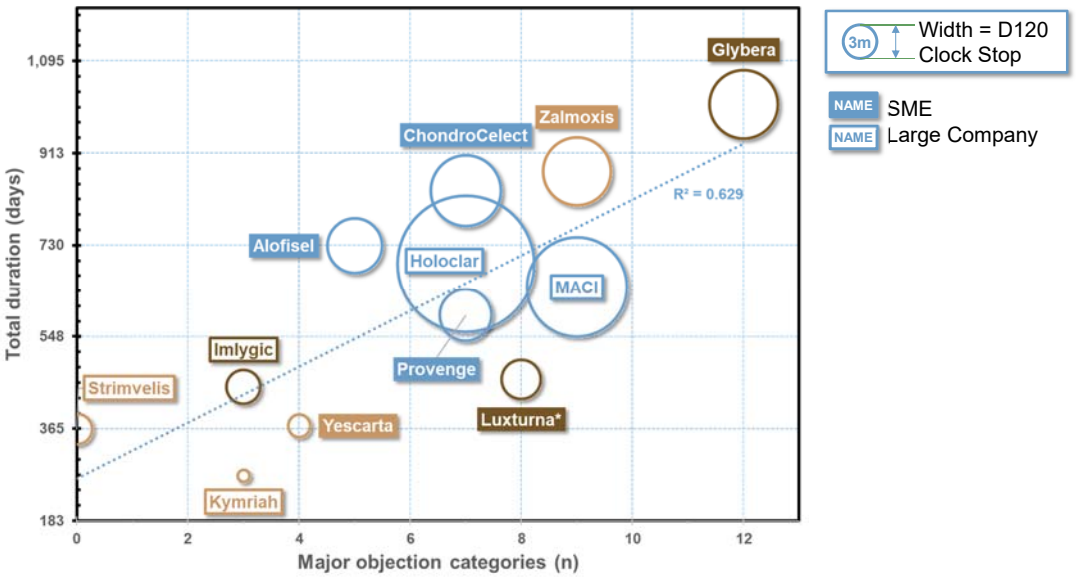


MAJOR OBJECTIONS
Impact on duration of MAA

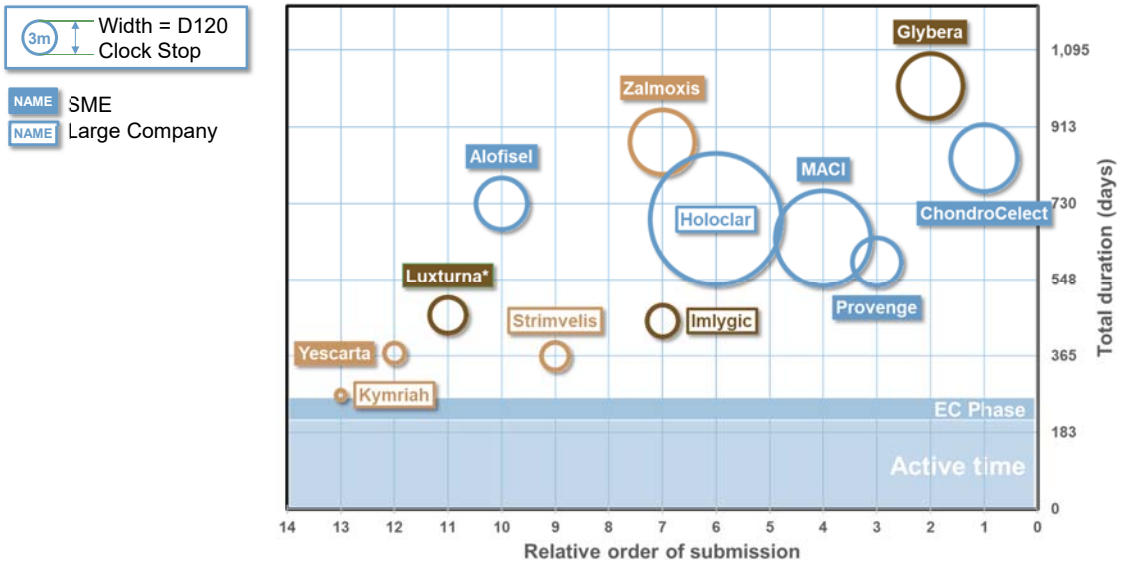


- Approved ATMP average 608 days (~1y 8m) excluding Spherox;
  - SME 696 days (371 to 1009, n=7) excl. Spherox
  - Large 484 days (272 to 692, n=5)
  - These are longer than typical for all medicines
- EMA data excludes any re-examination time.

MAJOR OBJECTIONS
Impact on timelines



MAJOR OBJECTIONS
Impact on timelines



SUMMARY
First 22 ATMP submissions

- ATMP applicant may not be using scientific advice effectively
  - ~50% didn't seek advice on the main study before it started
  - Also suggests they did not discuss the commercial process until after the main study started either
- EMA data consistently shows applicants that sought advice and those that didn't do not have a different chance of success.
  - But if advice is sought and not taken this reduces the chance of approval
  - We did not find this affect for ATMP.
- Major objections increase procedure duration
  - ATMP approval times are longer than typical
  - Large companies get fewer major objections and take less time than SME to be approved.

END

THANK YOU

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Advbiols