Bioanalytical assays & IVDR: Roche Case Study: AAV study with a “vector shedding” PK Assay

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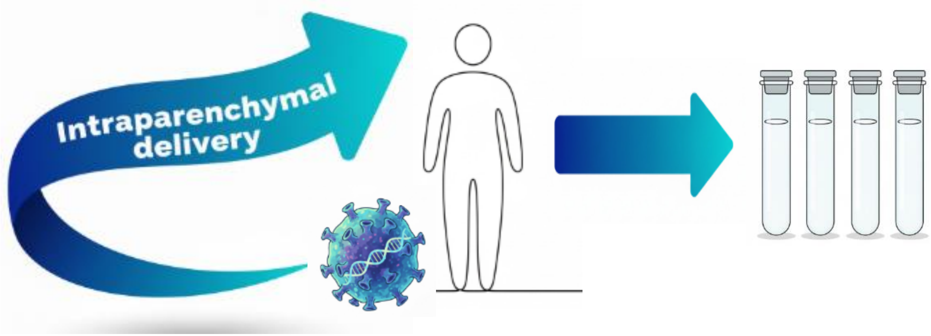
Louis Christodoulou, IVD & Regulated Biomarker Subject Matter Expert

AAV Gene Therapy

Gene Therapy Program; Surgical administration of an Adeno-Associated Virus (AAV) vector (replication deficient, non-integrating) to deliver (one time) a Gene Therapy payload in patients with a devastating brain disorder.



Samples collected for quantitative polymerase chain reaction (qPCR) of vector genome copy number in whole blood, saliva, urine and semen *to provide information about the likelihood of transmission to untreated individuals*[1] through an assessment of vector shedding.

It is Vector shedding which is the focus of this presentation, to explore the considerations around the necessity for running a CPS and the wording within the protocol.

[1] Design and Analysis of Shedding Studies for Virus or Bacteria-Based Gene Therapy and Oncolytic Products. Guidance for industry, FDA, CBER, August 2015

Detection and duration of vector DNA in peripheral fluids

The administration route is specifically chosen to keep the vector localized within the Central Nervous System (CNS) and minimize systemic exposure. To assess we look at vector shedding.

Fluid	Anticipated Half-Life / Clearance Time	Key Considerations
Blood	If detected, clears rapidly. A systemic half-life of ~12 hours has been observed for CSF delivery, serving as a rough proxy.	The amount escaping the brain is expected to be very low.
Urine	Transient detection, peaking at 24-36 hours and often undetectable after 4-5 days.	Primarily fragmented DNA is detected, not intact vector.
Saliva	Transient detection, peaking at 48-72 hours and often undetectable after 4-5 days.	Levels are typically very low.
Semen	Very low to no shedding is anticipated. If detected, clearance is expected to be rapid (weeks).	A critical safety monitoring parameter, but significant shedding is not expected with this route of administration.

Low transient levels in the periphery shed, rapidly cleared.

Vector shedding sampling

Baseline, Day.3 & 7, Month.1,2,3, .6,9,12,18, Year.2, 2.5, 3, 4, 5

Instruction to Clinical site

Results

Results

Joint Monitoring Committee

Results are not returned to the investigator at the clinical site.

How is data used?

lifting lifestyle restrictions & discontinuing sampling

Lifestyle restrictions (e.g., contraception, pregnancy, breastfeeding) and sampling will persist until three consecutive samples yield negative results, defined as at or below the lower limit of detection (LLOD) for the assay[1].

The utilization of data across various matrices and sampling timepoints mitigates the risk of a "false negative" result impacting the decision to "lift restrictions."

It is not uncommon for patients to be unable to provide samples.

For patients with a debilitating neurological disease, ethical considerations must be applied when requesting continued sampling beyond three consecutive negative results, given the substantial burden on these individuals.

We seek to reduce the burden on these patients.

1 Design and Analysis of Shedding Studies for Virus or Bacteria-Based Gene Therapy and Oncolytic Products. Guidance for industry, FDA, CBER, August 2015

Considerations for our future AAV-GT studies in EU

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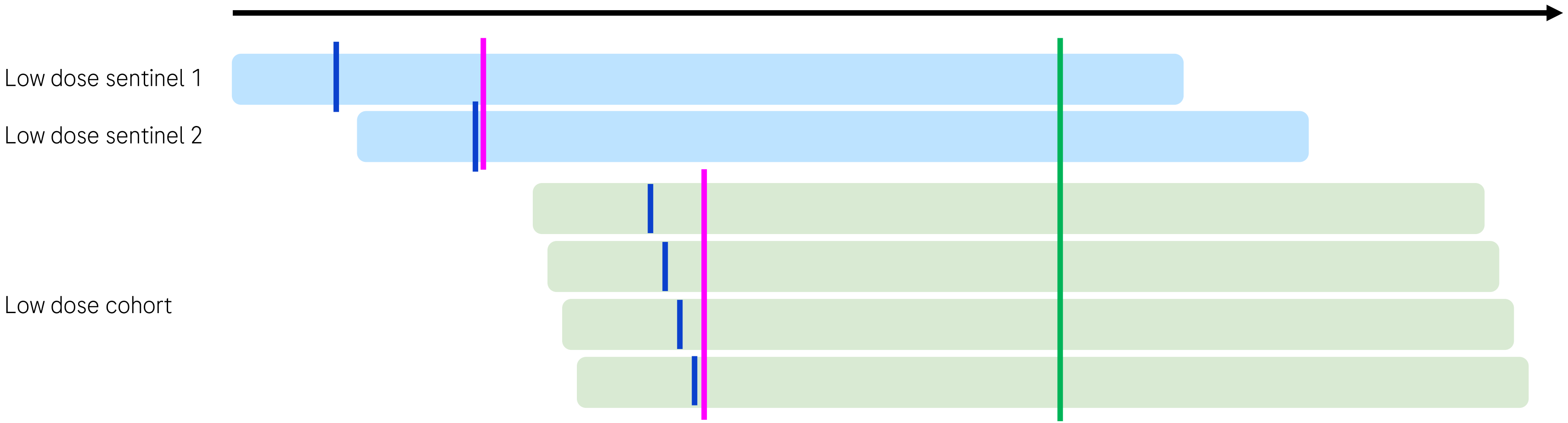


Option A	Lift restrictions for <u>patient</u>, 3rd BLQ
Option B	Lift restrictions for patients, 3rd BLQ
Option C	Lift restrictions at arbitrary time point

Increasing Burden on patient

Does such a PK assay, across these sampling and data uses trigger the need for a CPS in the EU?

Protocol Wording

This is how the references to the vector shedding assay were referred to in the protocol.

Patients agree to a highly effective method of contraception until notified by the investigator or designee that contraception may be discontinued (based on vector shedding data).

Data is open to the Joint Monitoring Committee (JMC) and remains blinded to the Medical Monitor, study participant, investigator and other site personnel.

A JMC member will review the accumulated, unblinded vector shedding data during the Month 3 review and the JMC chairperson will advise the site investigator if sampling may be discontinued (ie, after 3 consecutive negative samples) and whether lifestyle restrictions may be lifted (ie, contraception, pregnancy, breastfeeding) or if sampling and lifestyle restrictions should be continued until a subsequent review.

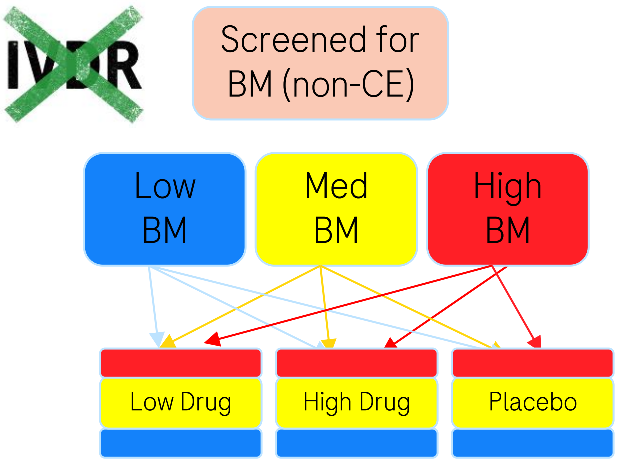
Sampling will continue until 3 consecutive samples are negative (defined as at or below the LLOD for the assay)

Question, how can this be better worded to describe how data is used whilst ensuring this remain out of scope of the requirement for a Clinical Performance Study?

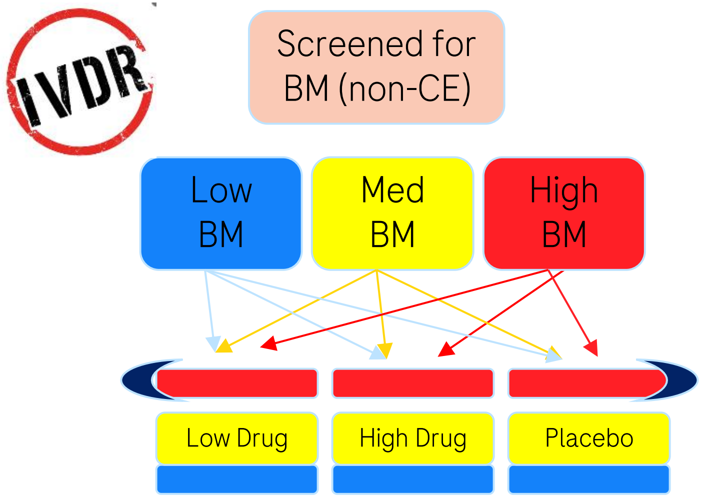
Following slide was used to facilitate discussion around stratification.

Patient Stratification: Understanding when a test is in scope of IVDR

Non-CE marked Biomarker-based stratification for balancing treatment arms (no enrollment caps) *does not* necessitate a Performance Study Application. This clarifies the distinction from capped stratification, which can fall inscope of IVDR requirements.



1:1:1 Randomisation per BM stratum. BM at no point determines dose, fully BALANCED from stratums. Test is not interventional! Hence no Medical use = not an IVD.



1:1:1 Randomisation per BM stratum. Patient enrollment from High stratum is CAPPED once the target number of patients with the High BM level in each cohort is reached. Test becomes interventional!