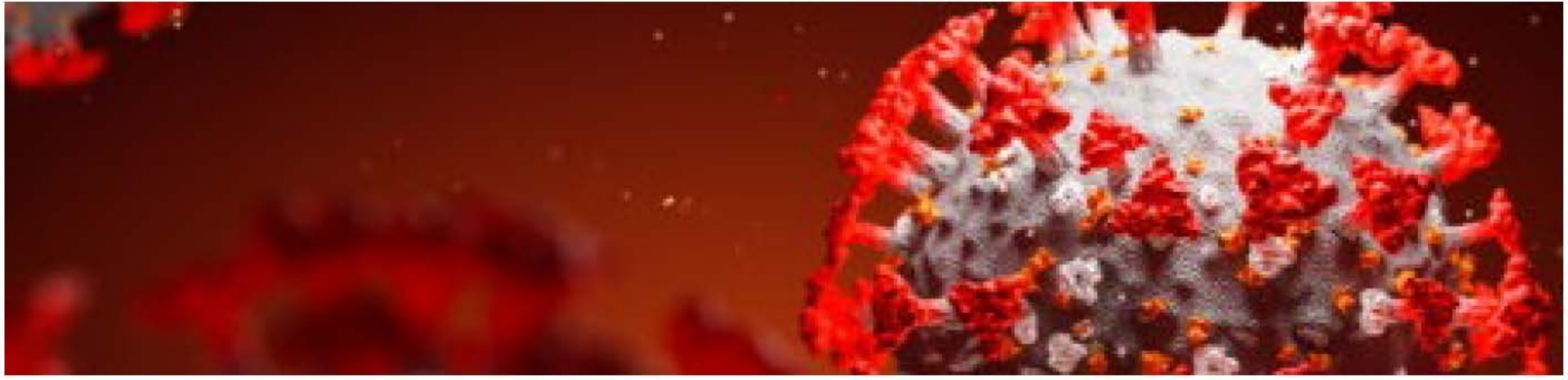
AZD1222 (formerly referred to as ChAdOx-1 nCoV-19)

Meeting with EMA Rapporteurs / Co-Rapporteurs

Strictly Confidential
31 July 2020



Agenda

- Introduction – Agenda, Participants, Objectives (10 min)
- Status of AZD1222 development program
  - Clinical Development (10 min)
  - Vaccine Product Development (10 min)
- Key Sponsor Questions
  - Clinical (35 min)
  - CMC (35 min)
  - Regulatory (10 min)
- Meeting Summary (10 min)

[redacted]

AstraZeneca and University of Oxford Attendees

[redacted]

Head of Analytical Sciences
Head of Development Quality, Biologics
Director Reg CMC
Regulatory Project Manager
Sr Director Biometrics
Sr Director Regulatory CMC
Assoc Director Clinical Virology
Sr PV Medical Director
Vice President Clinical Development
Global Regulatory Lead
Professor of Paediatric Infection and Immunity, University of Oxford
Senior Director, Fellow, R&D
Senior Director Quality
Director, Regulatory Affairs - CMC
Principal Toxicologist
Regulatory Affairs Director
Director R&D
Global Clinical Head
EU Lead Regulatory Affairs Director
Global Franchise Head

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Meeting Objectives

- Present current status of the development program for AZD1222
- Seek feedback on Sponsor questions
- Discuss and agree on proposed rolling submission approach

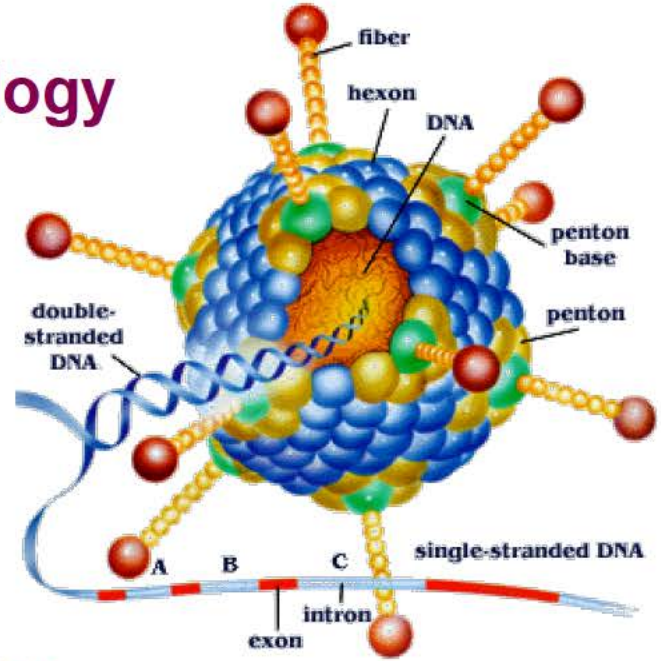
AZD1222 Vaccine

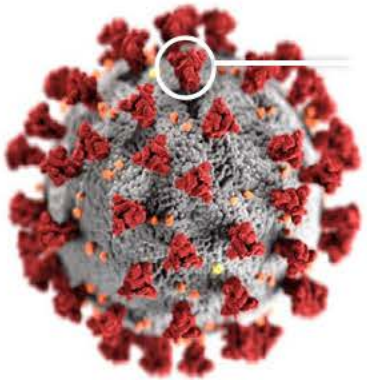
Current status of the development program

- Vaccine Construct / Technology
- Clinical Development Program

AZD1222 Vaccine: Construct / Technology

- Based on existing recombinant adenovirus vector (ChAdOx1)
  - Non-replicating
  - Avoids issues with pre-existing immunity to human adenoviruses
  - Induces strong B and T cell responses
  - Early clinical safety data from MERS study
- Contains genetic material of the SARS CoV-2 spike protein

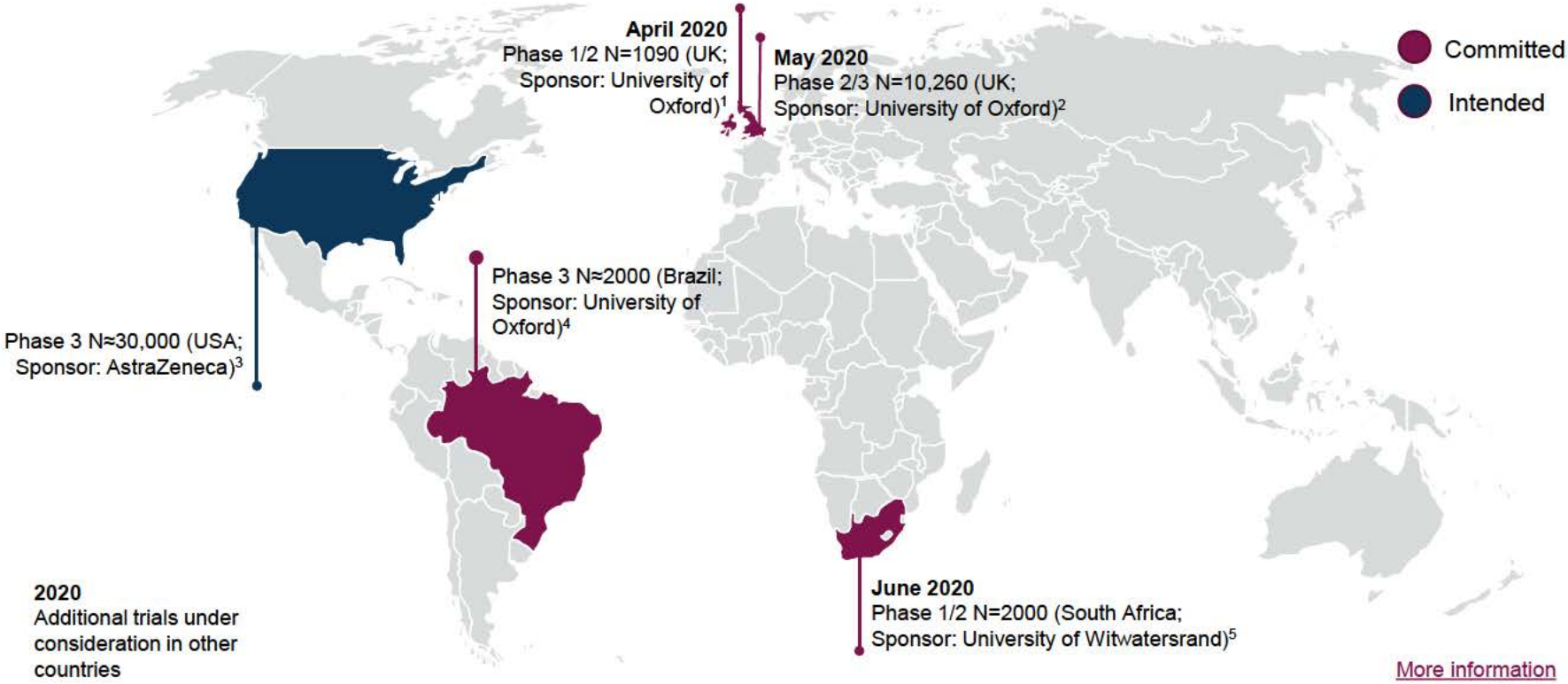




NHP MERS study: van Doremalen *et al.*, Science Advances DOI: 10.1126/sciadv.aba8399
Phase I MERS trial: Folegatti *et al.*, Lancet ID DOI: 10.1016/S1473-3099(20)30160-2

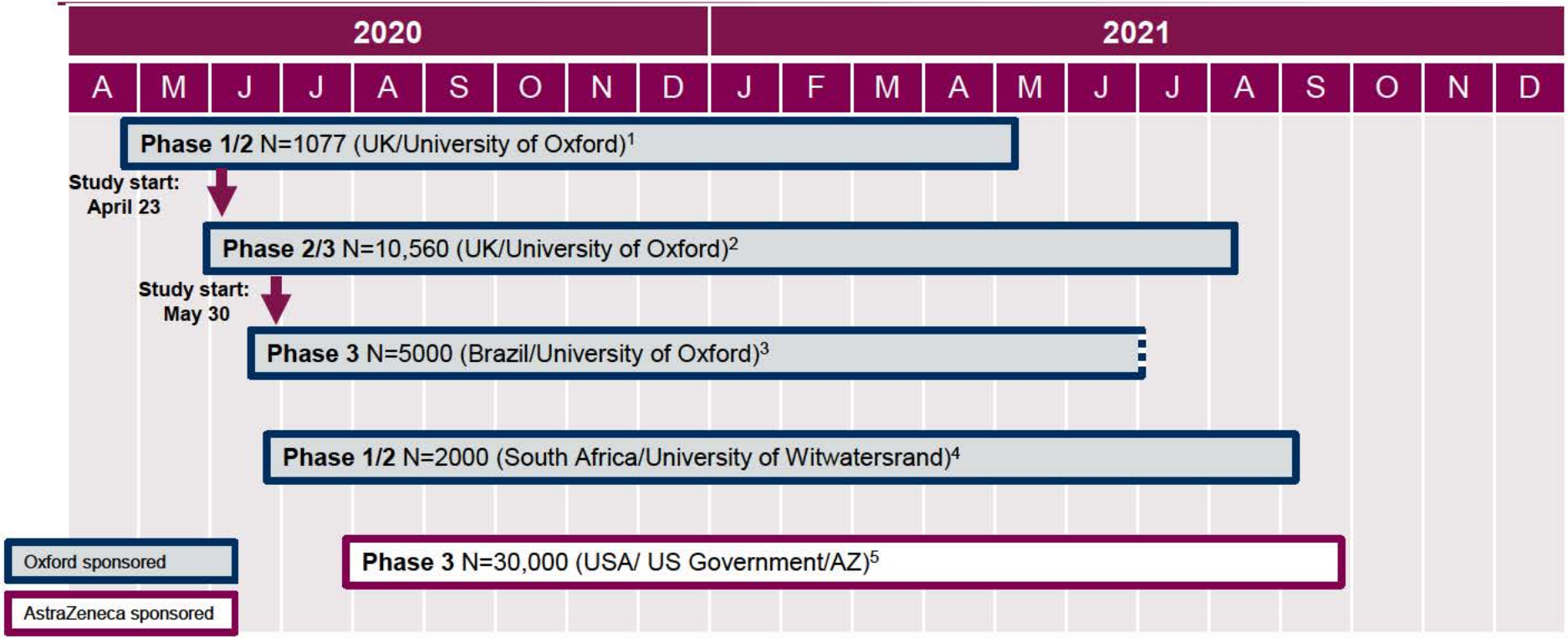
AZD1222 Vaccine: The clinical development plan is evolving globally

Clinical studies are focused on countries with increased transmission of SARS-CoV-2 (US, Brazil and S. Africa) and/or where direct funding for studies was received from the country government (UK and US)



1. Study NCT04324606. ClinicalTrials.gov website; 2. Study NCT04400838. ClinicalTrials.gov website; 3. AstraZeneca Pharmaceuticals LP press release. Published May 21, 2020; 4. University of Oxford press release. Published June 4, 2020; 5. Study NCT04444674. ClinicalTrials.gov website.

AZD1222 / ChAdOx1 nCoV-19 clinical trial plan



1. NCT04324606; 2. NCT04400838; 3. ISRCTN89951424
4. NCT04444674; 5. AstraZeneca Pharmaceuticals LP press release. Published May 21, 2020.

Oxford-sponsored efficacy studies

Phase 2/3 study in the UK:

- Randomized controlled (MenACYW, 1:1) single blind
- N = 10,560 healthcare workers and others at increased risk of SARS-CoV-2 exposure
- Subjects ≥ 18 years of age, age escalation into small (N<250) safety/immuno cohorts (56-69, 70 and above)
- Primary objectives: safety and efficacy
- Subgroup receiving paracetamol/acetaminophen to decrease transient reactogenicity

Phase 3 study in Brazil :

- Randomized controlled (MenACYW, 1:1) single blind
- N = 5,000 healthcare workers and others at increased risk of SARS-CoV-2 exposure
- Subjects ≥ 18 years of age
- Primary objective: efficacy
- Subgroup receiving paracetamol to decrease transient reactogenicity

Phase 1/2 study in South Africa:

- Randomized controlled (placebo, 1:1) double blind
- N = 2000 (adaptive) 18-65 years
- Sub-cohort of people living with HIV (N=50)
- Primary objective : Safety and efficacy

Oxford-sponsored studies: safety and efficacy endpoints

- **Common primary efficacy endpoint:** PCR (oral/nasal) positive symptomatic cases of COVID-19

- **Secondary/exploratory efficacy endpoints:**
  - Deaths & hospital admissions recorded in all studies
  - Severe COVID-19 disease and LRTI (South Africa)
  - COVID-19 ICU admission & asymptomatic illness (UK)

	UK	Brazil	South Africa
Hospital admissions	X	X	Recorded
ICU admissions	X		
Deaths	X	X	Recorded
Asymptomatic infxns	X		
WHO Severe disease			X
LRTI			X

- **Common secondary/exploratory efficacy endpoint**
  - Seroconversion against non-Spike SARS-CoV-2 antigens

- **Common safety endpoints:**
  - Occurrence of SAEs throughout the study duration
  - Solicited local reactogenicity signs/symptoms for 7 days following vaccination
  - Solicited systemic reactogenicity signs/symptoms for 7 days following dosing
  - Unsolicited adverse events (AEs) for 28 days following vaccination
  - Change from baseline for safety laboratory measures (except Group 4 – main group)
  - Occurrence of disease enhancement episodes

AZD1222 Vaccine

Current status of the development program

- DS Production Process
- DP Formulation, Presentation
- Manufacturing and Supply
- Testing and Specification

AZD1222 Drug Substance Production Process

AZD1222 Vaccine DP Formulation, Presentation

AZD1222 Manufacturing

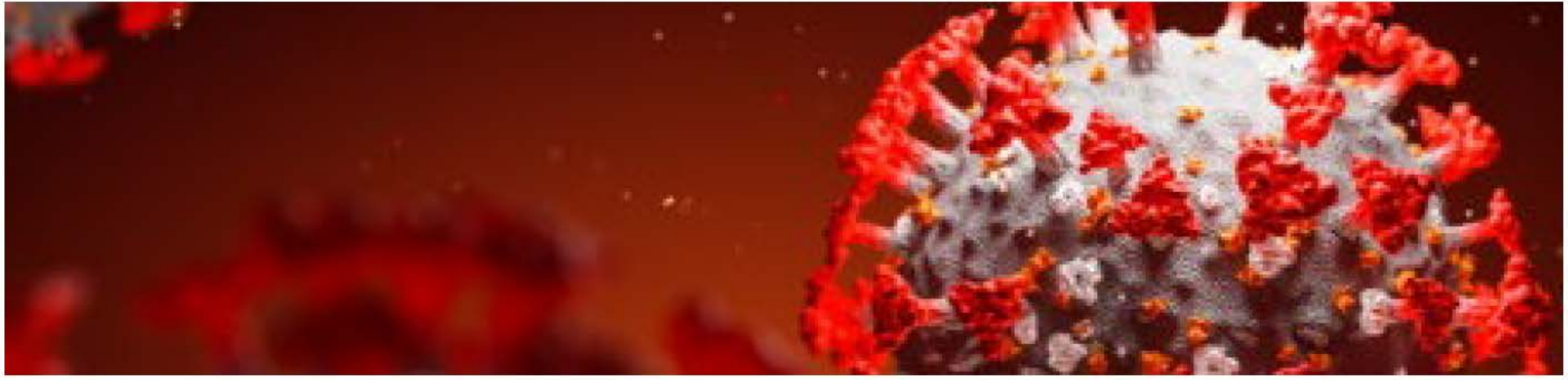
AZD1222 Proposed Specification Testing

[redacted]

AZD1222 Commercial Supply for EU

As of: 20 July 20

Key Sponsor Questions for Discussion with EMA

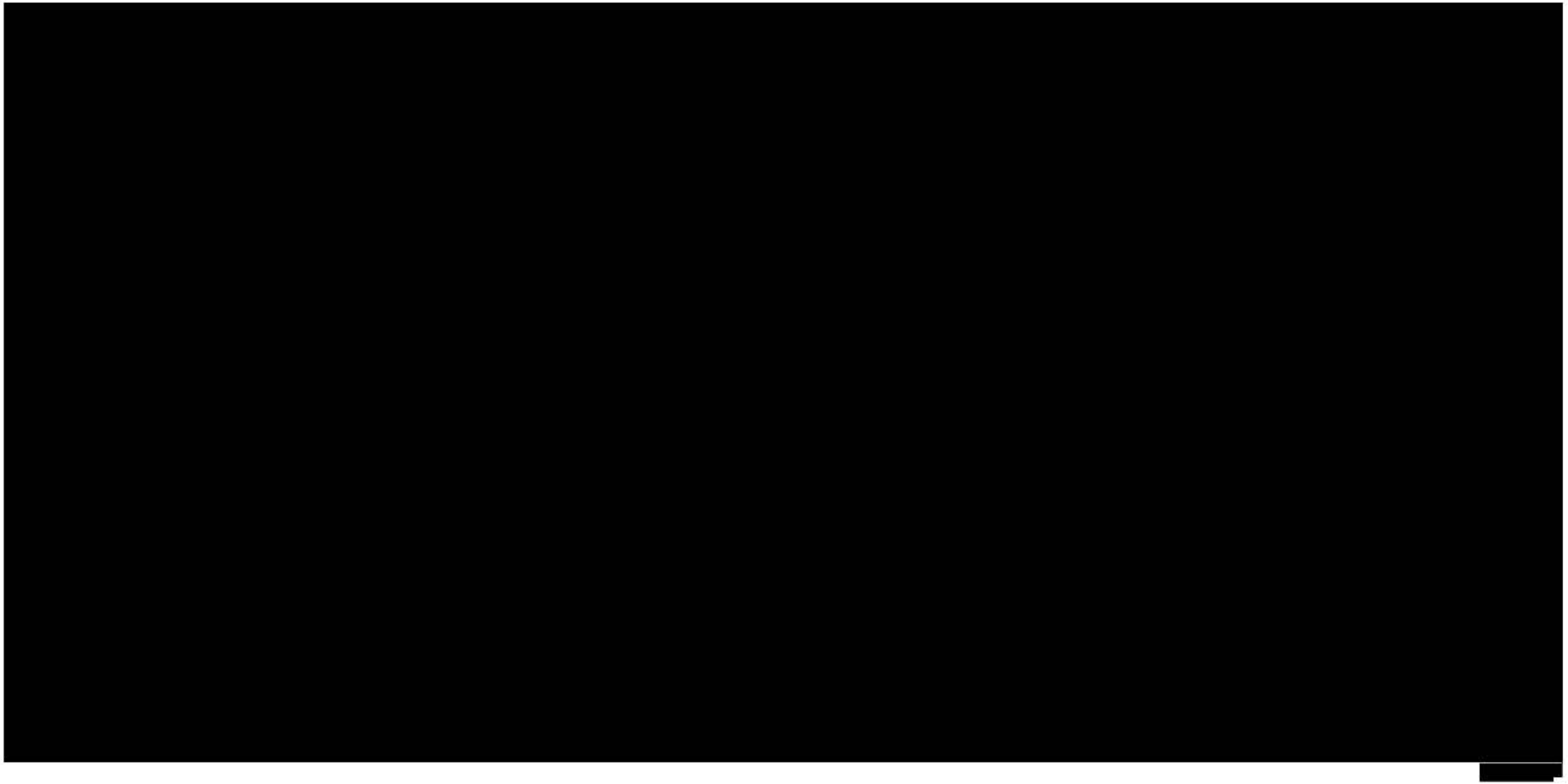


AZD1222 Vaccine

Key Clinical Questions

Clinical Question: Pooled assessment for evidence of efficacy and safety

Safety Question: Clinical safety data presentation on a rolling basis



Proposal to the agency:
Pooled assessment for evidence of efficacy and safety

Studies used in the pooled efficacy assessment

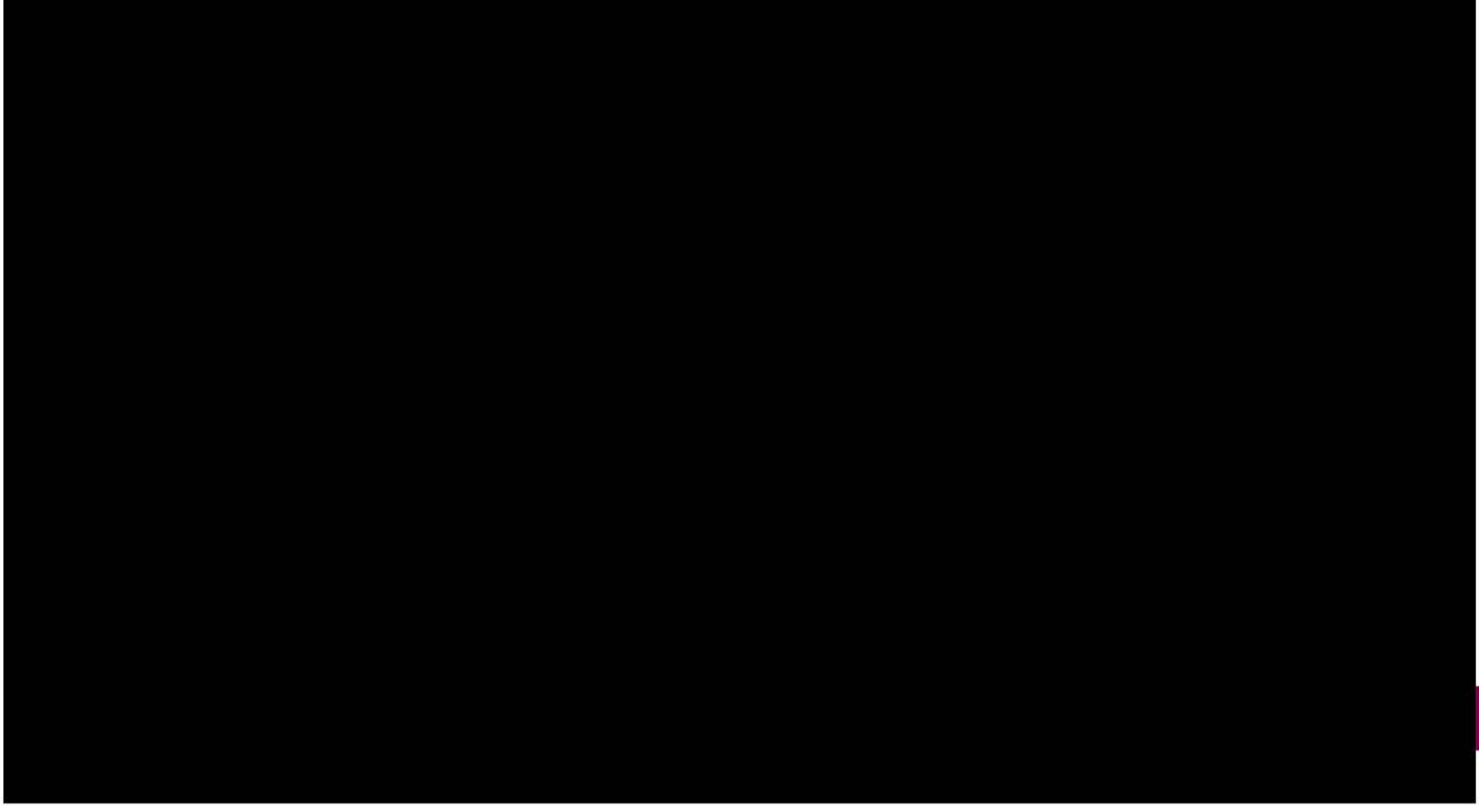
	Design	Population	Treatment	Endpoints	Current efficacy readout
UK P2/3 (COV002)	Single-blind, randomised safety and efficacy study, with immunogenicity sub studies	Main efficacy trial: Healthy adults aged ≥18 years. Sequential age escalation to immunogenicity sub studies: 1. Healthy adults aged between 56 – <70 years 2. Healthy adults aged 70 years or older	Approximately 10,000 participants 1:1 ratio to receive AZD1222 or MenACWY and followed for 12 months.	COVID-19 virologically confirmed symptomatic cases (PCR positive).	Interim ~15 primary endpoint cases Primary ~30 primary endpoint cases
Brazil P3 (COV003)	Single-blind, randomised study of safety, efficacy, and immunogenicity	Health professionals and adults with high potential for exposure to SARS-CoV-2, aged ≥18 years.	Approximately 5,000 participants 1:1 ratio to receive AZD1222 or MenACWY and followed for 12 months.	COVID-19 virologically confirmed symptomatic cases (PCR positive).	Primary ~30 primary endpoint cases
South Africa P1/2	Double-blinded, randomised, placebo controlled	Healthy adults aged 18-65 years, living with and without HIV	~2000 participants 1:1 ratio to receive AZD1222 or Placebo and followed for 12 months.	PCR positive COVID-19 disease cases	
Pooled			~17,000 participants (~8500 AZD1222 and ~8500 Placebo) followed for 12 months.	COVID-19 virologically confirmed symptomatic cases (PCR positive).	Proposed: Interim ~20 primary endpoint cases Primary ~40 primary endpoint cases

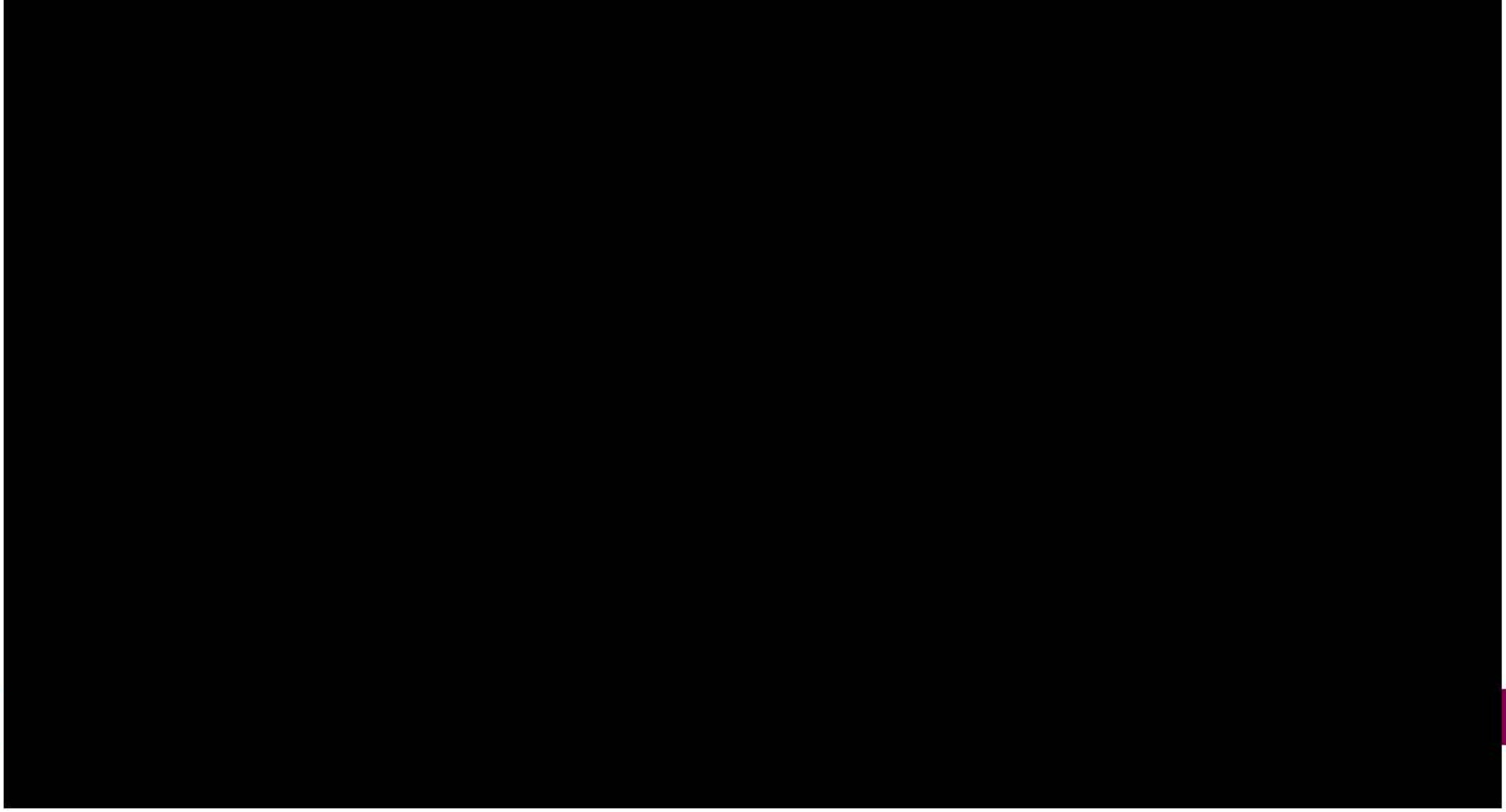
AZD1222 Vaccine

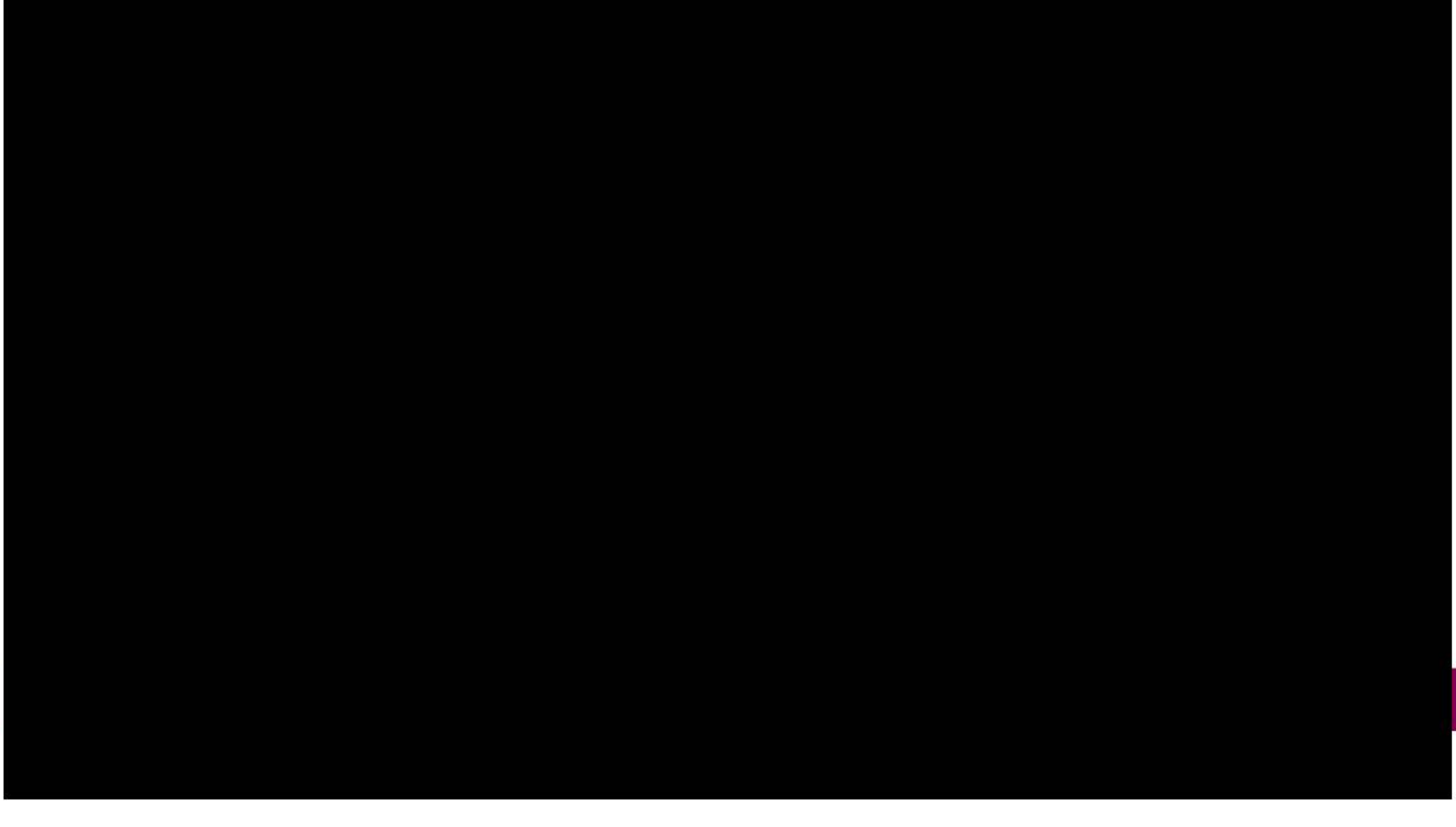
Key CMC Questions

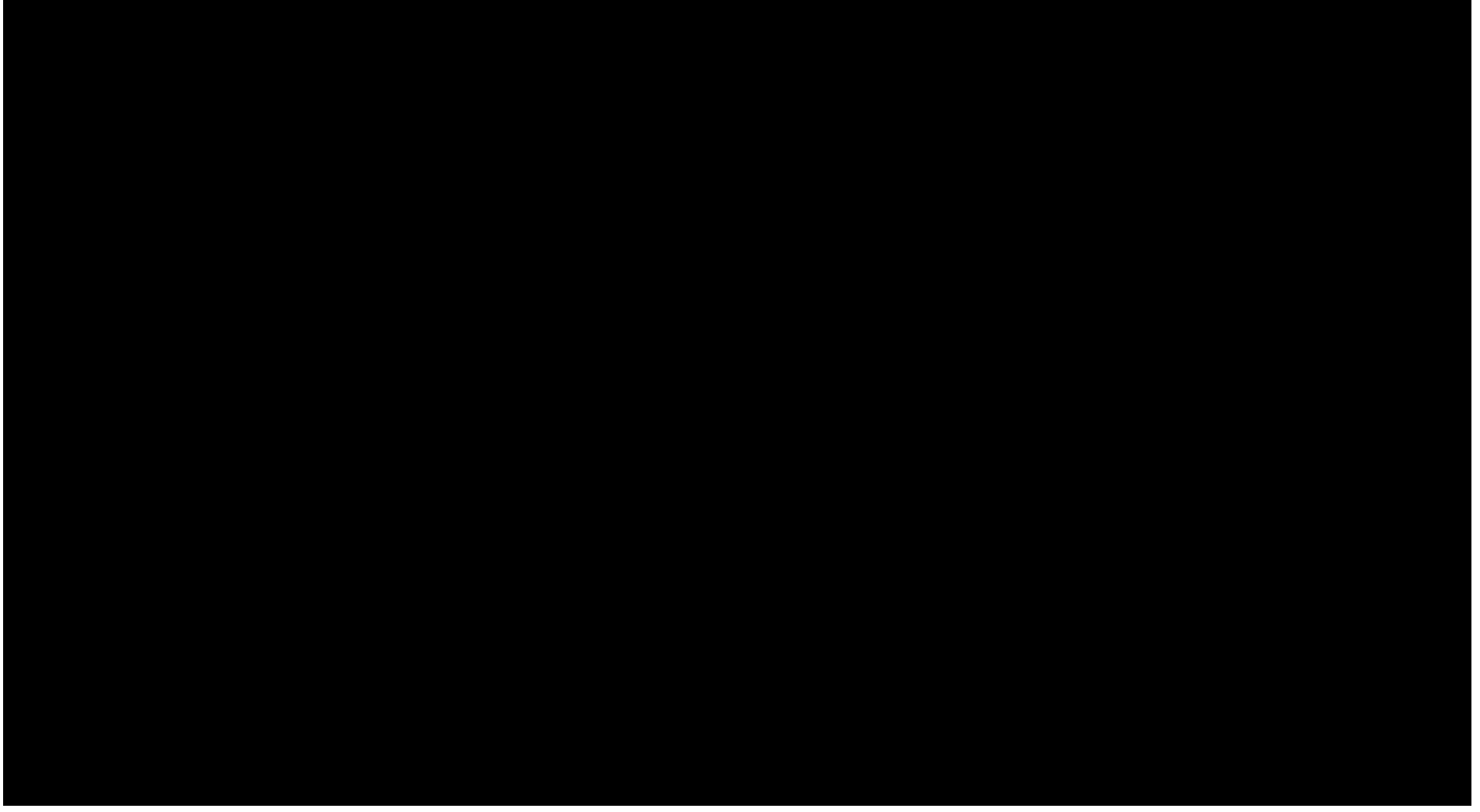
CMC Question: Process Validation and Analytical Comparability Strategy

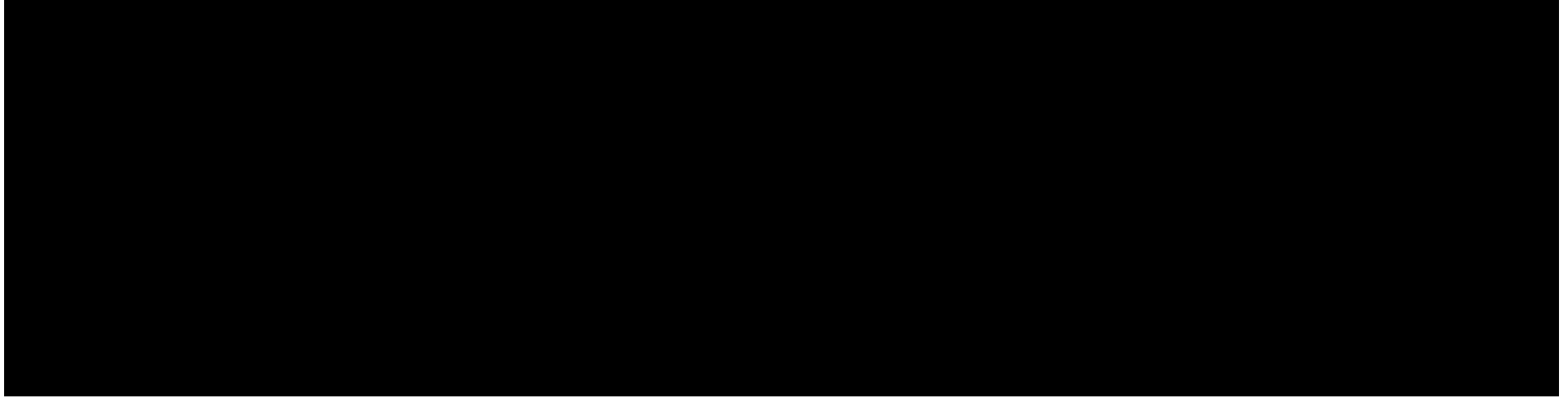
Question:







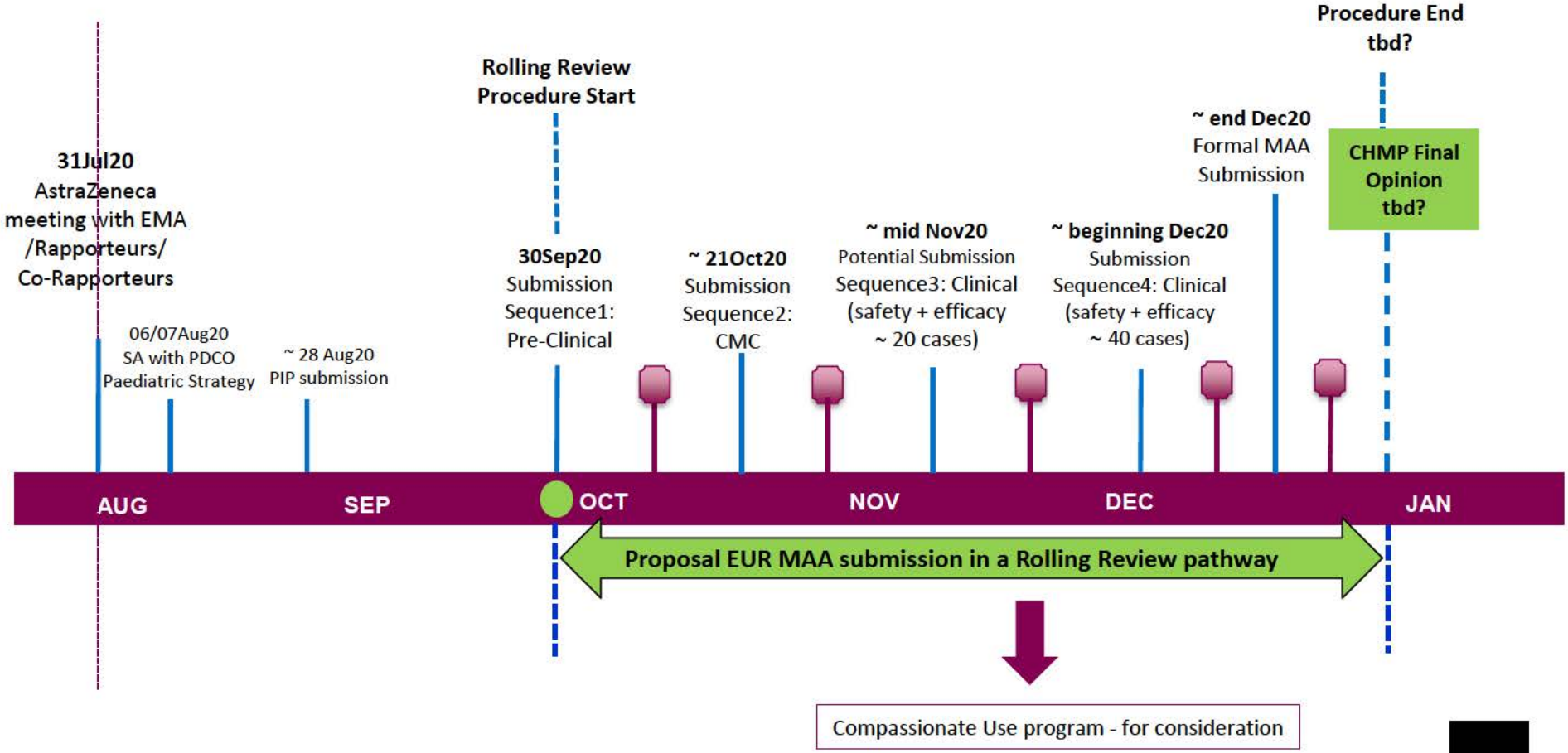




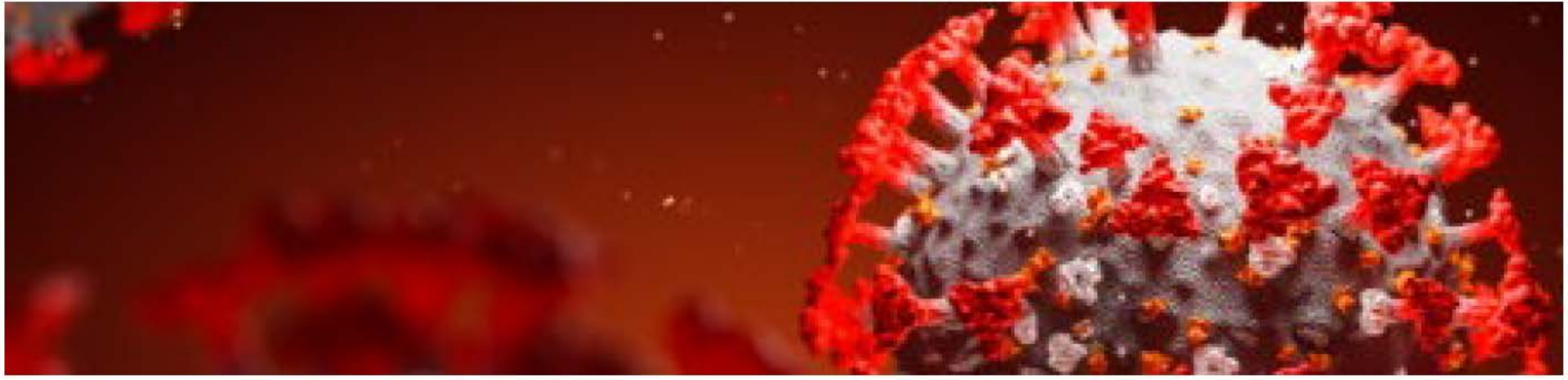
AZD1222 Vaccine

Key Regulatory Questions

Proposed timelines for the MAA submission in a rolling review

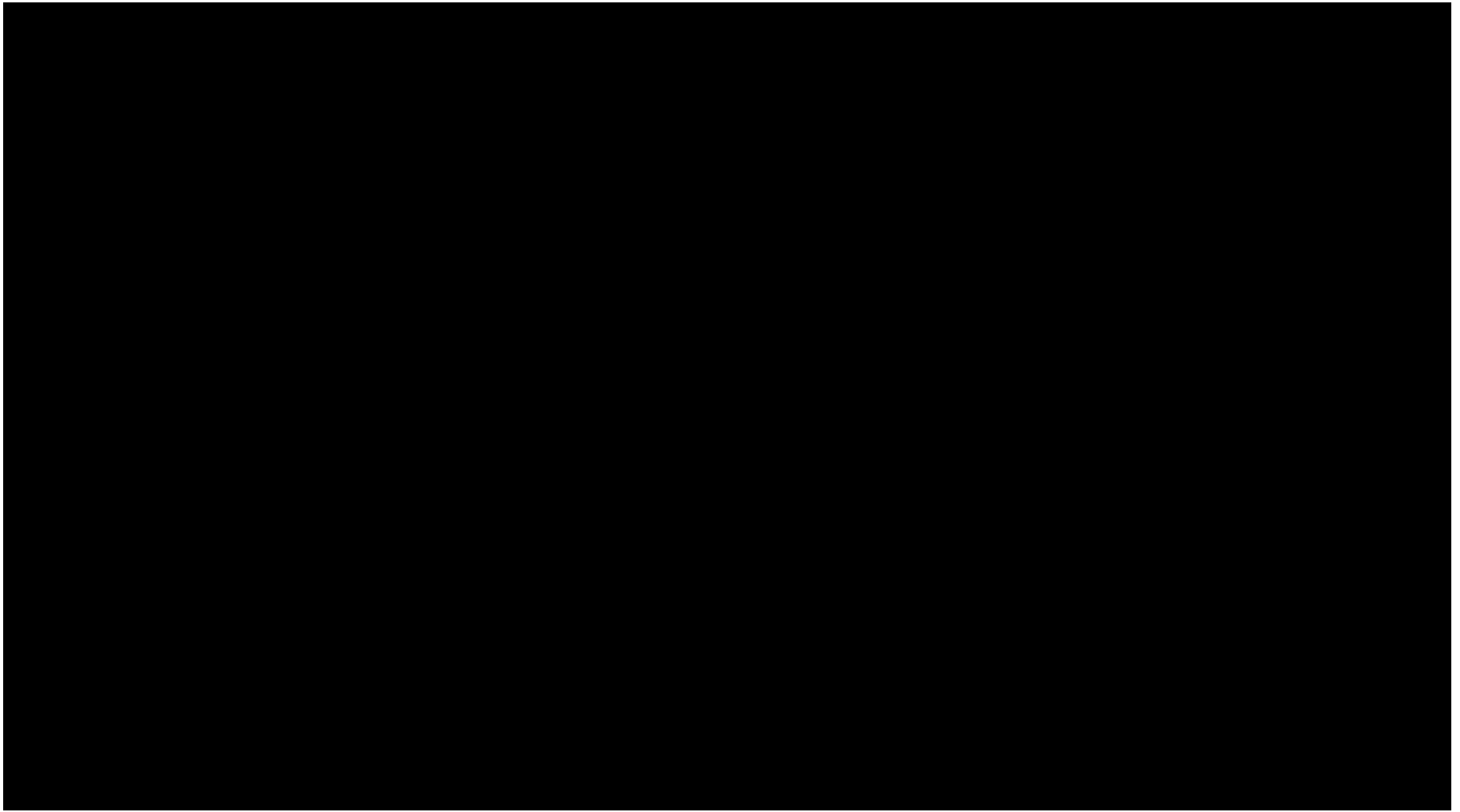


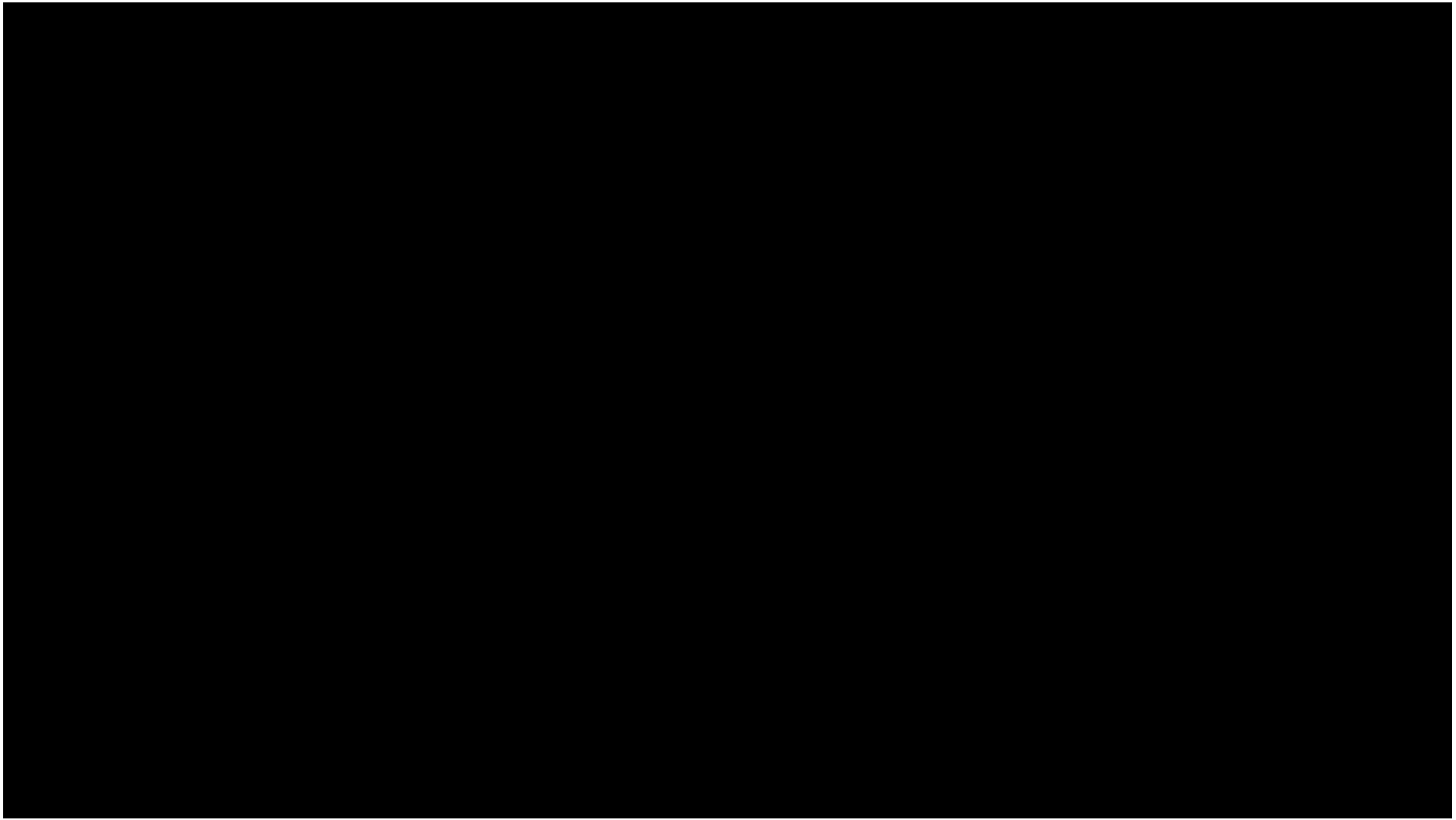
Other Sponsor Questions – Sponsor appreciates EMA Written Response by 07Aug20

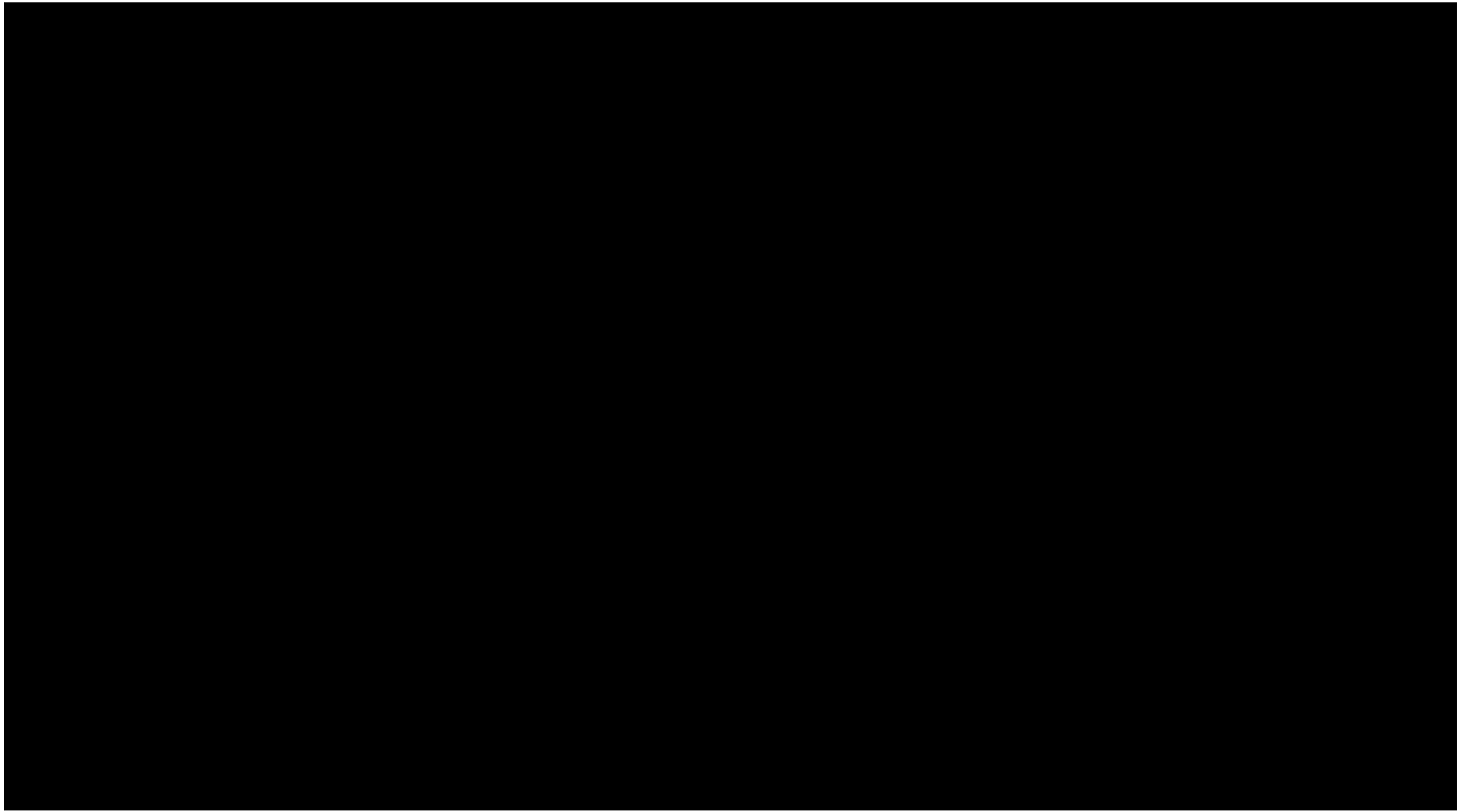


AZD1222 Vaccine

Other CMC Questions

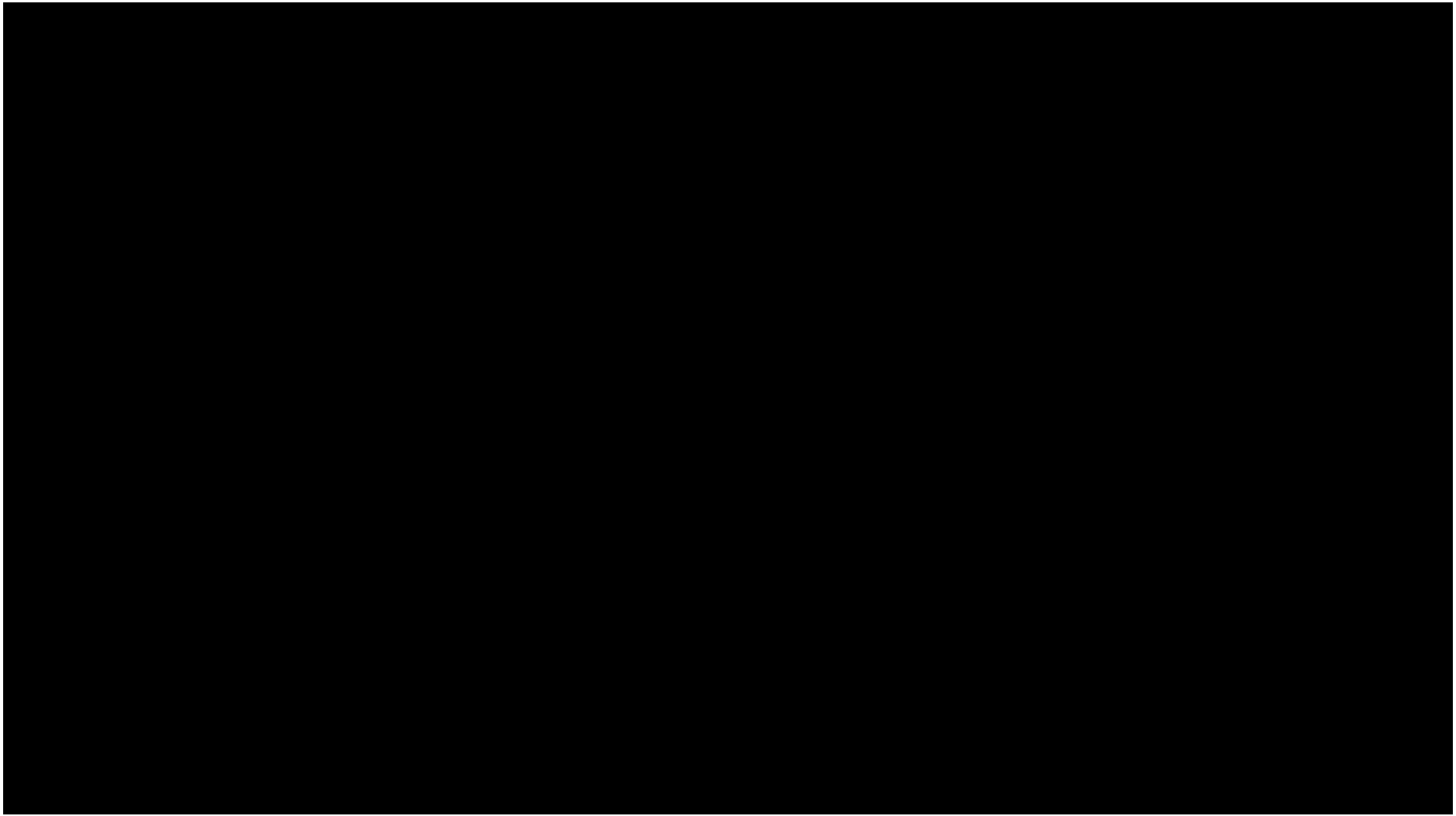






AZD1222 Vaccine

Non-Clinical Question



AZD1222 Vaccine

Other Regulatory Questions

Regulatory Questions

[redacted]

Regulatory Questions

[redacted]

AZD1222 Vaccine

ERA Questions

Environmental Risk Question

Question:
Can the Agency advise on the following:

- **Applicable document format and content for the ERA (Annex II)/technical and scientific information (Annex IIIA and IV)/SNIF/ proposed post-marketing environmental monitoring plan (or justification for omission)**

- **Review process (assessors and timing of review questions), if known**

- **Possibility of a meeting specifically focused on the ERA in Sept/Oct to discuss the results of the gap analysis (see below)**

Company Position:

A gap analysis of data required for Module 1.6.2 is being conducted. The ERA, based on available data, will be submitted with Sequence 4 (Dec). Given the expedited nature of the programme, it is expected that some information will not be available at submission. AstraZeneca would like to discuss the content of the ERA at the proposed meeting in Sept/Oct.

[redacted]

AZD1222 Vaccine

Labelling Questions

Labelling Question

Question:
Does the EMA support the proposed vial label and carton mock-ups provided?

Company Position:

- The carton meets the minimum requirements as described in *EMA Lessons Learned from the review of the labelling of centrally authorised pandemic vaccines 25th January 2016 – section 5.4 Outer Labelling*
- Due to the size of the vial label (vial size 5ml, 6ml, 10ml), it is proposed that only the Proper Name is used due to size constraints.
- AstraZeneca propose English only vial label and carton for all EMA markets.

Labelling Question

Question:
Does the EMA support the proposal for the abbreviated printed Patient Information Leaflet (PIL) and HCP Instructions and the use of a dedicated AstraZeneca website to access approved Product Information electronically?

Company Position:

- Due to logistical and space constraints of the carton, AstraZeneca proposes to provide a printed abbreviated PIL and HCP instructions in the form of a paper pad, which will be dispatched along with the vaccine cartons.
- The abbreviated PIL which will contain core information for patients and HCPs and inform them to visit the www.azcovid-19.com website to access the full approved PIL or SmPC, respectively.
  - Core information only is to avoid the printed component from becoming out of date and to allow printing in advance of regulatory approval to enable fast vaccine deployment.
  - The printed abbreviated PIL will be provided in English.
  - www.azcovid-19.com will be available for patients and HCPs to be directed to their country specific/language information which will be the most up to date following regulatory approval.
- Whilst website journeys are still under development, we do anticipate that patients and HCPs will enter the site at the same point. After which they will be able select information that is most appropriate to them.

Labelling Question

Question:
Does the EMA support the proposal for consultations with target patient groups for the package leaflet?

Company Position:

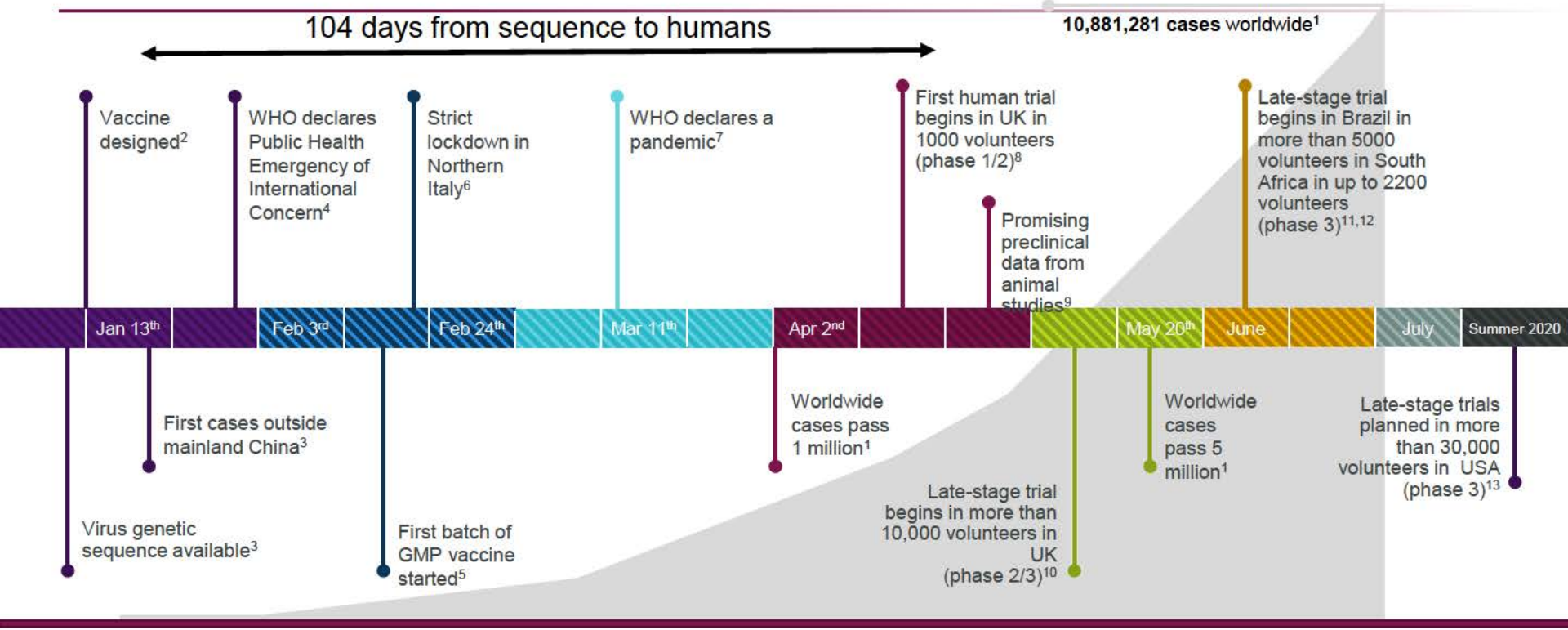
- As the QRD contains efficacy and safety data this will come in the one of the later rolling review sequences.
- Therefore, conducting consultations with target patient groups for the package leaflet will not be possible in the accelerated timeframe.
- AstraZeneca proposes to defer the consultations until after approval and any updates to the package leaflet can be captured as the result of the report in a post-approval variation.


Thank you & Closing

Confidentiality Notice

Back-up slides

From the ChAdOx1 platform to a vaccine candidate against COVID-19



Collaboration has made this possible[14]

COVID-19 Oxford Vaccine Trial

NIH National Institute of Allergy and Infectious Diseases

Public Health England

CSIRO

1. COVID-19 Dashboard. John Hopkins University website. Accessed June 25, 2020; 2. University of Oxford press release. Published March 18, 2020; 3. Novel coronavirus situation report – 1. World Health Organization website. Accessed June 22, 2020; 4. Global research and innovation forum consensus. World Health Organization website. Accessed June 22, 2020; 5. University of Oxford press release. Published February 7, 2020; 6. Italy imposes rules to stop coronavirus. The Guardian website. Accessed June 22, 2020; 7. COVID-19 situation report – 51. World Health Organization website. Accessed June 22, 2020; 8. Study NCT04324606. ClinicalTrials.gov website; 9. van Doremalen N et al. Online ahead of print. *bioRxiv*. 2020; 10. Study NCT04400838. ClinicalTrials.gov website; 11. University of Oxford press release. Published June 28, 2020; 12. Study NCT04444674. ClinicalTrials.gov website; 13. AstraZeneca press release. Published May 21, 2020;
14. COVID-19 Oxford vaccine trial – sponsors and partners. University of Oxford. Accessed June 25, 2020.

Emerging technology: The ChAdOx1 platform

ChAdOx1 MERS induced T-cell and antibody responses in humans[3]

ChAdOx1 MERS provided protective immunity in rhesus macaques[1]

ChAdOx1 MERS elicited neutralizing Abs and cellular immune response in mice[2]

ChAdOx1-vectored vaccine against MERS-CoV encoding the full-length MERS-CoV S protein developed[2]

ChAd-vectored vaccines against malaria, HIV, influenza, hepatitis C, tuberculosis, and Ebola well tolerated in humans, good immunogenicity[1]

Ab = antibody; CoV = coronavirus; HIV = human immunodeficiency virus; MERS = Middle East respiratory syndrome; S = spike

1. van Doremalen N et al. *Sci Adv*. 2020. http://dx.doi.org/10.1126/sciadv.aba8399. Accessed June 25, 2020; 2. Alharbi NK et al. *Vaccine*. 2017. http://dx.doi.org/10.1016/j.vaccine.2017.05.032. Accessed June 25, 2020; 3. Folegatti PM et al. Published correction in *Lancet Infect Dis*. 2020. http://dx.doi.org/10.1016/S1473-3099(20)30160-2.

Clinical back up slides

Phase 2/3 UK study, safety and efficacy endpoints

- **Primary efficacy endpoint:** PCR (oral/nasal) positive symptomatic cases of COVID-19
  - Participants tested if they present with a new onset of fever (≥37.8 C) OR cough OR shortness of breath OR anosmia/ageusia

- **Secondary efficacy:**
  - Hospital admissions associated with COVID-19
  - Intensive care unit (ICU) admissions associated with COVID-19
  - Deaths associated with COVID-19
  - Seroconversion against non-Spike SARS-CoV-2 antigens

- **Exploratory efficacy:**
  - PCR positive SARS-CoV-2 infection
  - Differences in viral loads between those with severe, mild, and asymptomatic PCR+ SARS-CoV-2

- **Primary safety endpoint:** Occurrence of SAEs throughout the study duration

- **Secondary safety (assessed after both dose 1 and dose 2):**
  - Solicited local reactogenicity signs/symptoms for 7 days following vaccination
  - Solicited systemic reactogenicity signs/symptoms for 7 days following dosing
  - Unsolicited adverse events (AEs) for 28 days following vaccination
  - Change from baseline for safety laboratory measures (except Group 4 – main group)
  - Occurrence of disease enhancement episodes

UK Phase 2/3 Study: Statistical Considerations

- Approximately 10 000 participants will be randomized in a 1:1 ratio to receive AZD1222 (n~5,000) or MenACWY (n~5,000) and followed for 12 months.

- For the primary efficacy analysis, approximately 30 cases are required across the active and control groups to detect a vaccine efficacy (VE) of 70% with ~ 85% power and ~50% power at the interim analyses.
  - These calculations assume an observed attack rate of 0.5% with a study success criteria if the lower bound of the confidence interval (CI) for VE is greater than 0%.

- An interim analysis for efficacy is planned for when approximately 50% of the total amount of statistical information is available (~15 cases). A Pocock boundary has been used to account for multiplicity, where the Type I error at the interim and primary analyses is 2.939% such that the overall Type I error is controlled at 5%.
  - An independent Data Safety Monitory Board (DSMB) will facilitate the interim analysis for efficacy and have the responsibility of evaluating cumulative safety and other clinical study data at regular intervals.

- Analysis of the primary endpoint:
  - VE, calculated as 1-relative risk (Relative risk is the incidence of infection in the vaccine group relative to the incidence of infection in the control group).
  - Evidence of efficacy if statistical significance is demonstrated at an adjusted 2.939% significance level using a Chi-squared test at either the interim or primary analyses.

- A statistically significant finding at the interim or primary analysis will not be considered a reason to stop the trial, however instead will be interpreted as evidence of efficacy.

Oxford-sponsored studies: Current efficacy analysis

Phase 2/3 study in the UK:

- Interim analysis planned after 15 accrued cases
- Primary analysis planned after 30 cases accrued (87% power to detect VE 75%).
- Pocock alpha spending method
- DSMB will review case accrual and assess sample size assumptions

Phase 3 study in Brazil :

- Primary analysis planned after 30 cases accrued (80% power to detect VE 70% (30-87), 5% alpha
- DSMB will determine probability of reaching trial objective and highlight need to detect more cases

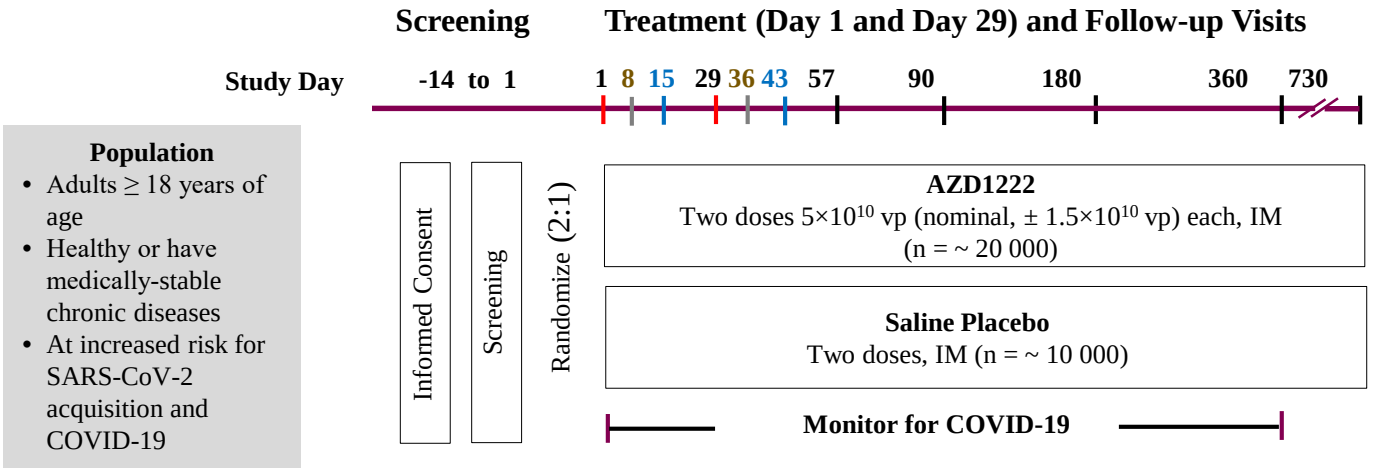
AZD1222 US Phase 3 Study Design

Design: Randomized, double-blind placebo-controlled

Number of subjects: 30,000, randomized 2:1 to two doses of either AZD1222(5 x10^{10} viral particles, nominal, ± 1.5 × 10^{10}) or placebo

– 3,000 subjects in a substudy that evaluates immune responses and reactigenicity

Study population: Adults ≥ 18 years of age who are healthy or have stable chronic diseases, and are at increased risk for SARS-CoV-2 acquisition and COVID-19



Study will gather data on vaccine's ability to prevent all SARS-CoV-2 infections as well as more serious illnesses

Primary endpoint:

- To estimate the efficacy of 2 IM doses of AZD1222 compared to placebo for the prevention of COVID-19 is adults ≥ 18 years of age
  - Participant defined as a COVID-19 case if their first case of SARS-CoV-2 RT-PCR-positive symptomatic illness occurs ≥ 15 days post second dose of study intervention

Additional efficacy endpoints:

- To estimate the efficacy of a two IM doses of AZD1222 compared to placebo for the prevention of SARS-CoV-2
  - Asymptomatic infections
  - Symptomatic COVID-19 using CDC criteria
  - University of Oxford-defined symptomatic COVID-19
  - Emergency department visits
  - Severe/critical COVID-19 and death

US Phase 3 Study: Statistical Considerations

- Approximately 30 000 participants will be randomized in a 2:1 ratio to receive AZD1222 (n~20,000) or placebo (n~10 000) and followed for 12 months.

- For the primary efficacy analysis, approximately 80 cases are required across the active and control groups to detect a vaccine efficacy (VE) of 70% with > 90% power and ~65% power at the interim analyses.
  - These calculations assume an observed attack rate of 0.5% with a study success criteria if the lower bound of the confidence interval (CI) for VE is greater than 30%.

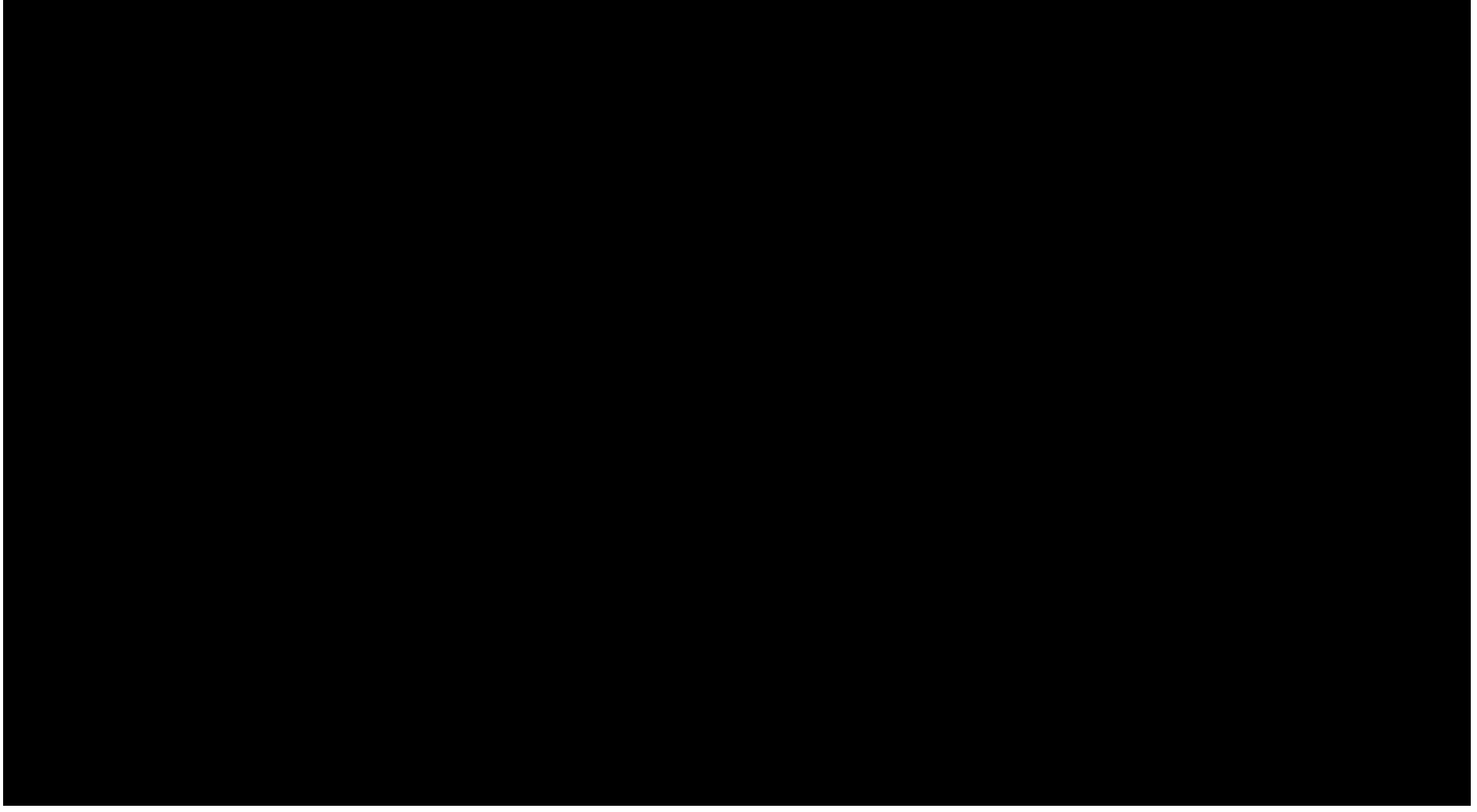
- An interim analysis for efficacy is planned for when approximately 50% of the total amount of statistical information is available (~40 cases). A Pocock boundary has been used to account for multiplicity, where the Type I error at the interim and primary analyses is 2.939% such that the overall Type I error is controlled at 5%.
  - An independent Data Safety Monitory Board (DSMB) will facilitate the interim analysis for efficacy and have the responsibility of evaluating cumulative safety and other clinical study data at regular intervals.

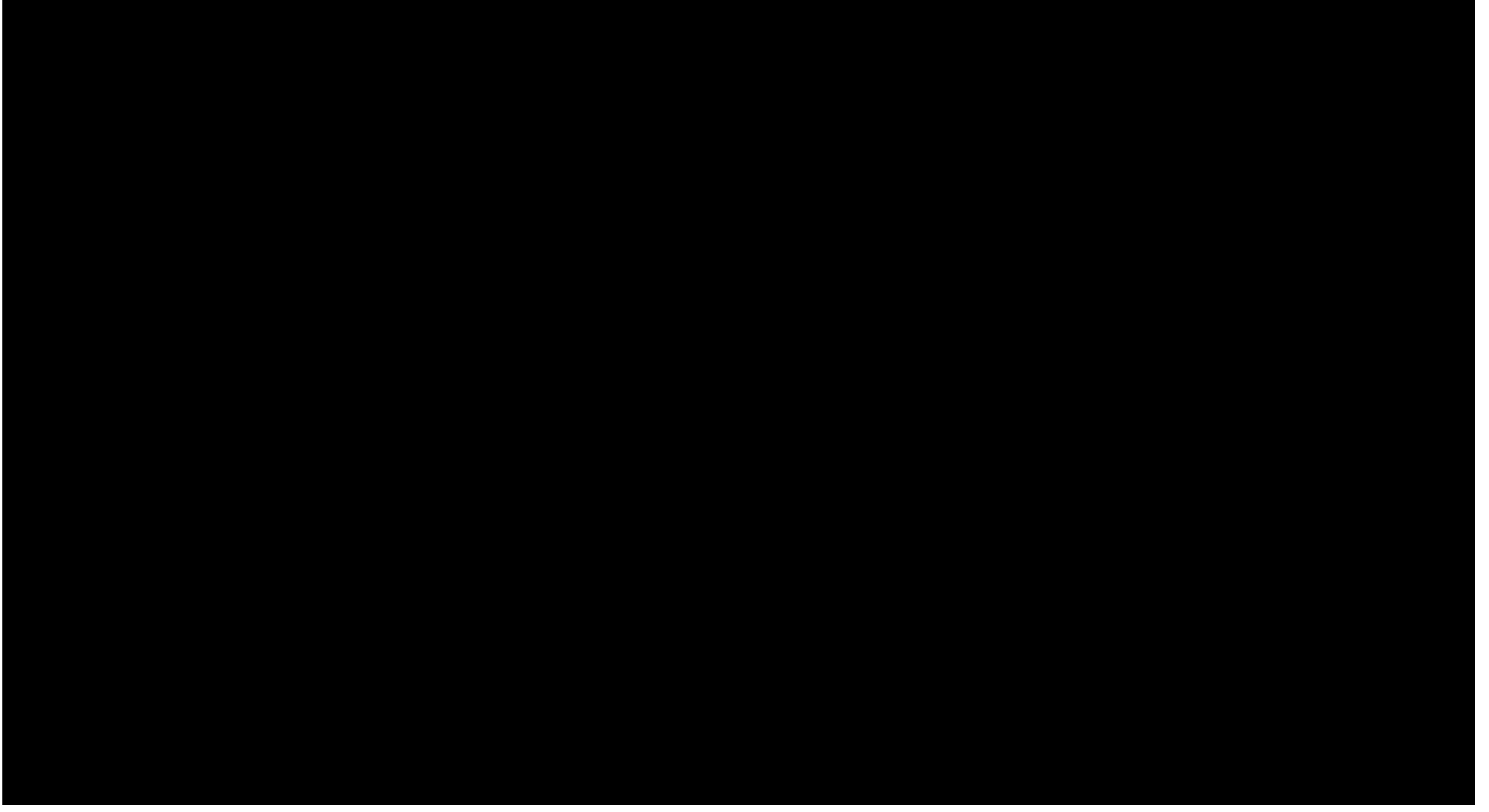
- Analysis of the primary endpoint:
  - VE, calculated as 1-relative risk. (Relative risk is the incidence of infection in the vaccine group relative to the incidence of infection in the control group).
  - Evidence of efficacy if the lower bound of the two-sided 97.06% CI above a 30% threshold using a Poisson regression model with robust variance at either the interim or primary analyses.

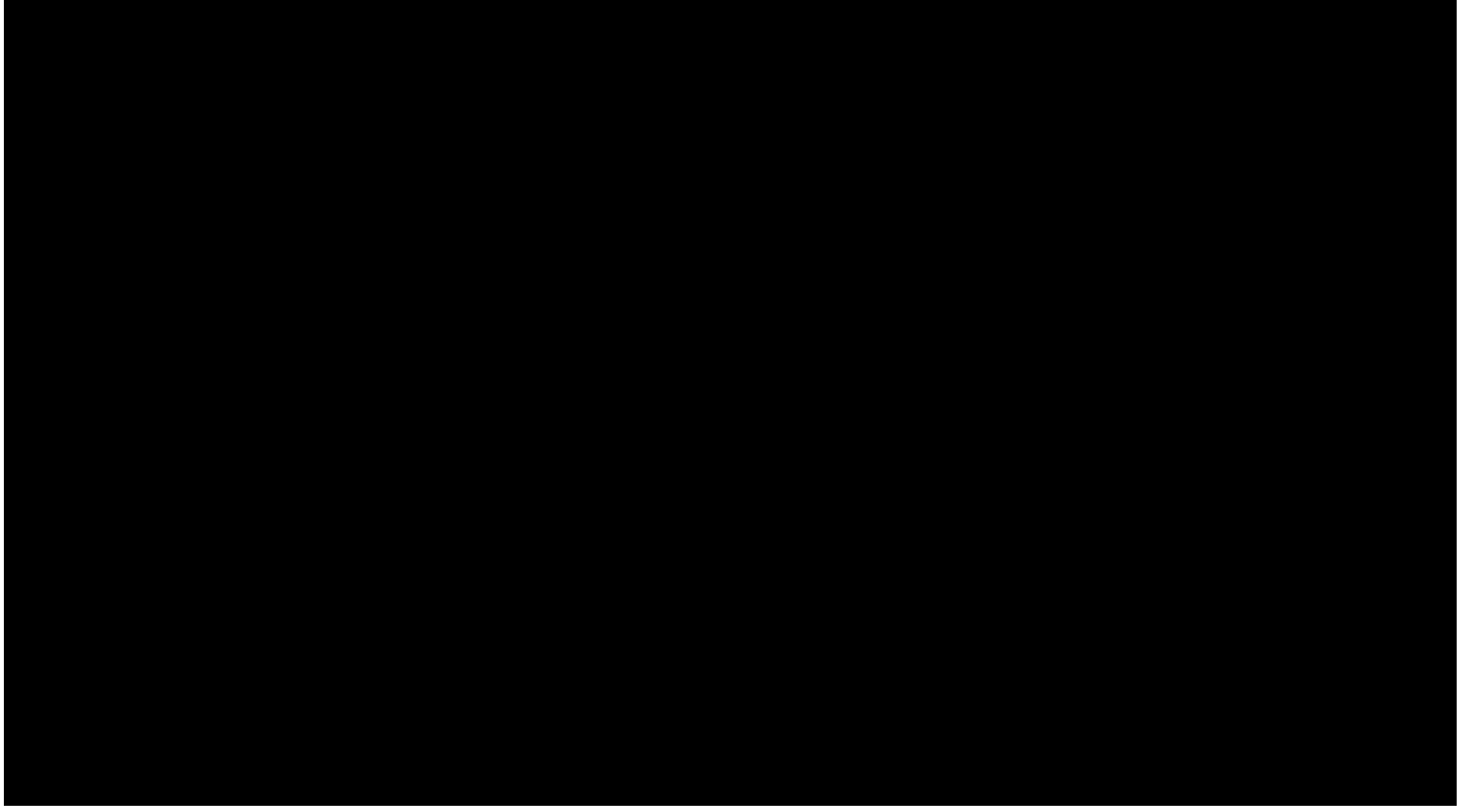
- A statistically significant finding at the interim or primary analysis will not be considered a reason to stop the trial, however instead will be interpreted as evidence of efficacy.

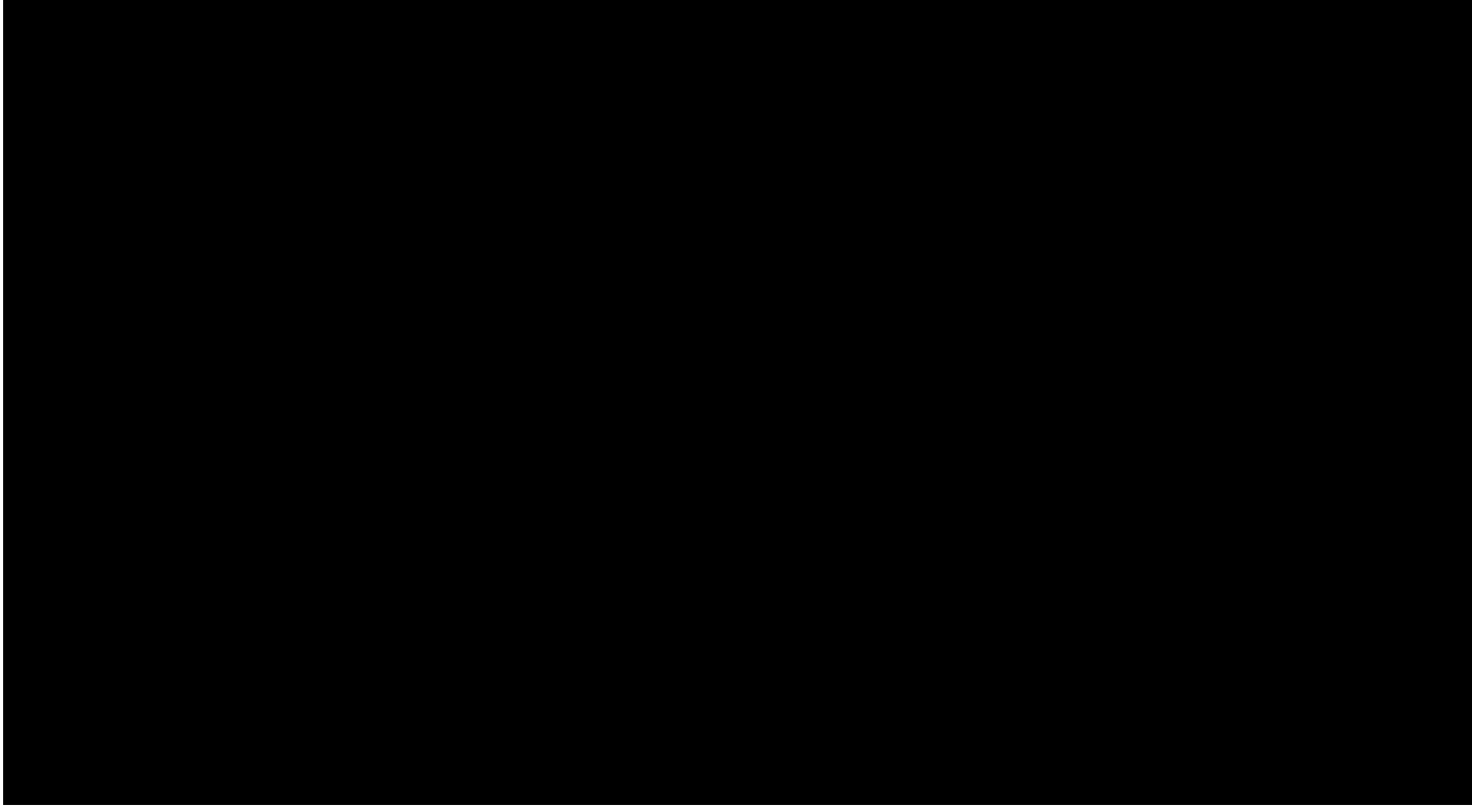
CMC back up slides (Analytical Comparability/Process Validation Details)

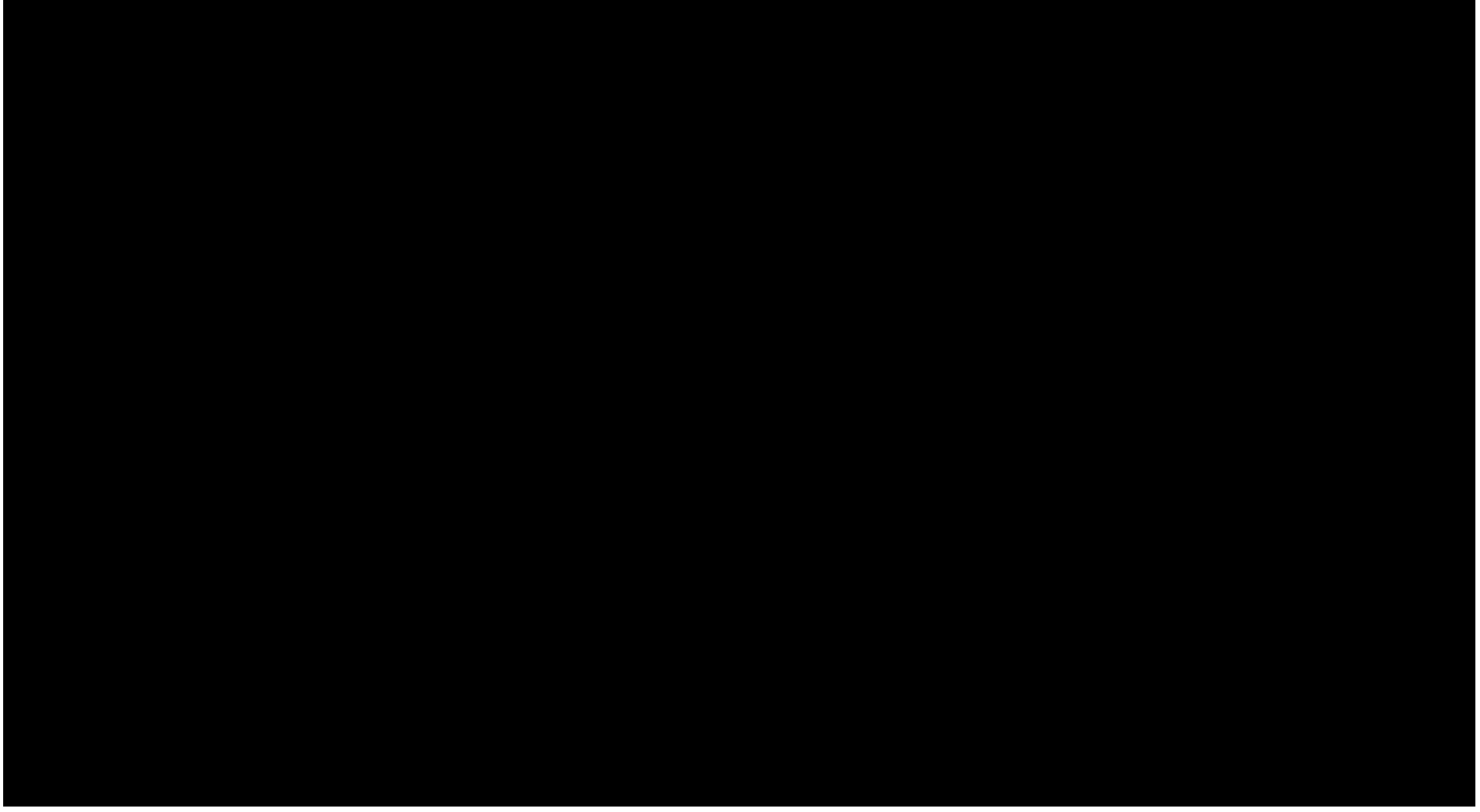
Pre-PV SOP Details

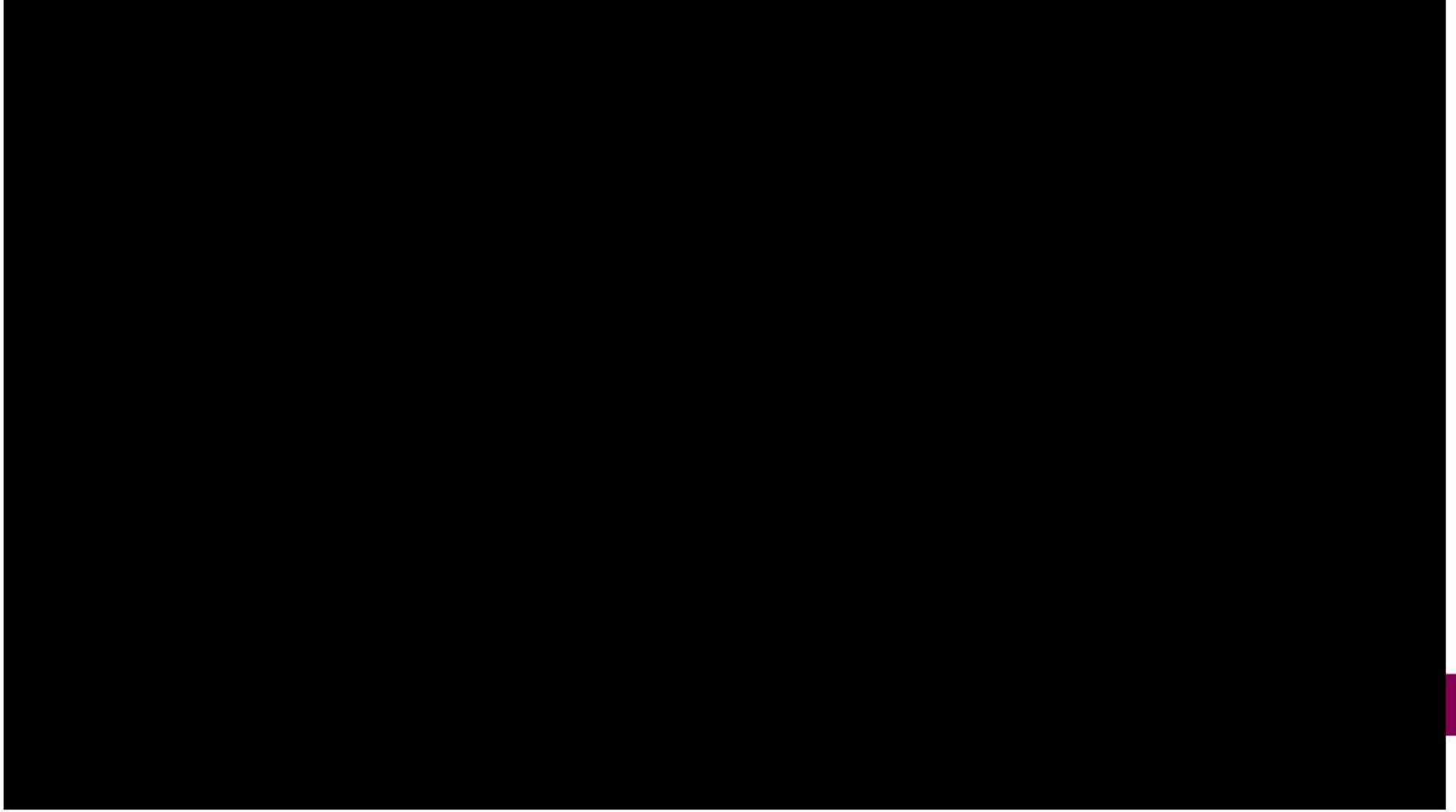








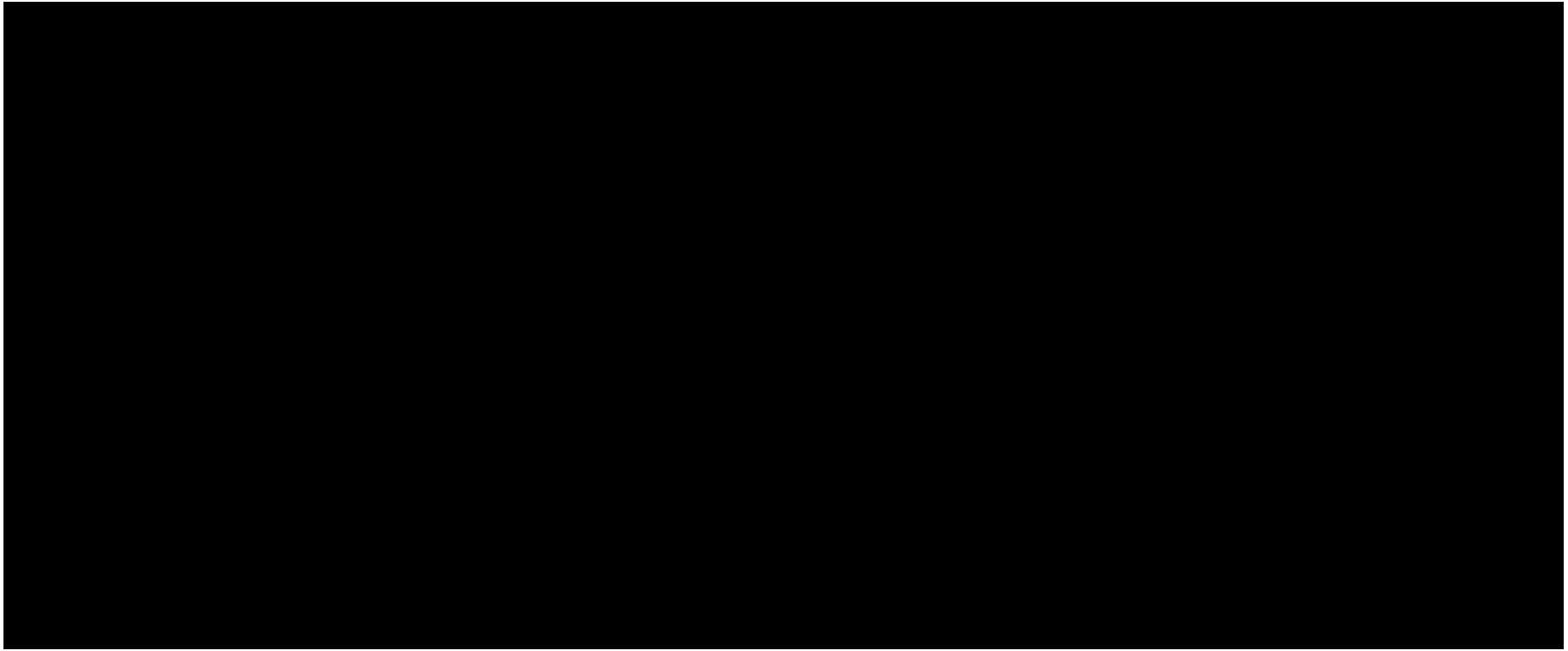




DS Release and Characterization

DS Release and Characterization

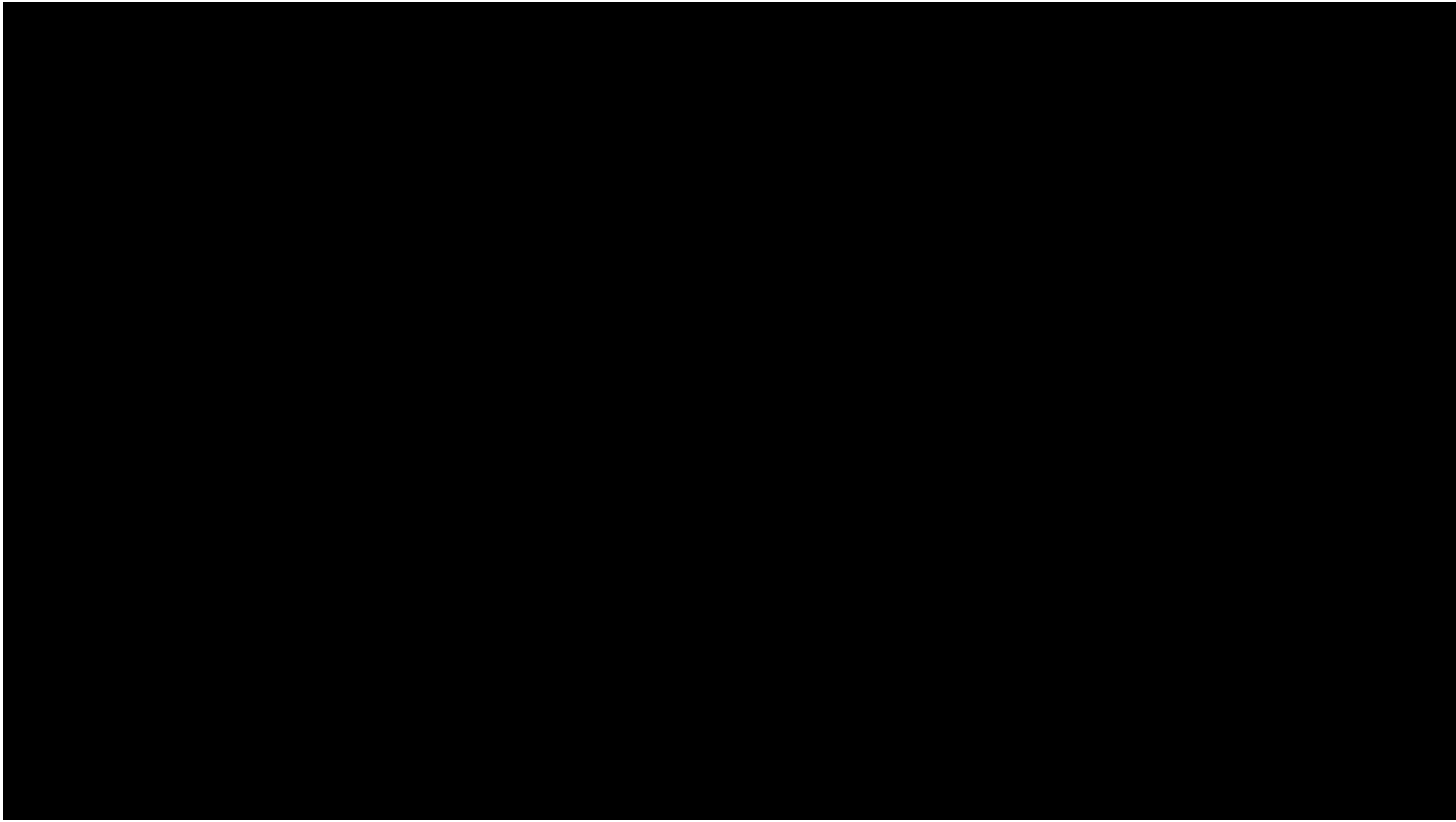
DP Release and Characterization

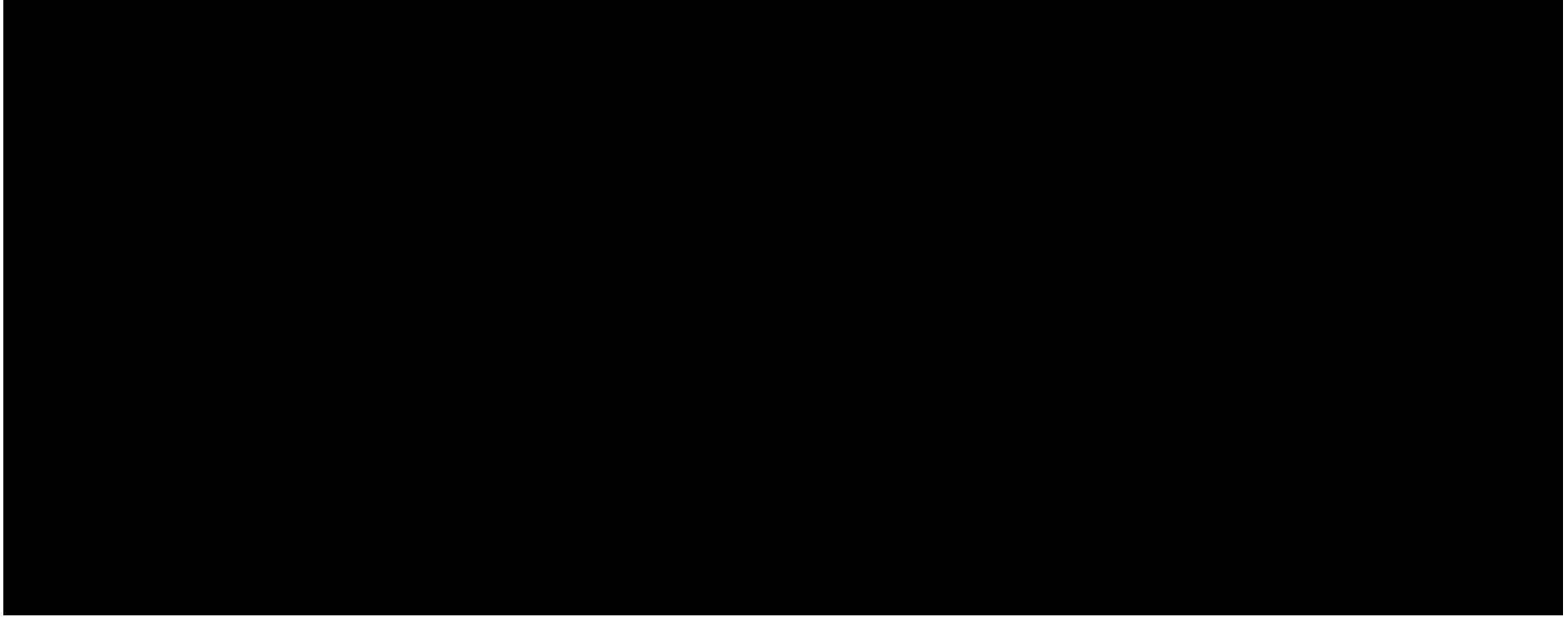


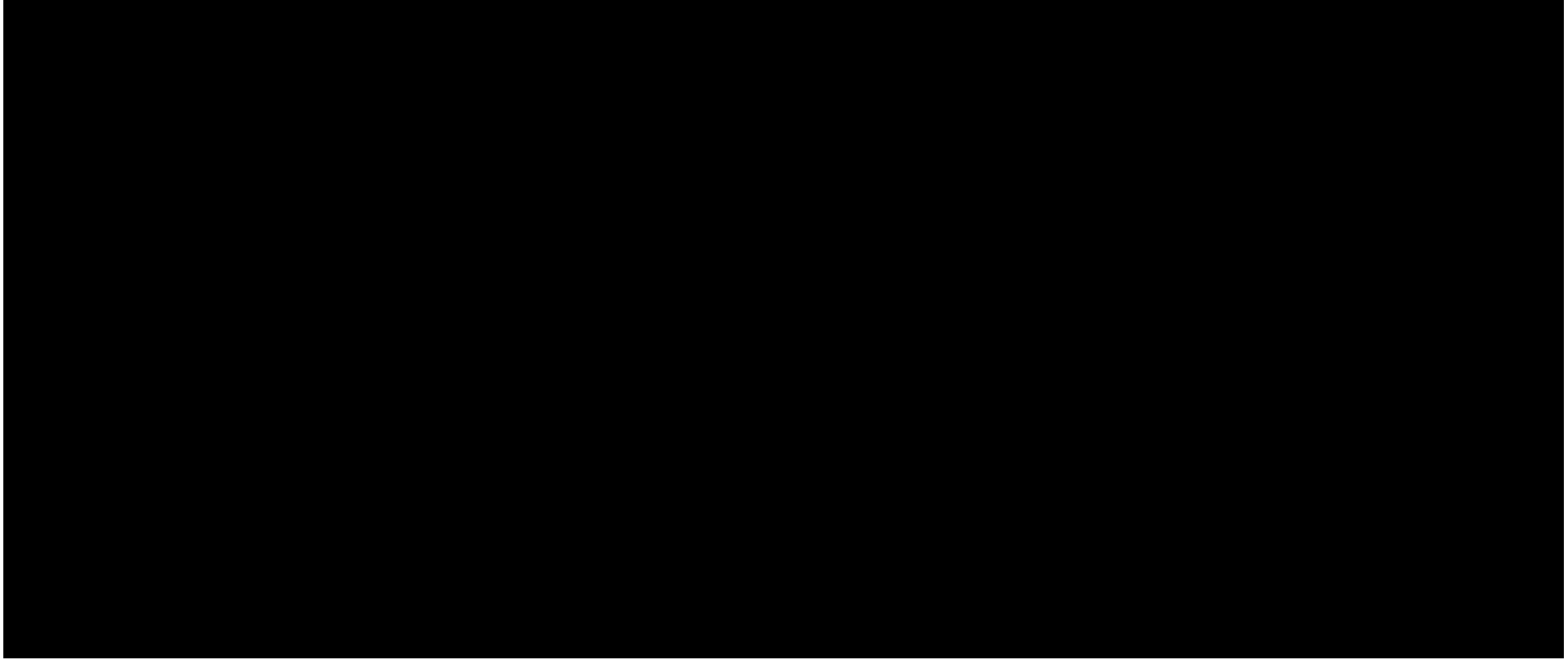
DP Release and Characterization

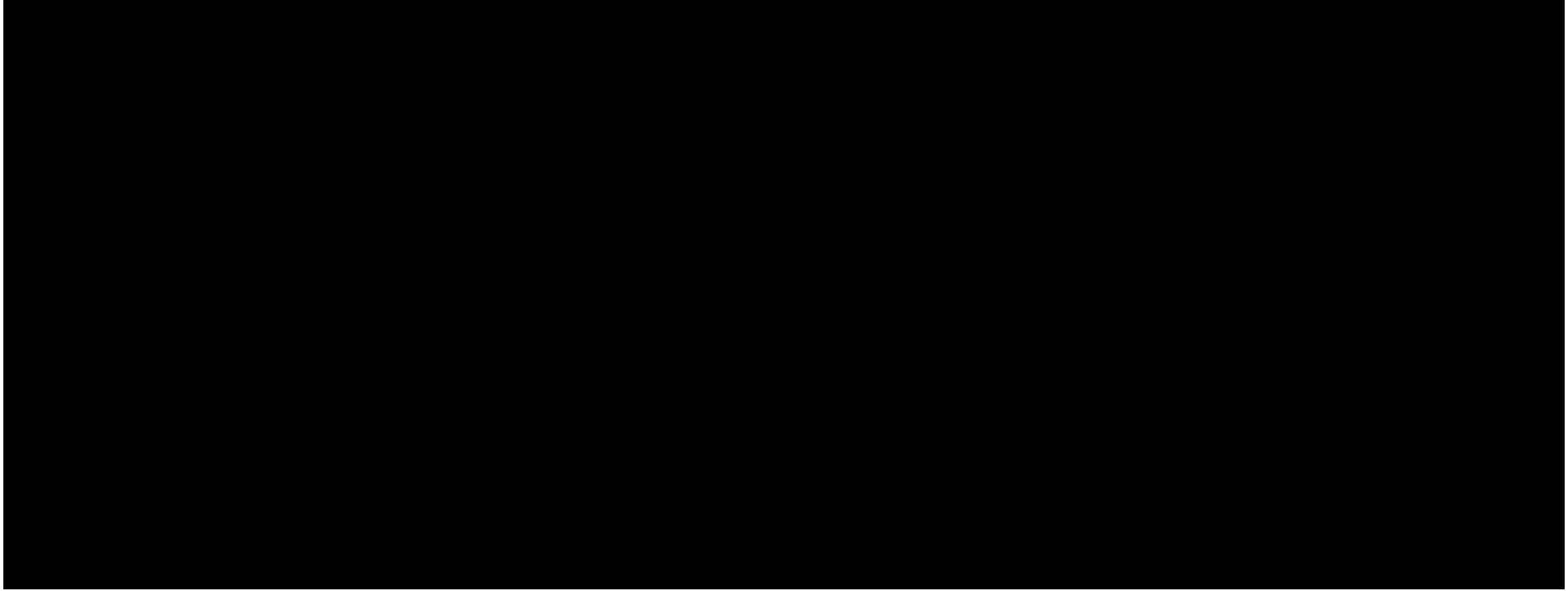
Comparative Stability

Process Validation Details



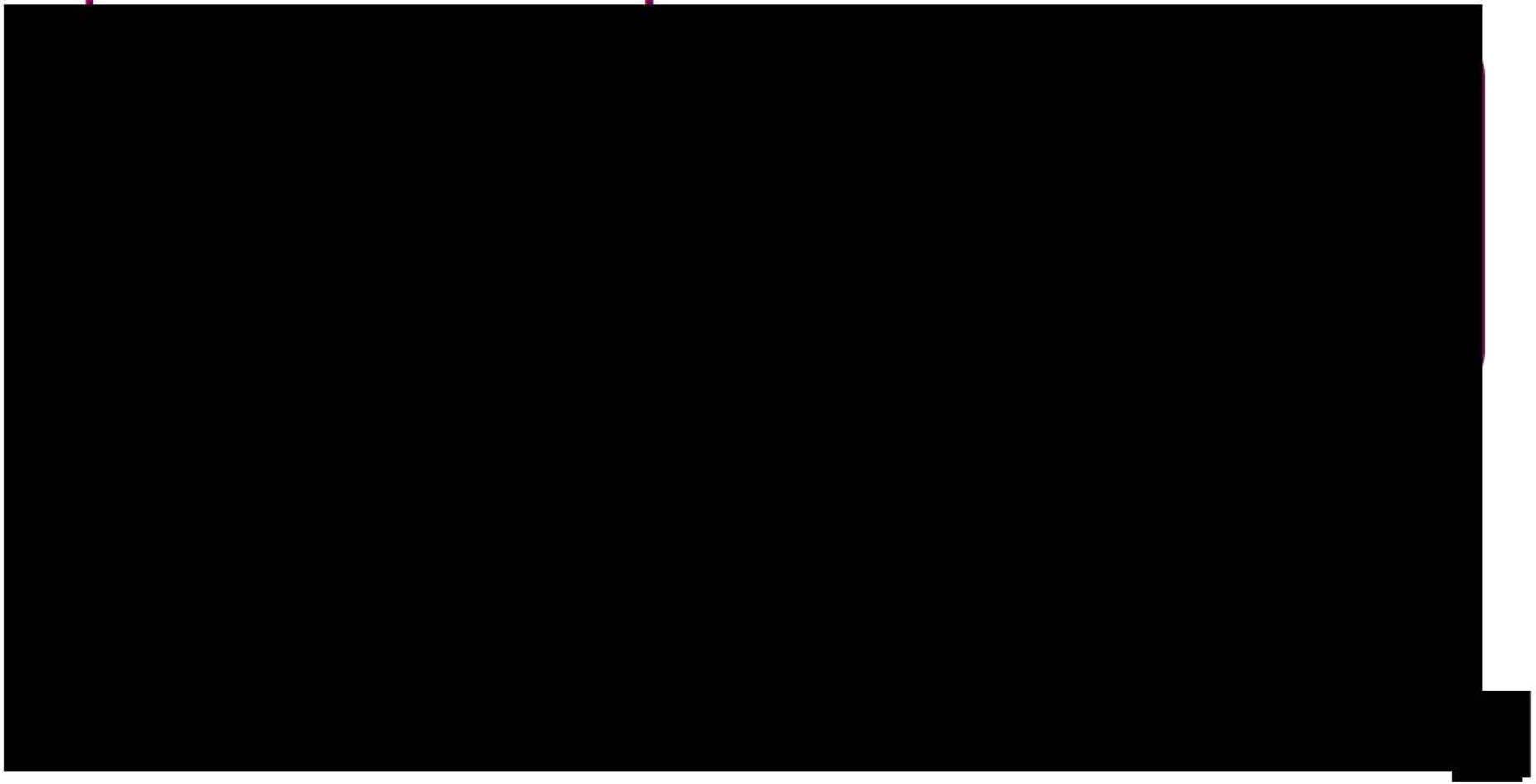




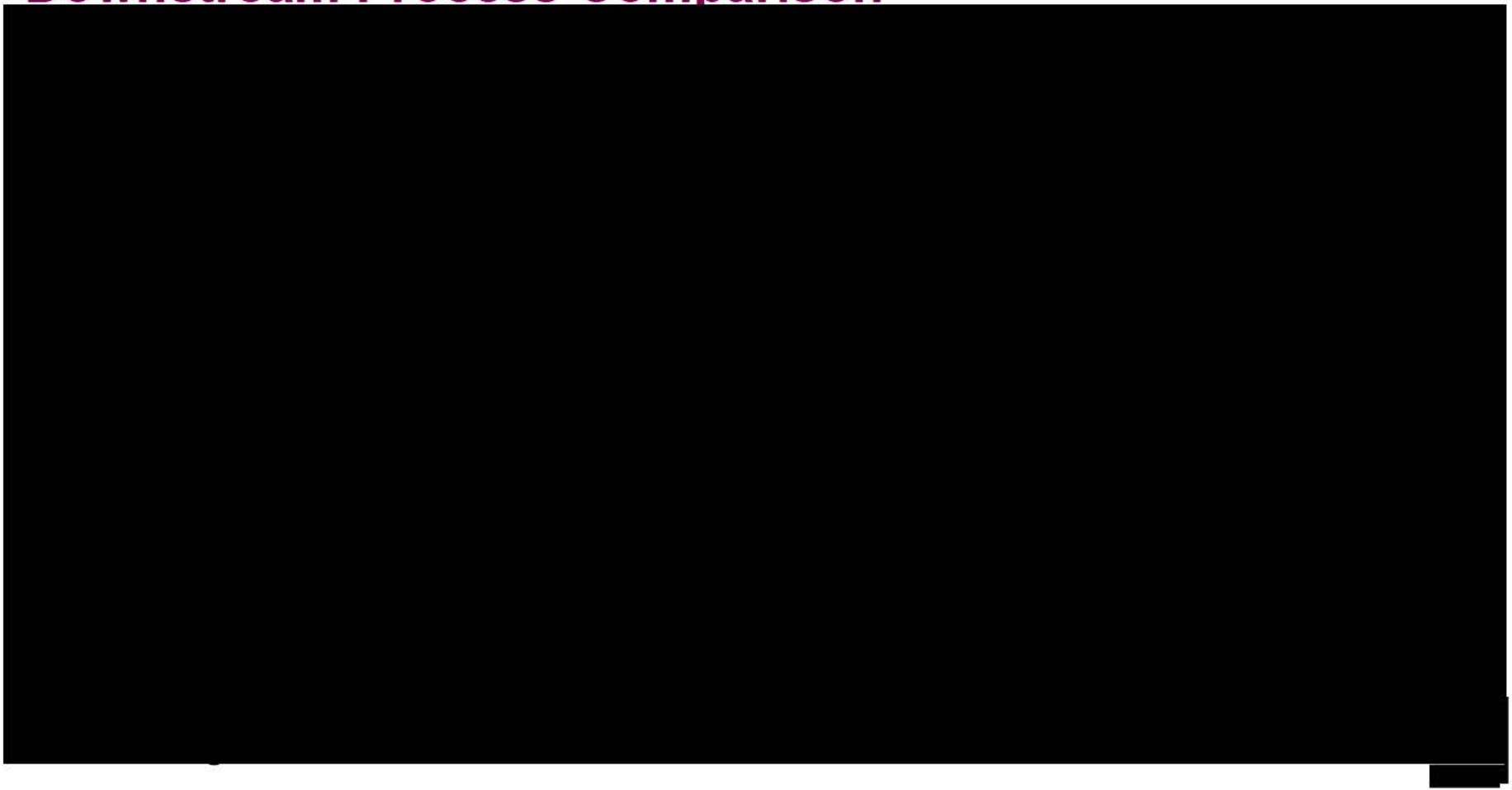


Process Comparison: Process 3 Clinical to Process 4 Commercial

Upstream Process Comparison



Downstream Process Comparison



Briefing Document for TGA

Drug Substance AZD1222

Briefing Document

TGA presubmission meeting

AZD1222

Invented Name:	N/A
Active substance:	AZD1222
Pharmaco-therapeutic group:	AZD1222 is a recombinant chimpanzee adenovirus expressing the severe acute respiratory syndrome-coronavirus-2 (SARS CoV2) Spike (S) surface glycoprotein.
Intended indication(s):	Prevention of coronavirus disease 2019 (COVID-19).
Sponsor:	AstraZeneca Pty Ltd
Version:	1
Date:	9 September 2020

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or special term	Explanation
ABN	Australian biological name
AUST R	Australian registration number
CMI	Consumer Medicine Information
COVID-19	coronavirus disease 2019
CSP	Clinical study protocol
DIR	Dealings involving Intentional Release (GMO)
GMO	Genetically Modified Organism
GMP	Good Manufacturing Practice
EMA	European Medicines Agency (EU Regulatory Authority)
EU	European Union
HCP	Healthcare professional
IMP	Investigational medicinal product
MAA	Marketing Authorisation Application
MedSafe	New Zealand Regulatory Authority
NBE	New Biological Entity Category 1 submission
OGTR	Office of the Gene Technology Regulator
PI	Product Information
PIL	Patient Information Leaflet (EU CMI equivalent)
PRAC	Pharmacovigilance Risk Assessment Committee
SARS-CoV-2	severe acute respiratory syndrome-coronavirus 2
SmPC	Summary of Product Characteristics (EU PI equivalent)
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons (The Poisons Standard)
TGA	Therapeutic Goods Administration (Australian Regulatory Authority)
TGO91	Therapeutic Goods Order 91 – Standard for labels of prescription and related products

1 INTRODUCTION

This briefing document has been prepared to support the AZD1222 Covid-19 Vaccine TGA presubmission meeting to be held on the 16th September 2020.

The objectives of this meeting are:-

(a) To update the TGA on the current status of the development programme for AZD1222.
(b) To discuss the key questions/issues described in the supporting documents
(c) To agree on the appropriate Australian regulatory pathway(s) to enable delivery of AZD1222 COVID-19 vaccine to the Australian public in the quickest way possible during this pandemic.

Where time permits, additional questions/issues raised within the supporting documents can also be discussed or can be considered for further post meeting dialogue.

AstraZeneca acknowledge that the current situation is unprecedented and as a consequence there are still many aspects of the product development which are ongoing or are under discussion. Some of the issues to be discussed do not yet have the full details in order to make a fully informed decision, so we are seeking guidance from TGA on potential scenarios. Others aspects of the future regulatory submission may not have the required information available within the usual timeframe so we are seeking guidance on alternative options. We expect that we will need to be in close dialogue with TGA during this initial pre-submission planning stage as well as the evaluation phase as further data are delivered and strategies further defined.

1.1 Current status in EU

A meeting was held with the EMA on the 31st July 2020 to discuss the proposed EU regulatory pathway and key questions for the quality, non-clinical and clinical documentation. A copy of the full EMA[1] slide deck has been provided to the TGA as the primary briefing document for the TGA pre-submission meeting.

[1] Rapporteur (Spain) / Co-Rapporteur (Netherlands); PRAC rapporteur (Belgium) / co-rapporteur (Spain)

An accelerated rolling review regulatory pathway was proposed by AstraZeneca, with the first rolling sequence to be lodged by the end of September (Non-clinical), with subsequent quality and clinical sequences following. The aim was to provide a formal consolidated MAA submission by the end of December 2020, with an accelerated EMA evaluation and approval to follow. The EMA agreed in principle to the proposal for a rolling review during the meeting, however at the time of preparing this TGA briefing document, AstraZeneca had not received the formal EMA feedback on this proposed pathway. We hope to provide a further update on the EMA status in the TGA pre-submission meeting.

AstraZeneca has sought rapid scientific advice from the EMA for the key questions for the Clinical (submitted 17 August), Non-clinical (submitted 20 August) and Quality (submitted 28 August) documentation. At the time of preparing this TGA briefing document, AstraZeneca had not received the formal EMA feedback, however this is expected prior to the TGA meeting for Clinical and Non-clinical aspects. We hope to provide a further update on the EMA responses in the TGA pre-submission meeting.

1.2 Proposed Australian supply route

Given the challenges of supplying the world with equitable access to this COVID-19 vaccine there are multiple supply routes in development across multiple countries and continents. As a consequence many manufacturing and/or testing facilities are in various stages of transition, with some facilities with investigational medicinal product (IMP) manufacturing licences only and/or limited GMP inspections. The source(s) of the vaccine for each country is also in a state of flux.

The primary route for the Australian supply is from CSL Behring/Seqiris from their Melbourne manufacturing facilities. Discussions, including technology transfer of the proposed manufacturing process for drug substance and drug product, are ongoing and there are still many aspects to be confirmed (e.g. packaging options and final QC testing sites for all methods).

We have also confirmed that we will receive European labelled stock for our initial batches from one of the proposed European supply routes (currently anticipated to be Halix/Catalent Anagni).

These issues are discussed further below, and also in the accompanying Quality Briefing Document.

2 BACKGROUND INFORMATION/SUPPORTIVE DOCUMENTATION

2.1 Quality background information and key questions

See accompanying Quality briefing document package (including annexes) and EMA slide deck from 31 July 2020 meeting

2.2 Non-clinical background information and key questions

See accompanying Investigator's Brochure and EMA slide deck from 31 July 2020 meeting

2.3 Clinical background information and key questions

See accompanying Investigator's Brochure, pivotal clinical study protocols (CSP) for studies COV001, COV002, COV003 and COV005, and EMA slide deck from 31 July 2020 meeting.

3 AUSTRALIAN SPECIFIC QUESTIONS

3.1 Proposed Australian regulatory pathway for supply

3.1.1 Emergency supply

While Australia has no formal Emergency Use Authorisation pathway similar to the USA, *Section 18A Exemption because of emergency* allows the Minister to grant an exemption to urgently supply medicines in order to deal with an actual threat to public health caused by an emergency that has occurred. It has been mentioned that COVID-19 would constitute a threat to public health, however the benefit-risk for a vaccine for prevention of COVID-19 in the general public may not meet the criteria for consideration for supply under Section 18A.

QUESTION 1

(d) Would the TGA consider that supply of AZD1222 for vaccination of higher risk populations such as Aged care residents/workers and/or HCP in affected regions may be eligible under Section 18A?

(e) If yes, what level of evidence would be required to support the request and what process would be required?

3.1.2 Registration pathway

The first major regulatory submission is expected in the EU and, as discussed in Section 1.1, there have already been discussions with the EMA including a proposal for a rolling review and accelerated evaluation. It is currently expected that the EU MAA will be the base dossier for the Australian dossier, with our initial batches for supply to be sourced from an EU supply route and provided in the EU packaging.

Collaboration with the EMA, or other major regulatory authority(ies), could help facilitate a priority evaluation by the TGA, enabling fast access to patients.

QUESTION 2

(a) Would the TGA accept a rolling submission in line with that proposed for the EU?

(b) Would the dossier need to formally submitted via a provisional approval or priority review pathway?

(c) Are the TGA open to or indeed considering a formal or informal collaboration with the EMA and/or other country(ies) for the evaluation of AZD1222?

(d) If yes for EMA collaboration,

  (i) Does the TGA have a preference for how they wish to receive the rolling sequences, evaluations and responses eg provide either formally (as sequences) or informally (via email) as they are provided to/received from the EMA and/or provide in a consolidated form close to approval?

  (ii) At what stage would the Australian specific documentation be required for submission (including any Module 3 aspects eg Australian supply route documentation)

(e) Are there any other considerations for these proposals?

3.2 Labelling and packaging development

As discussed in Section 1.2, we anticipate Australian supply from two different sources:

- European labelled stock from an EU supply route
- Australian labelled stock from CSL/Seqiris

While the final agreed product is yet to be confirmed for each supply route, we are anticipating that both sources will provide the COVID-19 vaccine solution for intramuscular injection in 10R glass type I multi-dose vials. Ten doses (as 0.5 mL per dose) will be in each vial with 10 vials per carton (ie total of 100 doses per carton).

As accelerated evaluation pathways are proposed for most countries, there is a need to undertake packaging at risk, prior to formal regulatory approval, in order to be able to supply vaccine to customers as soon as supply is approved. Hence we are requesting Regulatory Authorities to consider the proposed packaging components as early in the evaluation process as possible to allow these to go into production prior to product approval.

In line with standard AstraZeneca Australia process, the Product Information (PI) and Consumer Medicine Information (CMI) documents will be available electronically – via the TGA website, Australian AstraZeneca website and via all of the relevant Guildlink on-distributors.

The following naming conventions are under considerations for Australia. These are consistent with those proposed for the EU:

- *Product name*: COVID-19 Vaccine AstraZeneca
- *ABN*[2]*/active ingredient*: COVID-19 Vaccine (ChAdOx1-S [recombinant])

3.2.1 Global COVID-19 website and QR code approach

Given the rapid development of this product, the need to consider the various updates to datasets (eg safety information, expiry dating etc) during evaluation as well as post approval, and the tight manufacturing timeframes to supply vaccine as soon as approved, a global AstraZeneca website (and associated QR code) has been proposed.

While this website will be hosted globally, the intent is that the end user (Health Care Professionals (HCP) and patients/careers) will be able to access country specific information that is relevant for their needs. This will include access to information such as the most up-to-date Australian PI and CMI.

This proposal is still being developed and further information can be provided at a later date.

[2] ABN still to be formally requested

QUESTION 3

In principle, does the TGA agree that we can include a globally hosted COVID-19 vaccine website on the Australian packaging components to allow provision of country specific information to HCP and patients? Are there any other considerations for this proposal?

Please also see related questions below.

3.2.2 European supply

The first initial batches proposed for supply in Australia will be in EU packaging which will not be SUSMP or TGO91 compliant. We will therefore require exemptions to supply these batches on the Australian market.

The EU carton and vial label are still under discussion with the EMA however the most recent mock-ups for the anticipated Catalent Anagni supply route have been provided with this briefing document. The majority of the content is consistent with the intent of TGO91, however EU terminology may be used or there are TGO91 requirements which have not been met (eg omission of the Australian Sponsor details, AUST R, quantity of the active (both components), no active ingredient (vial label), list of excipients and quantities, multi-dose vial anti-microbial statement).

The current EU proposal is to include one abbreviated Patient Information Leaflet (PIL) in the carton, in lieu of the EU requirement for a PIL per patient in the carton. They do not require the Summary of Product Characteristics (SmPC) to be included in EU packs. The PIL has not yet been developed but can be provided for TGA consideration during evaluation, however we expect that the content will be consistent with the key information in the TGA approved PI and CMI.

The proposed EU carton and vial label will both include the proposed global website/QR code discussed above. This will allow Australian HCP/patients to access the TGA approved PI and CMI documents.

QUESTION 4

In principle, does the TGA agree that we can supply the EU labelled stock with the appropriate S14 exemption for compliance with TGO91? Are there any other considerations for this proposal?

3.2.3 Australian supply

We propose to register Australian specific artwork for the CSL/Seqiris supply which is compliant with the SUSMP requirements and the majority of the TGO91 requirements with an S14 exemption for compliance with agreed TGO91 aspects.

For TGA reference we hope to provide a visual representation of the Australian carton and vial label content prior to the meeting. The primary TGO91 aspects for consideration include:

- *Active ingredient*: The proposed ABN and the product name are very similar and given the space limitations on this small container label we proposed not to include the active ingredient name. This information will be on the accompanying carton. This proposal is also consistent with the proposed EU vial label.
- *Quantity of the active*: In line with the approach in the EU and the US, we are proposing to not include the quantity of the active ingredient (number of viral particles) on the carton or vial label.
- *Excipient names and quantities*: In line with the proposed EU carton we propose not to include the excipient names and quantities. The excipients will be detailed within the PI and CMI.
- *Anti-microbial statement*: While this product is a multi-dose vial it is proposed for administration in more than one patient. We therefore propose not to include the TGO91 antimicrobial statement.
- *Expiry date*: We propose not to include the expiry date on either component but instead the HCP would access this via the website/QR code. This will provide the most up-to-date shelf life information as it is extended with progress of the stability programme post approval. This also allows for the product to go into production and packaging prior to shelf life finalisation.

We also propose not to include a package insert. CMI are not required to be included in Australian packs and while not a formal requirement injectable products are often approved with a condition of approval to include the PI in the pack. The inclusion of the registered PI in the pack would significantly delay the supply of the product while the package insert is finalised including the final registration date, the component ordered then upon receipt put into production. A hard copy PI is also subject to quickly becoming out-of-date, particularly for a product with potential for safety updates. Provision of the PI via electronic means (routine sources in addition to the proposed COVID-19 website/QR code on the packs) provides the HCP and patients with the most up-to-date information for the product.

QUESTION 5

(a) In principle, does the TGA agree to review and accept the proposed Australian carton and vial label artworks early during the evaluation to allow these to go into production prior to product approval?

(b) Does the TGA have any initial concerns with any of the proposed non-compliant TGO91 aspects for the Australian supplied carton and/or vial label?

(c) Would the TGA be open to provision of expiry dates via the website/QR code allowing these to be updated to reflect the most up-to-date TGA approved shelf life?

(d) Does the TGA agree that the PI does not need to be provided as a package insert?

3.3 GMP clearance strategy

As discussed in Section 1.2 and the Quality Briefing Package, the manufacturing supply chains for AZD1222 are still evolving and many facilities are in different stages of transition. There is potential for some sites required for Australian supply to have limited GMP evidence in order to support a GMP clearance submission to cover the required scope of manufacture.

We are currently assessing the anticipated supply chain for the initial EU sourced products and the potential overseas sites associated with the Australian sourced product (eg cell bank/host cells, testing facilities and release for supply options) for GMP inspections to cover the required scope for registration. The majority of these sites are EU based (as per the Quality Briefing Document), however some are likely to be US based.

Where there is adequate evidence we aim to submit the GMP clearance applications as soon as possible, however once identified we will need to discuss options with the TGA for any sites where there may be GMP evidence limitations based on the current TGA GMP clearance requirements.

QUESTION 6

(a) Is the TGA open for discussion on the GMP clearance strategy for any sites of concern, and if so should this be a three-way discussion with the GMP clearance section and the Biotherapeutics evaluation sections?

(b) Will the TGA be flexible regarding the GMP clearance requirements in this pandemic situation? For example, if a formal priority review determination is required can we submit without approved GMP clearance for all sites, and are the options for lodging the application form without all sites having a GMP clearance form submitted?

(c) Will TGA be able to fast track any compliance verifications if required for US sites?

(d) What options would TGA consider if there is no/insufficient evidence for a site(s) prior to TGA approval, eg:
   (i) Collaboration with another regulatory authority (eg Health Canada)?
   (ii) Evaluation of the documentation at hand with further evidence to be provided post approval once generated?
   (iii) A TGA virtual inspection?
   (iv) Other considerations?

3.4 Pharmacovigilance requirements

Standard pharmacovigilance obligations will be fulfilled by AstraZeneca for the vaccine. The following question relates to TGA pharmacovigilance activities.

QUESTION 7

Does the TGA have formal post-marketing surveillance plans for vaccine candidates at centralised or state level and how this will link to TGA adverse event monitoring activities?

3.5 Additional questions

3.5.1 Genetically Modified Organism (GMO)

AZD1222 is a GMO and preparation of various GMO dealings are currently underway to cover the transport, storage, manufacture and commercial supply within Australia. AstraZeneca (via our consultants) and CSL Behring/Seqiris have been working closely with OGTR on these applications and we aim to have these submitted prior to the TGA NBE dossier. Hence the *Module 1.5.3 Genetically modified organisms consents* submission requirements are expected to be met.

OGTR has already agreed to accelerated review of all dealings where possible, including the commercial supply DIR. They have requested a three-way discussion with TGA and AstraZeneca once the TGA regulatory pathway has been agreed to ensure that the TGA and OGTR timelines are aligned and all OGTR activities have been completed in time for TGA registration.

QUESTION 8

Is the TGA open to this OGTR request, and if yes please confirm who should attend from the TGA?

3.5.2 Human embryonic material

As the TGA are aware, the manufacture of AZD1222 involves the usage of Human embryonic kidney 293 (HEK293) cells. We are aware that the electronic submission declarations still include one regarding the product containing human embryos/embryonic stems cells or material derived thereof in accordance with Regulation 9B.

QUESTION 9

(a) Does the current submission declaration still require inclusion of a declaration in Module 1 if the product contains human embryos/embryonic stem cells or material derived therefrom.

(b) If yes, is this via inclusion of the form 'Therapeutic goods and use of human embryos or human embryonic stem cells or material derived therefrom' and where should this be included in Module 1 now that there is no longer a specific section for this information?

(c) In accordance with 9B the PI and CMI are required to include statements relating to this issue. Does the TGA have a preferred format/text for these statements?

3.5.3 TGA batch release

We are aware that TGA will be required to release all batches of vaccine planned to be supplied on the Australian market, including those from the Australian supply route as well as the fully imported European product. The initial batches are expected to be available for batch release in January-February 2021 (European supply) with the Australian supply following not long after.

Please note that some of the testing materials/reagents are in short supply and some are also GMO. We may also need to order further supplies from overseas depending on what is required by the TGA laboratories.

QUESTION 10

(a) Can the TGA confirm which tests they expect to physically conduct based on the proposed specifications provided in the Quality Briefing package provided for the presubmission meeting?

(b) Can the TGA request the required reagents/testing materials as soon as possible to ensure these can be provided in time to meet potential testing timelines?

(c) Does the current TGA OGTR dealing(s) already cover the provision of AZD1222 GMO materials?

(d) Will the TGA work with AstraZeneca to initiate the batch release testing for the European supply product prior to product approval?

(e) Is the TGA open to a three way discussion with Seqiris to agree on the most appropriate process for initiation and subsequent management of batch release of AstraZeneca product manufactured by Seqiris for release initially to the Department of Health.