ONE SINGLE ARM STUDY PLUS A HISTORIC COMPARATOR EQUALS TWO HISTORIC REGULATORY APPROVALS

- MY EXPERIENCE WITH THE BLINCYTO® MRD FILINGS

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ABOUT BLINCYTO®

- **Used to treat ALL (Acute Lymphoblastic Leukaemia) in adults and children**
  - **Rare disease ~6000 new cases/year in the US***

Dec 2014
Accelerated FDA approval (Adult Ph- R/R ALL)

Nov 2015
EMA conditional approval (Adult Ph- R/R ALL)

Sept 2016
FDA label expansion into paediatrics

July 2017
Full FDA approval (Ph- & Ph+ R/R ALL)

March 2018
FDA label expansion into MRD

June 2018
EMA full approval (Adult Ph- R/R ALL)

August 2018
EMA label expansion into paediatrics

Jan 2019
EMA label expansion into MRD

*National Cancer Institute. Cancer Facts & Figures 2019:Leukemia, annual incidence rates (acute lymphocytic leukemia)

ABOUT MINIMAL RESIDUAL DISEASE (MRD)

- **“Minimal Residual Disease” is measurable leukaemia in the marrow, at levels below those detectible with standard microscopy (which defines CR), identifying a group of patients at very high risk for relapse and death**
  - **Widely used in clinical practice as an indicator of incomplete response**

MRD +

- **Predicts disease recurrence and death**
- **For newly diagnosed population**
- **For patients receiving transplant**

MRD −

- **Correlated with improved survival**
- **In context of therapies studied in Berry meta-analysis**

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BLAST (MT103-203) STUDY

- **Multi-centre and multi-country phase II study in patients with MRD+ ALL**
  - **To confirm MRD response rate seen in earlier study**
- **Conducted in EU due to availability of centralised MRD assay**
- **MRD level >= 10-3, 3+ blocks of prior chemotherapy, aged 18+ years, in 1st or later CR**
- **Single arm study**
  - **Secondary analysis – September 2015**
  - **Final analysis (5 year follow up) – February 2019**

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20120148 STUDY

High-Level Study Details

- **Purpose:**
  - Understand historical outcomes of ALL patients with quantifiable MRD
  - Provide comparator for study 203
- **Primary Endpoints**
  - RFS
  - OS
- **Patients in CR1 or CR2 with MRD+ ALL**
- **Initial diagnosis between 2000-2014**
- **8 countries in Europe**

Key Inclusion Criteria

- **Presence of MRD:**
  - $\geq 10^{-4}$ by PCR
  - $\geq 10^{-3}$ by flow cytometry
- **Ph- B-precursor ALL**
- **3+ intensive chemotherapy blocks**
- **Age ≥ 15 years at ALL diagnosis**
- **No extramedullary disease**
- **No blinatumomab within 18 months of MRD detection**
- **No alloHSCT prior to MRD detection**

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WHY USE REAL WORLD DATA?

- **Investigators uncomfortable with randomising MRD+ patients who had already received 3+ blocks of chemotherapy**
- **SAWP meeting in 2009 said they would accept a single arm trial if good comparative controls, well matched, would be available**
  - **Other conditions too (indisputable clinical effect, RFS with more than 1 year follow up, increase sample size as much as possible)**

PROPENSITY SCORE ANALYSIS

- Data from 148 were filtered to match key inclusion criteria for 203
- Propensity scores derived for each patient via variable selection algorithm for logistic regression model
- Chosen propensity score weight-based formula was average treatment effects (ATE)
- Inverse probability of treatment weights (IPTW) were derived from the scores for each subject according to treatment and the balance between the 2 groups was assessed primarily by standardised differences.
- sIPTW were applied to the primary analysis

PROPENSITY SCORE RESULTS

- **sIPTW achieved sufficient balance between the 2 groups**

Treatment	18 month RFS	Median RFS	18 month OS	Median OS
Control	0.39 (0.33, 0.48)	8.3 months (6.2, 11.8)	0.55 (0.48, 0.63)	27.2 months (16.4, 38.6)
Blincyto®	0.67 (0.58, 0.78)	35.2 months (24.2, NA)	0.71 (0.62, 0.81)	36.5 months (24.2, NA)
Hazard ratio	0.50 (0.32, 0.78)		0.76 (0.47, 1.24)	

Results in table are for analyses unadjusted for HSCT and for ATE weighting
These results were supported by sensitivity analyses for different analysis sets, weighting methods and the exclusion of the HSCT time-varying covariate from the outcome model.[8]

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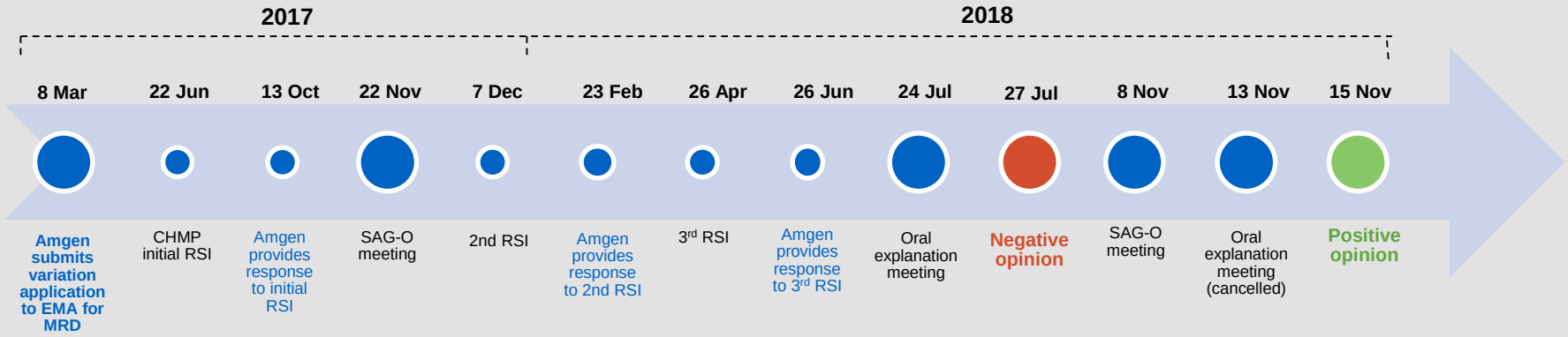
FDA ODAC MEETING

- Amgen invited to ODAC (Oncology Drugs Advisory Committee) meeting in March 2018
- FDA's independent analysis of our data for the 203 study confirmed the high MRD CR level and "remarkable" RFS compared to the historical control
- Concerns about
  - Confounding in propensity score analysis
  - Achieving undetectable MRD is a valid surrogate for or is reasonably likely to predict long term clinical outcomes (Berry et al meta analysis)
  - Level of cut off for MRD testing

Voting result: 8 to 4 that blinatumomab provides potential benefit that outweighs the risks

TIMELINE TO APPROVAL - EMA

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH



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EMA MEETING(S)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

- **Rapporteur feedback – in advance of 1st OE**
  - **Lack of randomised study**
  - **Uncertain about the long term clinical outcome (MRD not a surrogate for RFS/OS**
  - **RFS and OS should be calculated from time of first achieving a complete response**
  - **Benefit/risk in combination with HSCT cannot be established**
  - **Choice of MRD cut off was not stringent enough**

Committee trend vote in July 2018 was 26 to 5 NOT in favour.
"*too much uncertainty remains for a favourable opinion the majority of the committee wanted to rediscuss the application with the scientific advisory group (SAG-O)*"

EMA MEETING(S) – NOVEMBER 2018

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

SAG-O to consider

- *Does the prognostic value of MRD conversion prior to HSCT differ depending on the mechanism by which MRD-negativity is obtained?*
  - **There is no reason to believe that the prognostic value of MRD conversion would differ according to the mechanism involved. Potential that immunologically-mediated MRD-negativity might translate into more durable disease control compared to chemotherapy**
- *Are the other studies suitable for filling a knowledge gap from 203 study?*
  - **A number of important studies were discussed by the applicant. Understandably no study is primarily aiming to present a randomized comparison of overall survival of Blincyto v. no treatment since Blincyto has been shown to be highly effective in inducing MRD negativity. A direct comparison is considered unnecessary.**
- *Discuss whether available evidence supports the use of blinatumomab treatment in subjects deemed not fit for HSCT*
  - **Yes, available evidence supports the use of blinatumomab treatment in subjects deemed not fit for HSCT based on the ability of Blincyto to delay frank recurrence.**

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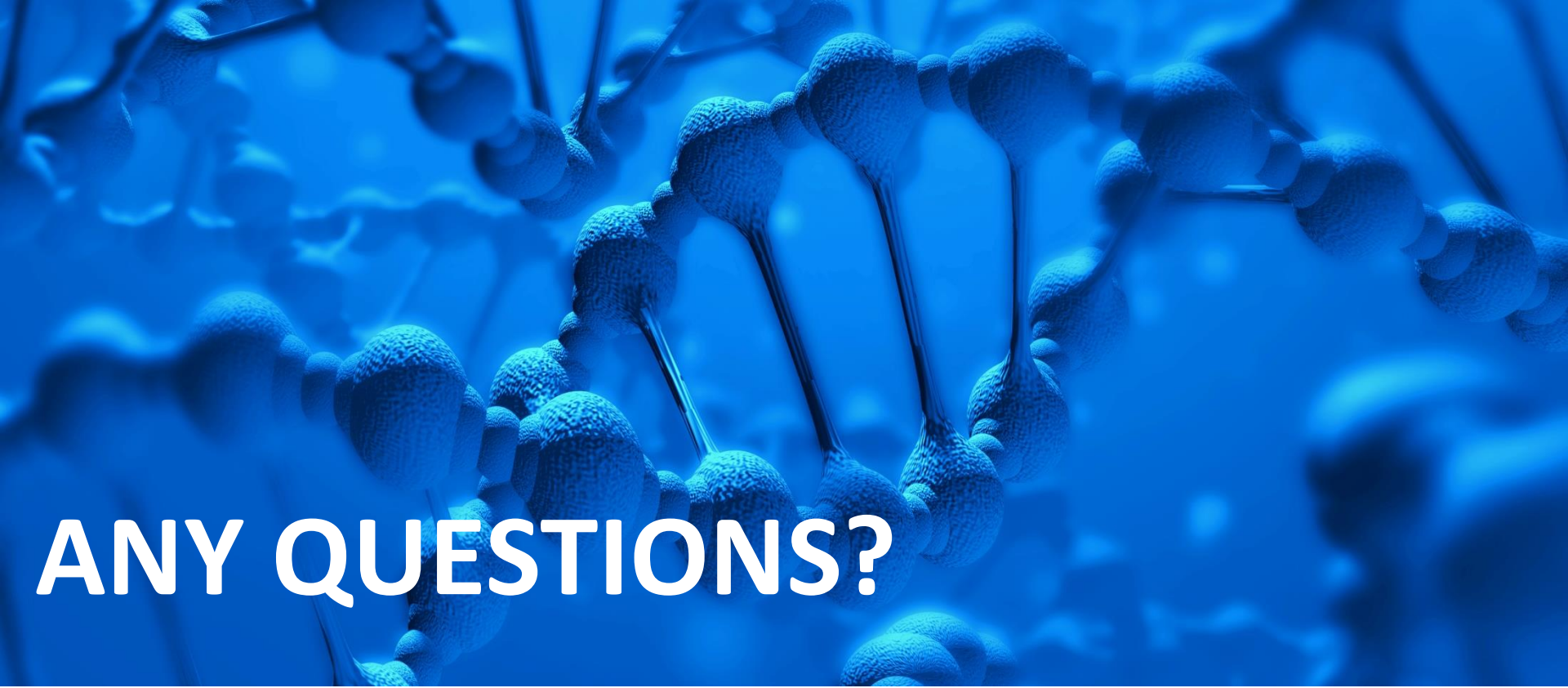

ANY QUESTIONS?

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