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)

- Of <u>all</u> 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

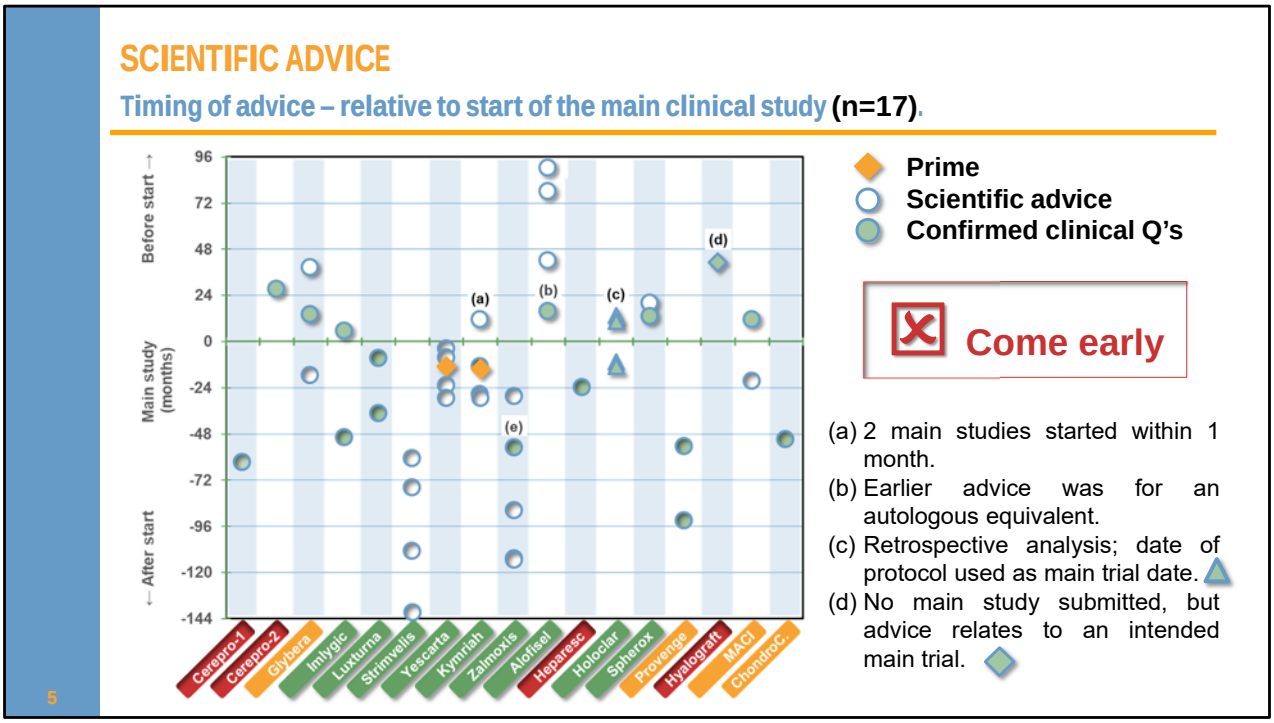

Figure 2: Relationship between date of scientific advice and start of main clinical study (n=17)

All applicants sought scientific advice at least once, and all sought advice on clinical although it wasn't always possible to identify which advice procedure. Where this was identified, the symbol is shaded pale green, where this couldn't be determined the symbol is left with a white fill.

(a) There were two main studies which started within 1 month of each other, the earliest date was used.

(b) Only the last advice related to the allogeneic product, earlier advice was for an autologous equivalent.

(c) Retrospective analysis of patients treated between 1998 and 2007; date of protocol used as main trial date.

(d) No main study submitted, but advice relates to an intended main trial which was to start in 2012.

(e) Dates relative to start of phase 2 study, advice related to pivotal study (due to complete 2021).

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

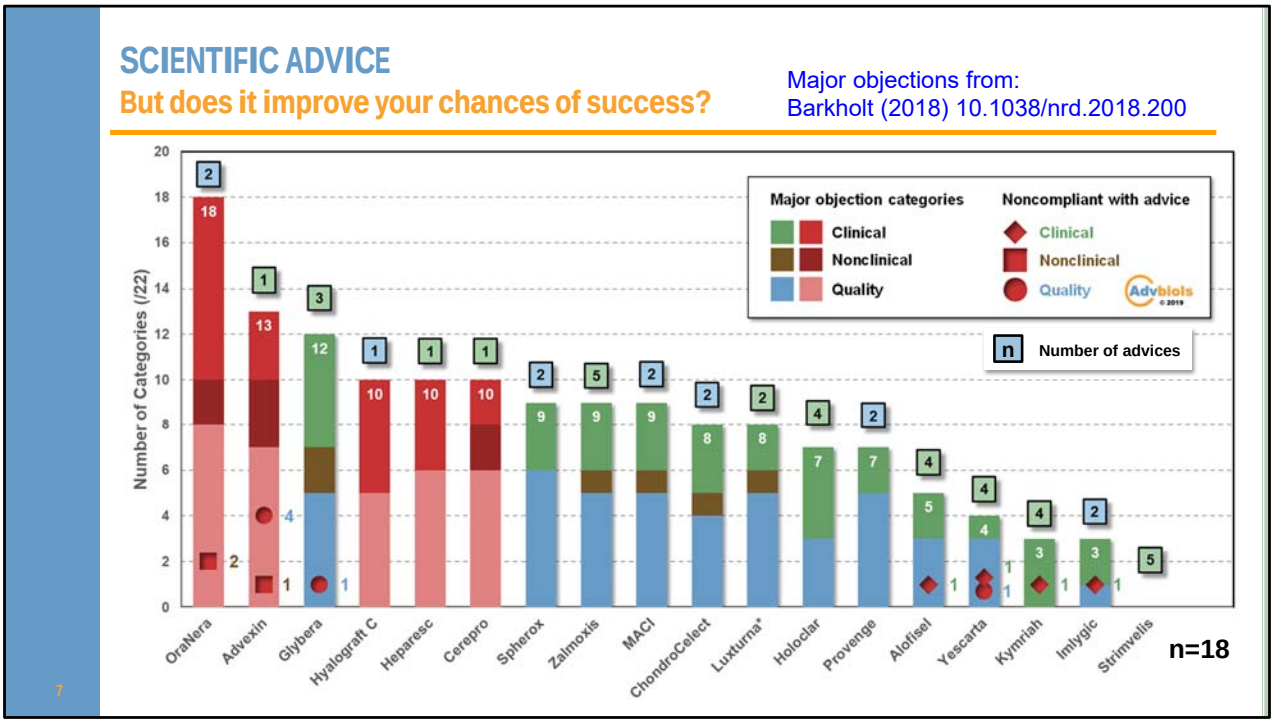

Figure 3: Number of scientific advice requests, Number of major objection categories, and number of categories with non-compliance with advice given (n=18)

Bars are ranked by the number of major objection categories from (1), out of 11 quality, 3 nonclinical and 8 clinical categories (maximum 22); value at top of bar are total number of categories.

Blue/brown/green bars were approved, red shades withdrawn or rejected.

Insert red symbols: number of categories where the EPAR specifically mentions non-compliance with advice related to a major objection category. Diamonds, clinical; squares, nonclinical, and circles, quality.

Number in box above the bar is the number of scientific advice requests submitted for each.

*The number of categories was estimated for Luxturna from the EPAR.

Only the first submissions of Cerepro and Advexin are included, and due to insufficient data Raligize and Apligraf are excluded.

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)

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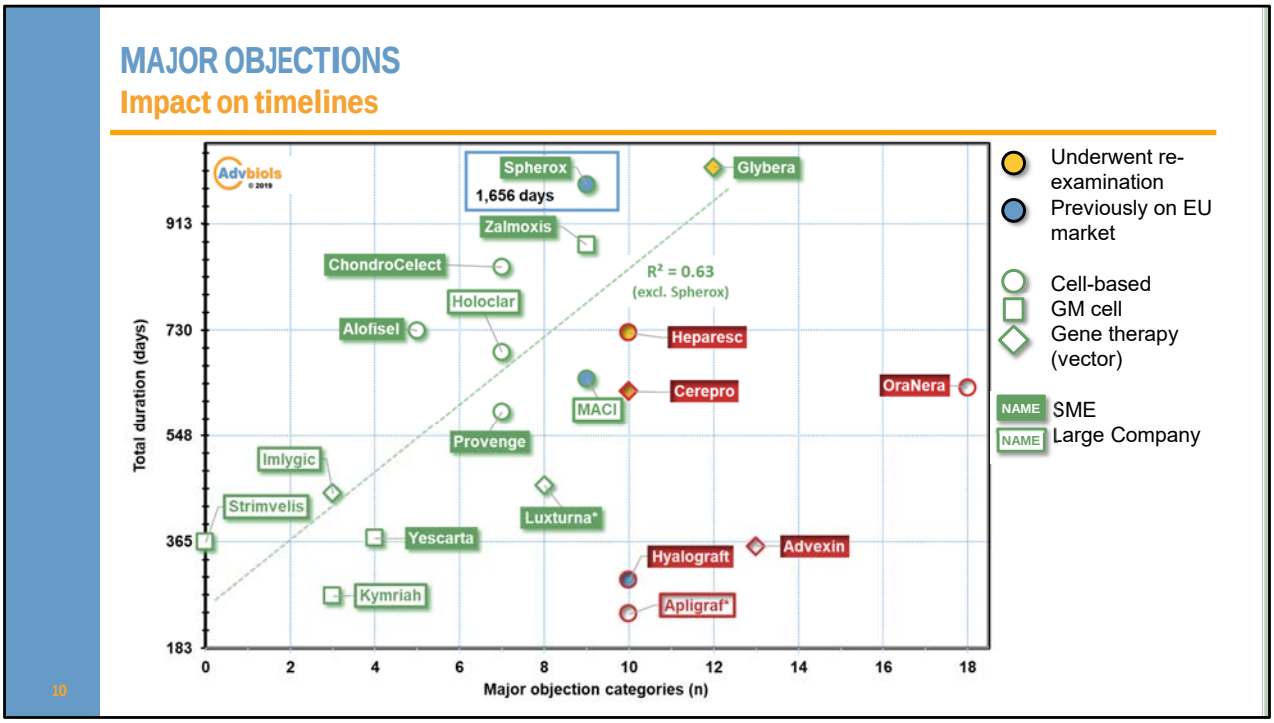


Figure 7: Impact of the number of major objections on procedure duration

Total duration (days): calculated as start of procedure to either, issue of MA by EC, confirmation of negative opinion by EC, or withdrawal of application by applicant. Total duration also includes any time spent seeking a re-examination after a negative opinion (symbols with blue fill).

The number of major objection categories as defined and scored by Barkholt *et al.*(1) except Luxturna and Apligraf which were scored by the authors (see text).

Green, approved; red, not approved; circles, cell-based medicinal products; squares, genetically modified cells; diamonds, gene therapy (vector) products.

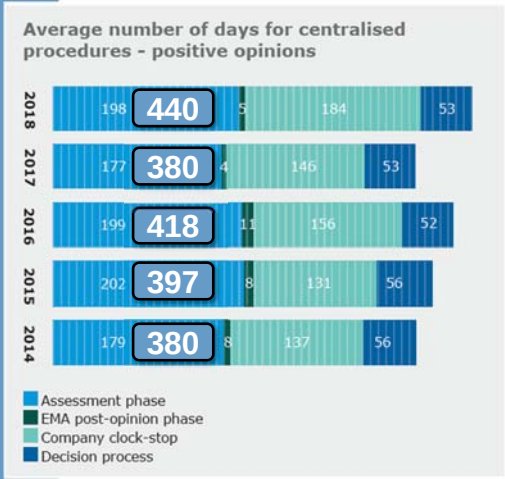
Orange filled symbols; products considered on the market prior to the end of 2009.

Company name: white text on coloured background, SME; colour text on white background, large pharma company.

Trendline: linear regression of approved products only, and excluding Spherox as an outlier.

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.

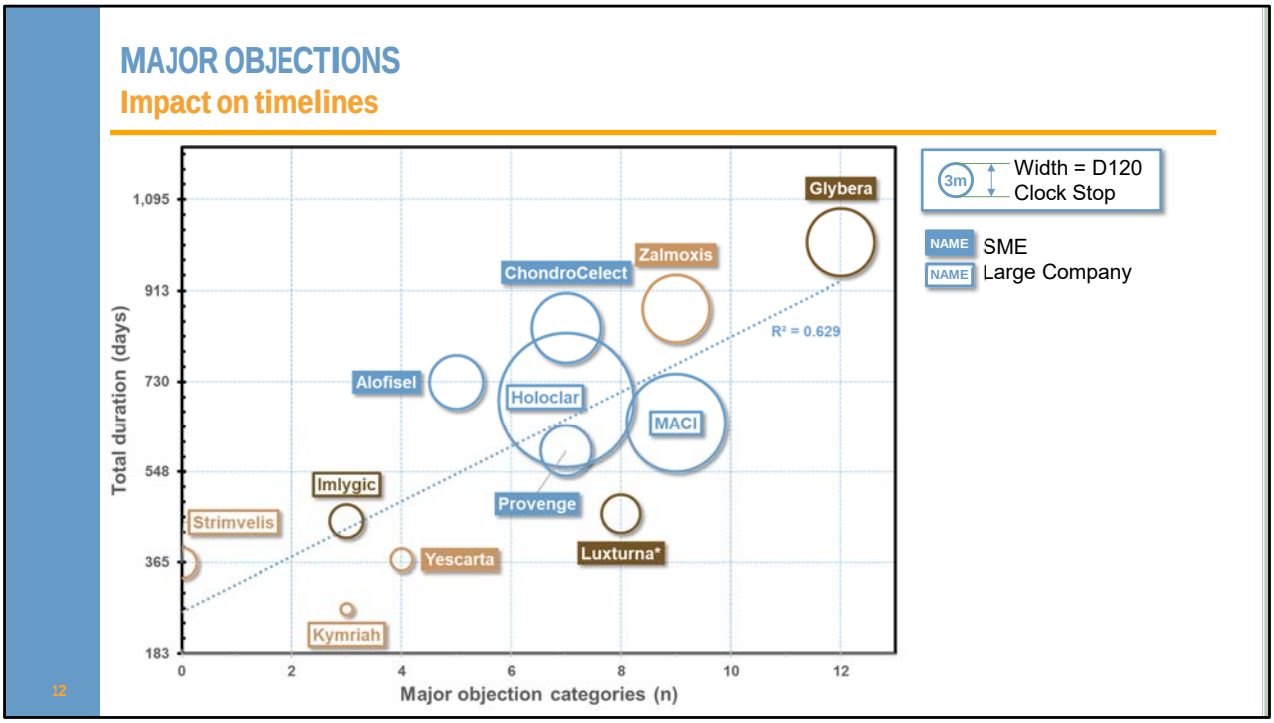


Figure 8: Contribution of the day 120 clock stop to overall duration

Total major objection categories plotted against total duration; each product is represented by a bubble, the width of which is proportional to the duration taken to respond to the first LoQ at day 120.

Blue, cell-based medicinal products (not genetically modified); pale brown, genetically modified cells; dark brown, gene therapy (vector) product.

White text on colour background, SME applicant; colour text on white background, large company applicant.

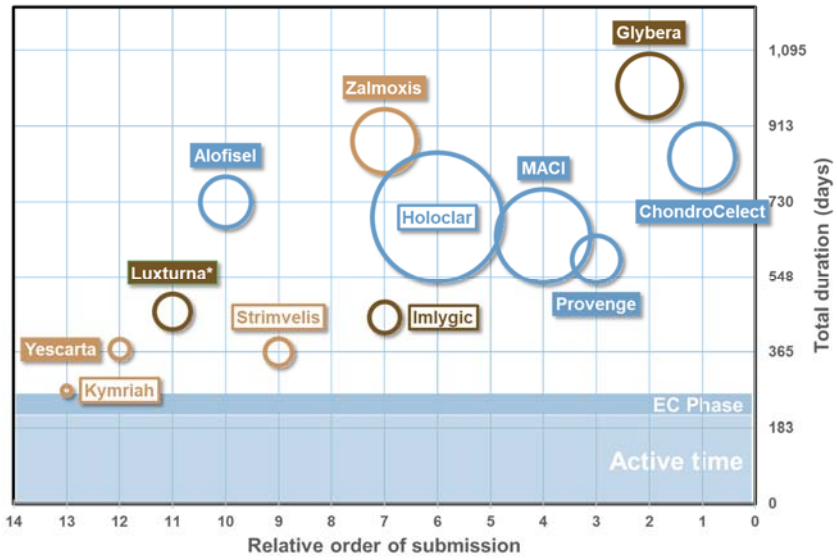
MAJOR OBJECTIONS

Impact on timelines

3m Width = D120 Clock Stop

NAME SME

NAME Large Company



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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