External control for approval and labeling: Two case studies

trying to figure out when it is worth it

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EFSPI regulatory statistics workshop, Basel, Switzerland
September 14th, 2023

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Acknowledgements

- Many thanks to Rob Hemmings for insightful feedback, suggestions and advice
- I am very grateful to Evgeny Degtyarev, Mireille Ladislas, Jufen Chu, Meike Angstenberger, Azzeddine Cherfi, Andrew Cavey, Oliver Jung for a wealth of background material and information, and thought provoking ideas and suggestions
- And of course, the larger respective project and study teams need to be commended for doing all the real (hard !) work

Approval and Labeling : a newer playground

- External controls : hope for non-RCT based decision making to be better informed, more robust and efficient, than without an external control.
- External controls not new in a diversity of decision settings (Development planning and trial design, orphan designation, pediatric plans,...). Focus here: approvability and labeling processes: use newer and still challenging.
- Regulatory guidance welcome to clarify expectations and ensure sustained standards of evidence in the decision process.
- Two examples to
  - try to learn guiding principles from real regulatory interactions with FDA and EMA,
  - discuss remaining uncertainty on actual benefit of using external controls.

Disclaimer

- This presentation is based on scientific work and selected regulatory interactions from two past Novartis projects (for ease of access to their stories). Those are used as case studies, to try to identify general considerations, raise broad questions and support a discussion among workshop participants.
- The presentation is not intended in any manner to question, challenge or revisit any decision or outcome of the respective procedures for those cold cases.

Overview

- Case study 1: Kymriah in Follicular Lymphoma
  - Background, research question, single arm trial
  - External controls features and analysis
  - Regulatory outcomes
- Case Study 2: Promacta in Severe Aplastic Anemia
  - Background , research question, single arm trial
  - External controls features and analysis
  - Regulatory outcomes
- Questions and conclusions

Kymriah in Follicular Lymphoma

- Kymriah: CAR-T cell therapy, approved for r/r pALL & r/r DLBCL ≥3L (US, EU,...)
- Relapsed / Refractory Follicular Lymphoma after at least 2 lines of therapy :
  - incurable rare disease, with multiple relapses
  - Diversity of available treatments, with limited Complete Response Rates (CRR~15%)
- Scientific questions of interest:
  - «Can Kymriah demonstrate a CRR (determined by independent review committee, IRC) significantly greater than Ho=15% in patients with r/r FL ≥3L ? »
  - « Can Kymriah improve Overall Survival over standard of care in patients with r/r FL ≥3L ? »
- Single Arm Trial (SAT) ELARA:
  - EMA HTA Parallel Scientific Advice, April 13th 2016: *"Given the unmet medical need, novel mechanism of action and promising, albeit very limited, data in FL as provided by the Applicant, a single-arm non-randomized trial in this indication may be a possible basis for licensur".*
  - EMA Scientific Advice, February 25th 2021: *"Overall, an uncontrolled trial may be a possible basis for marketing authorisation (...) the totality of the data will be taken into account, and results are expected to be exceptionally compelling. "*
  - FDA Pre-submission meeting, July 27th 2021: "*Based on the topline data submitted in the briefing package, the data appear sufficient to support submission of a marketing application*. (...) *Accelerated approval may be considered for an agent that addresses an unmet medical need based on an appropriate surrogate or intermediate clinical endpoint reasonably likely to predict clinical benefit (e.g., response rate, durability of response*)."

Kymriah: external control requested

- Questions from the EMA rapporteur, at (single arm trial) protocol review (2018):
  - « *The rationale for choosing a null hypothesis of ≤ 15% is unclear. Further, we (...) remind the Sponsor that the use of external control design is restricted to situations in which the effect of the treatment is dramatic. Thus, the chosen level of the null hypothesis must reflect the expected dramatic effect.* »
  - « *Being a single-arm trial, we assume that (...) the external control will be pre-specified and consist of a population (e.g. from registries or historical trials) where there is access to individual patient-level data. (...). The (...) Agency acknowledges that the external control is not specified as of now, but we assume that the control will be specified in a substantial amendment*»

➢ Interesting unprompted feedback:
  - ➢ External controls planned for EMA submission
  - ➢ Systematic Literature Review (SLR) also proposed

Kymriah: external control added value ?

- RWD package not supportive of regular (traditional) approval by FDA:
  - Pre-submission meeting, July 27th 2021:« *the proposed primary endpoint in the real word data (RWD) is not concordant with traditional approval in this clinical setting* »,
    « *It is unlikely that a registry approach would be sufficient to satisfy verification of the clinical benefit of tisagenlecleucel (should it receive accelerated approval). (...) In this case, we consider randomized control studies in patients with r/r FL to be feasible.* »

➢ Very useful early feedback: External controls not provided in FDA submission

- Complete Response (CR), with Duration of Response (DoR) is enough to isolate the treatment effect, which needs anyway to be exceptionally compelling.
  Single arm trial acceptable for approval/accelerated approval.

➢ Which part will the external control play in the approvability decision, beyond confirming the relevance of the null hypothesis ?
(Could the Systematic Literature Review be sufficient for this ?)

Kymriah: external control data

- Two sources of patient-level data

ReCORD

- a non-interventional retrospective cohort study based on chart review
- Data collection in academic centers in EU and North America by an electronic data collection form (eDCF) via a secure web-based data collection portal

Flatiron

- a non-interventional study utilizing electronic health records from the US Flatiron Health Research Database (FHRD)
- Mostly community-based cancer centers in US

- Scientific Advice (February 2021):
  - Contextualization of the uncontrolled pivotal study results by indirect comparisons to patient-level external controls is considered useful to understand the efficacy of Kymriah in the current therapeutic landscape. These analyses are only supportive in nature and compelling results from the pivotal study will be required.
  - (...) formal hypothesis-testing (..) may therefore not be appropriate . Despite that, both approaches may be used for contextualization of data(...) The inferential B/R estimation will be based on the absolute outcomes in the (...) study, in terms of efficacy primarily based on ORR and DoR.

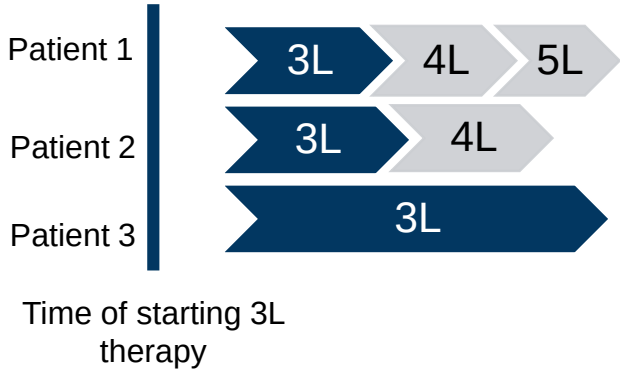
Kymriah: Addressing the RWD challenges

Bias

- Baseline confounding
- Selection bias
- Immortal time bias
- Missing data on prognostic factors

Selection of index line

- Patients in external cohort could meet the eligibility of ELARA multiple times



- 50 pages in briefing book to describe approach to RWD:
  - data sources and selection of RW patients, with summary of differences in incl/excl criteria and in endpoints
  - target trial framework and estimands to emulate a target randomized trial
  - analysis plan aligned with research question including planned sensitivity analyses

DOI: 10.1080/19466315.2023.2190931
Leveraging RWD for the analysis of a pivotal single arm study (ELARA, CTL019E2202) (oncoestimand.github.io)

Kymriah: target trial & estimand frameworks

Question: ***What's the treatment effect of prescribing Kymriah vs SoC in the patient population who participated in the ELARA trial?*** – average treatment effect on treated (ATT)

Component	Target RCT	Emulated trial		Our strategy
		ELARA	ReCORD	
Population /Eligibility criteria	ELARA inclusion/exclusion (I/E) criteria	**Same as target RCT**	ELARA I/E criteria that are feasible to apply retrospectively	Be transparent and summarize all criteria that were not feasible to apply in ReCORD
Treatment/ Treatment strategy	**CAR-T treatment strategy** vs **Current SoC**	**CAR-T treatment strategy as target RCT**	Current SoC	
Treatment assignment	Block randomized to either CAR-T arm or SoC arm	**Emulate simple randomization**		Propensity score weighting method to mitigate confounding bias Worst-case scenario as sensitivity analysis
Variables	OS is time to death from any cause	**Same as in target RCT**		
	CR best overall response of complete remission per Lugano criteria	**Same as target RCT**	CR and progression based on real-world response criteria	Subgroup analysis of "≥ 2014" was conducted as year of introduction of Lugano response criteria
	PFS is time to first progression or death from any cause	**Same as target RCT**	Progression dates unavailable for many patients	**To consider new anticancer therapy as PFS event** and pre-specify in SAP

Kymriah: target trial & estimand frameworks

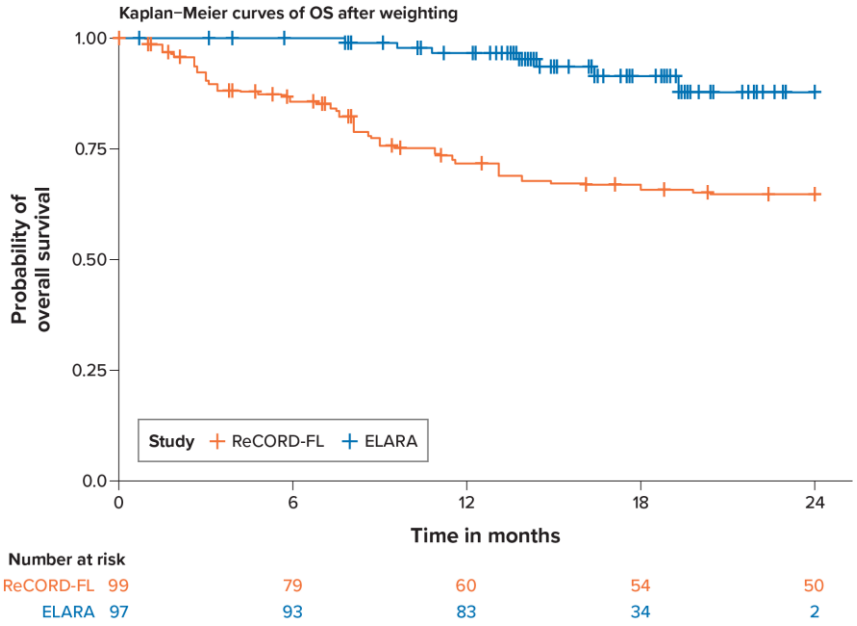
Component	Target RCT	Emulated trial		Our strategy
		ELARA	ReCORD	
Start of follow-up	Start: date of randomization	Start: enrollment, regarded as prescription date	Start: start date of SoC treatment • Multiple line of therapy	One eligible LoT per patient in ReCORD is systematically selected based on the highest propensity score to be in ELARA
Intercurrent event(s)	**IE: new anti-cancer therapy** OS: Treatment policy strategy CR: ICE reflected in Variable PFS: Hypothetical strategy	Same as target RCT for OS and CR PFS: Composite strategy		
Causal effect	**ATT:** Effect of prescribing tisagenlecleucel vs SoC in patients meeting ELARA inclusion/exclusion criteria	Same as in target RCT		
Summary measure	Binary endpoints: Difference in marginal response probabilities on CAR-T vs SoC Time-to-event (TTE) endpoints: Marginal HR	Same as in target RCT		
Analysis	Binary: Difference in response rates TTE: Cox regression	Binary: Difference in weighted proportions of responders TTE: HR obtained from a weighted Cox regression		

Kymriah: Results (ReCORD external control)

	ELARA N = 97	Before Weighting ReCORD N = 143	After Weighting ReCORD N = 99*
Complete response (CR)			
CR rate (95% CI)	69.1 (59.8-78.3)	37.3 (26.4-48.3)	30.5 (13.1-47.8)
Difference in CR (95% CI)		31.8 (18.1-45.3)	38.6 (19.3-57.9)
Overall survival			
HR (from Cox regression) 95% CI		0.25 (0.03, 0.46)	0.20 (0.02, 0.38)

* The effective sample size was 95.

Overall survival
(after weighting)



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Kymriah: Regulatory outcome

HA	Interactions/ Outcome
EMA	• Positive CHMP opinion in March 2022 (CAT assessment report): "*To contextualise the findings presented in the pivotal clinical study E2202, the MAH carried out two analyses of real-world data, ReCORD and Flatiron in addition to a systematic literature review.*" "*These studies are despite the remaining uncertainty of the effect estimates nevertheless providing valuable context, and are in general deemed supportive of the pivotal study, due to the clear differences in outcomes they show*." • Tisageneleucel approved in r/r Follicular Lymphoma in April 2022 – RWE data not accepted for inclusion in the EU label "*This information on RWE does not describe a feature of the product and hence should not be part of the SmPC according to the current guidelines. The SmPC should only contain data on the product which is relevant to the prescriber*." – RWE data is reflected in EPAR after approval
FDA	• Tisageneleucel approved in r/r Follicular Lymphoma based on ELARA trial alone

➢What is necessary to make external control results relevant to the prescriber
  – for CRR ? for OS ?

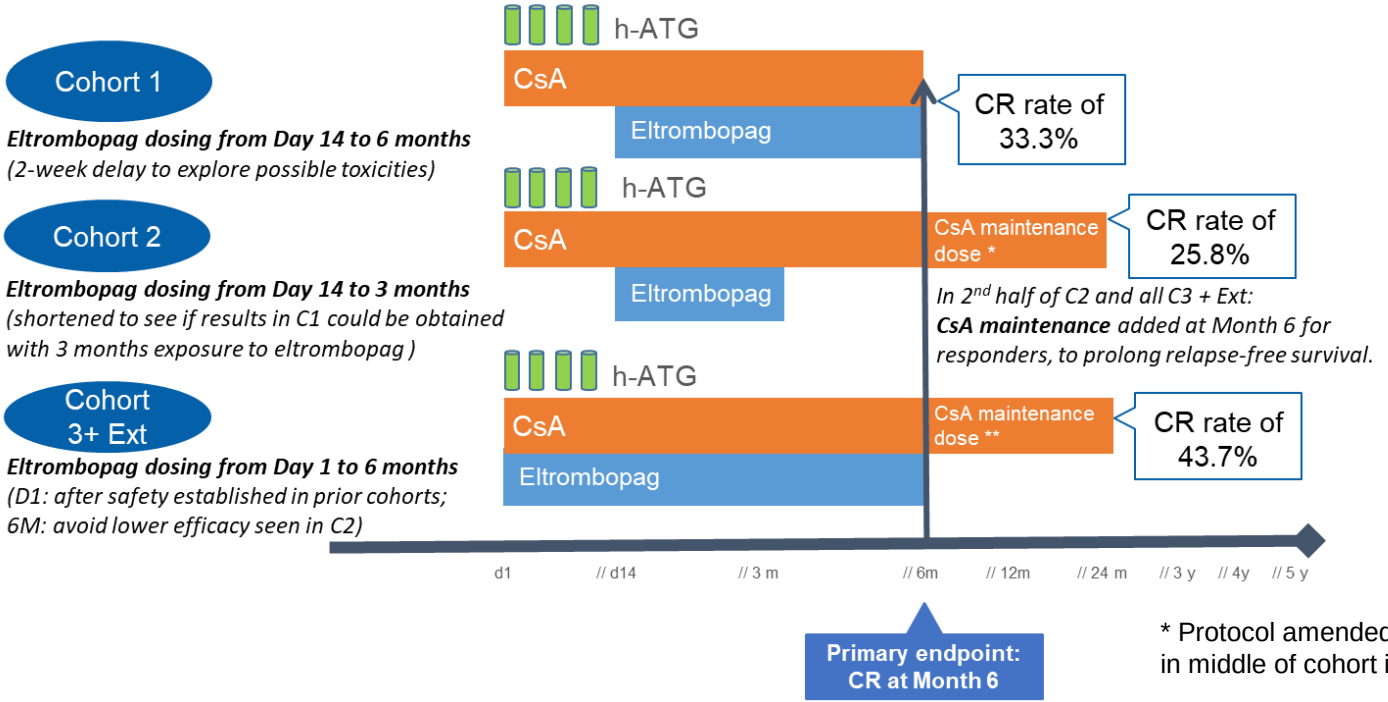
➢How critical is the « contextualisation » in the approvability decision process ?

Eltrombopag in Severe Aplastic Anemia

- Eltrombopag : TPO-R agonist, approved for SAA patients either refractory to prior immunosuppressive (IST) therapy or heavily pretreated and unsuitable for haematopoeietic stem cell transplantation (HSCT)
- First line SAA (1L):
  - Rare (2/million in western world), life-threatening acquired bone marrow failure due to an immune-mediated attack on the bone marow
  - HSCT preferred treatment but only possible for <30% of patients, IST otherwise (ATG/Cyclosporine A CsA): 10-15% CR, not improved since 20 years
- Scientific question of interest: «Can Eltrombopag combined with standard IST demonstrate greater CRR at 6 months than IST alone in patients with 1L SAA not eligible to HSCT ? »
- Single Arm Trial (SAT) NIH study US01T:
  - NIH regimen finding study of h-ATG+CsA+ Eltrombopag with three cohorts investigating different starting points and durations of Eltrombopag on safety profile and CR Rate at six months
  - Preliminary results of study AUS01T presented at the 57th American Society of Hematology (ASH) Annual Meeting in 12/15, and viewed as transformative.

Eltrombopag: Single Arm Trial in SAA

Patients enrolled in **sequential cohorts** that differ by:



* Protocol amended to add CsA maintenance in middle of cohort in responders only

** Responders only

Eltrombopag: external control requested

- FDA type B meeting (2016): Study adequate to support label expansion ?
  - «*No. The effect of eltrombopag has not been isolated in this single center trial that enrolled patients who have not received ATG. The study does not provide a comparison of the effect of adding eltrombopag to ATG plus CsA.* »
  - « *The Sponsor will develop a plan for a historical control including a plan for a statistics analysis and submit for discussion with the Agency.*»
  - « *The efficacy evaluation endpoints appear acceptable. (...). you will need to provide evidence that the addition of eltrombopag contributes to the effect of ATG and CSA*»

➢ External controls planned for FDA submission

- FDA type C meeting (2017):
  - «*Yes. It appears that the totality of data that will be submitted from study US01T and the historical controls is adequate to support filing of a sNDA.* »

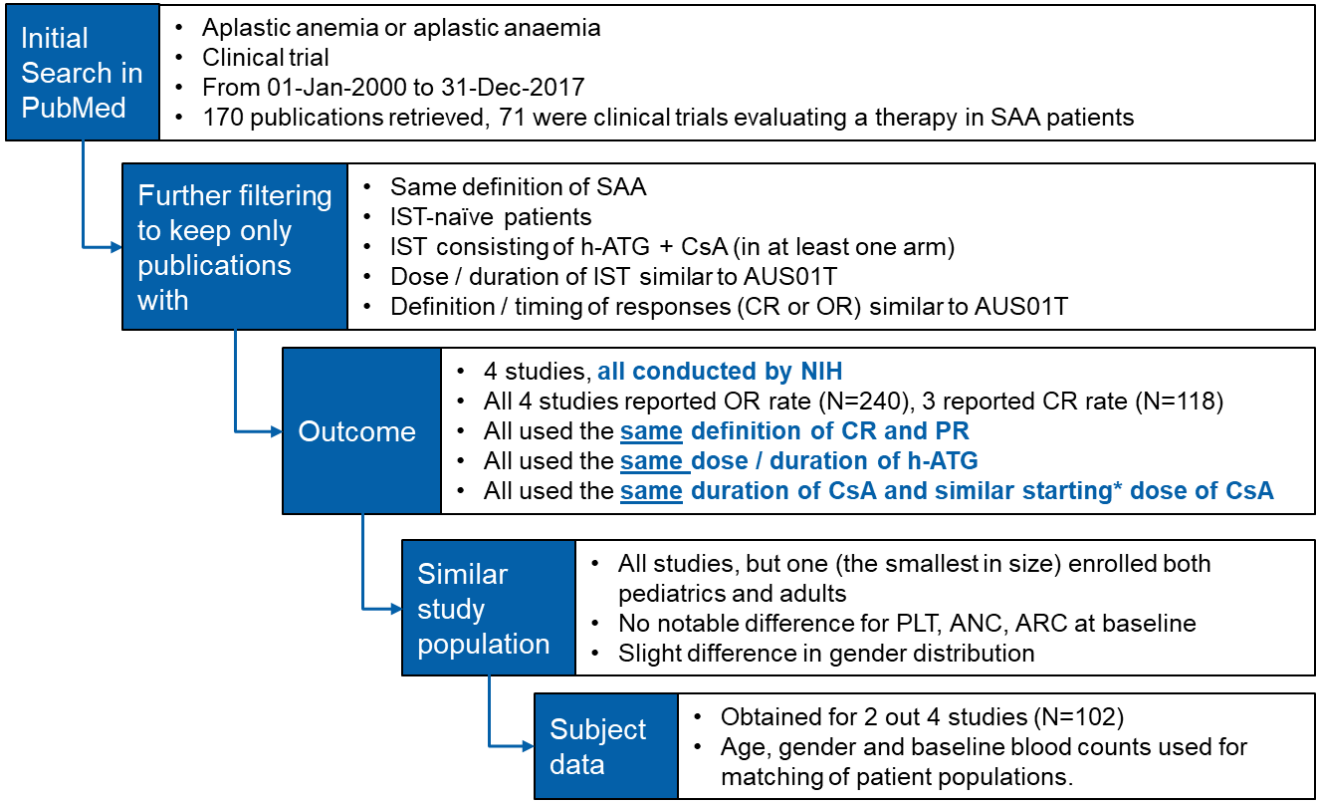
Eltrombopag: external control requested

- EMA rapporteur meeting meeting (2016): Study adequate to support label expansion ?
  - «(*Rapporteur) recognized that the 6 months data is very promising (...). Novartis should demonstrate the improvement of this treatment setting in comparison to current IST standard of care*. »
  - «(*Rapporteur) commented that it would be ideal to have a comparator arm in the trial; however, in the absence of this comparator arm, a high quality comparison of matched historical control data will be important in the discussion of the overall results of the trial.* »
- EMA co-rapporteur meeting meeting (2016): Study adequate to support label expansion ?
  - «*In principle, the data could support the variation because of the compelling results that would not have happened without a true treatment effect. It will be important to provide information on the historical control data, ensure that it is well-matched to the pivotal trial US01T.* »

- Compelling results indicative of a treatment effect but need to demontrate improvement vs. Standard of Care (SoC).
  Single arm trial with external control could support the expansion of indication.

➢ External controls also planned for EMA submission

Eltrombopag: careful control selection



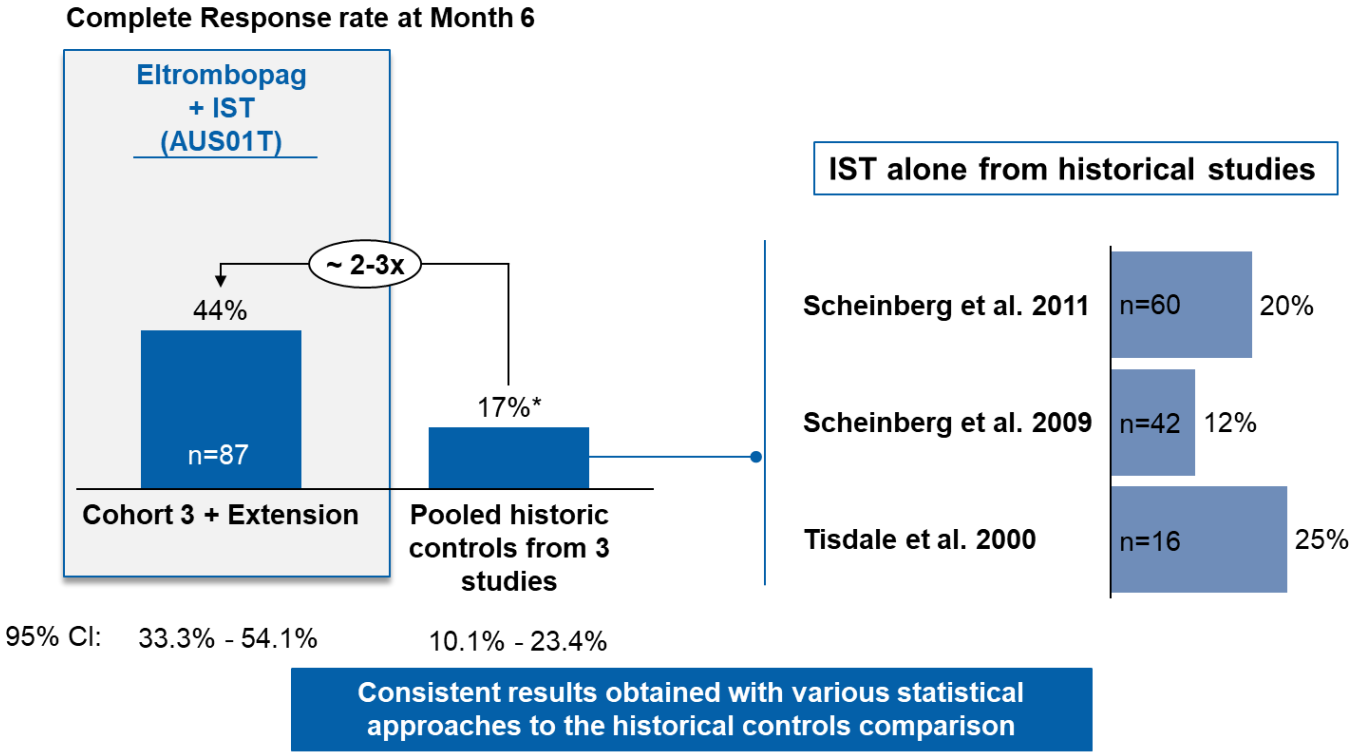
(*) later adjusted based on CsA concentration to reach the therapeutic range.

Eltrombopag: different analyses methods

Methods using study-level summaries (3 historical studies, 118 patients in total)	1. **Frequentist fixed effects meta-analysis** which does not account for between-trial heterogeneity. 2. **Frequentist random effects meta-analysis** accounting for between-trial variability ➔ Led to the same result as 1. 3. **Bayesian Meta-analytic predictive** (MAP) considering different prior for between-trial variability (from very small to large heterogeneity).
Methods using subject-level data (2 historical studies, 102 patients in total)	4. **Propensity score (PS) matching** where PS were estimated using age, gender and, baseline PLT, ANC and ARC as independent variables. The resulting matched sample consisted of 67 pairs of AUS01T and historical patients. 5. **IPTW* propensity score** (PS) which allows to estimate the difference in response rate between AUS01T and historical control, adjusted for baseline characteristics (as above).

(*) Inverse Probability Treatment Weighting

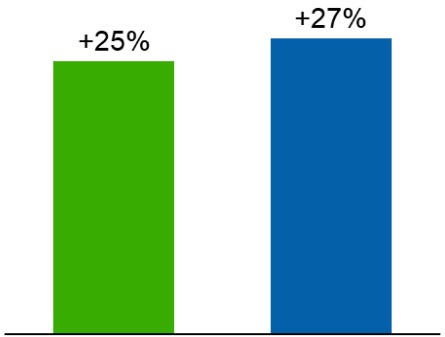
Eltrombopag: Results vs. external controls



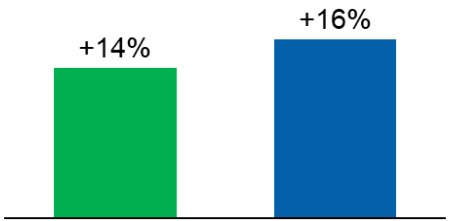
*Using fixed effect model. Similar results were obtained using subject-level data from the two Scheinberg studies. OR in AUS01T is 79% compared to an OR of 63% from the pooled historical control.

Eltrombopag vs. broadened controls pool

Treatment effect on CR rate
Difference CR rate AUS01T and historical



Treatment effect on OR rate
Difference OR rate AUS01T and historical



AUS01T vs	Extended pool (15 studies)	Original pool (3 studies)	Extended pool (17 studies)	Original pool (4 studies)
95% CI	[13.1%, 36.8%]	[14.6%, 39.3%]	[4.3%, 23.1%]	[5.8%, 26.7%]

Pooled response rate derived using random effects meta analysis

Eltrombopag: EMA regulatory interactions

- 07/18 1st Req. for Suppl. Information (RSI): 3 major objections + 22 other
  - Assessor assessment of responses to 1st RSI:
    « *The search criteria used by the MAH to retrieve historical control studies seems reasonable and the effort made by the company to match patients on Revolade with historical controls is acknowledged. Nevertheless, in the absence of randomisation it is not possible to exclude the influence of other known or unknown prognostic factors on the efficacy results.* »
- 11/18 2nd RSI: 2 major objections + 5 other
  - Assessor assessment of responses to 2nd RSI:
    «*The selection of these four studies and the statistical approach to compare AUS01T and historical studies can be considered acceptable. (...) Nevertheless, there are shortcomings and limitations in the comparisons with historical controls, that have been previously mentioned, and that mainly refer to the bias derived from the lack of randomisation. Moreover, in principle, one arm studies could be considered acceptable if comparative trials are unfeasible, e.g., due to the impossibility to recruit patients because of the rarity of the disease.* »
- 02/19 3rd RSI: 1 major objection:
  - « *The submitted data (study NIH AUS01T) do not allow a reliable and valid assessment of the efficacy and safety of Revolade as first line treatment of aplastic anaemia due to the lack of a robust comparison against the established treatment. The indirect comparison with historical data cannot overcome this deficiency.*»

➢ Is the acceptability of external comparisons driven by pre-defined general principles ?
E.g., Was the initial question of interest (effect of a combination treatment, in first line) impossible to address with a SAT + historical control, as a principle ?
Could that feedback be provided at the stage of early consultation?

Eltrombopag: EMA regulatory interactions

- 03/19 Rapporteur clarifying TC
- 06/19 First Oral Explanation (OE) :
  - CHMP negative opinion (31/33 votes), scientific evaluation: « *the evidence provided is insufficient as it comes from a phase I/II, single arm clinical trial in combination with IST and mainly relies on the haematological response compared with historical controls. Such comparisons are problematic due to the impossibility that all known and unknown prognostic factors that can impact on the results have been controlled in the absence of randomisation.*»
  - 2 divergent positions: « *The clinical study AUS01T has drawbacks as pointed out by the CHMP, but the totality of data could be assessed to justify an approval. A randomized trial may be difficult to conduct after approval of eltrombopag in first-line SAA by several agencies, including FDA and PMDA.* »
- 07/19 Request for Re-examination
  - Rapporteur: « *Although conducting a randomized controlled trial in this clinical setting may be challenging, the performance of a controlled trial would have been crucial to assess in a robust way the efficacy results in the treatment-naïve severe aplastic anaemia. (...) The absence of a comparator is the main limitation for assessment of the additive effect of eltrombopag to IST.*»
  - Co-rapporteur: « *Data provided suggest some treatment effect of eltrombopag on top of IST as a first line treatment in adults in terms of CR. However, the lack of a comparator in the pivotal study is the crucial unresolved issue that prevents from reaching a positive conclusion on the benefit/risk ratio of Revolade as the first line treatment of SAA patients. .*»
- 10/19 SAG, 2nd OE, same final negative opinion (27/29) with same 2 divergent positions

Eltrombopag : Regulatory outcome

HA	Interactions/ Outcome
EMA	• Negative CHMP opinion in October 2019: "*The efficacy and safety data of eltrombopag on top of standard of care as first line treatment of patients with severe aplastic anemia has not been sufficiently demonstrated. The submitted data, based on study NIH AUS01T, do not allow a reliable and valid assessment of the benefit of Revolade when added to the standard of care (SOC) due to the lack of a robust comparison against established treatment. The indirect comparison with historical data cannot overcome this deficiency.*."
FDA	• Eltrombopag approved in 1L SAA in 2018, on US01T trial data & historical controls

➢ How could the appreciation by the sponsor of the likelihood of success of the use of a SAT+external control be better guided before filing ?

➢ Is the consideration of the « feasibility » of a randomized study expected to remain as critical, with evolving external comparison data sources and methods?

Conclusions

- Use of external controls in the regulatory process of approval and labeling is relatively new : learning curve for all stakeholders
- Significant time and resource investment, including space taken in the regulatory discussion process
  - Early guidance valuable to ensure
    - Completeness and adequate focus of the submission package
    - Adequate focus of the regulatory interactions
    - Areas of uncertainty properly addressed by sensitivity analyses
  - Any principled show-stoppers to be clarified upfront

Questions

- Remaining lack of visibility on external controls usefulness
  - What does contextualization of SAT results - required to be compelling anyway - really mean ?
    - When is it not really **necessary** for approval ?
    - When is it not **sufficient** for approval (provided adequate data selection and analysis) ?
  - What is necessary for sufficiently low "uncertainty of the treatment effect estimates“ ?
    - How can a sponsor know when assumptions are considered so strong than no amount of sensitivity analysis can provide reassurance that estimated effects are reliable?
  - When is this contextualization useful to the patients and prescribers ?
    - What influences whether an estimate on a particular variable is relevant to the prescriber?
    - What is required to support inclusion of estimates based on external controls in a label ?