Assessing device compatibility through assay matrix approach ensures therapeutic consistency & patient welfare

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Abstract

The study aimed to assess the impact of exposure time to the subretinal injection device on the drug product, a pivotal consideration for clinical trial efficacy and safety. The drug product was subjected to dilution following the investigator's brochure protocol to create sample sets representing potential low and high dosages, and exposure durations longer than clinically anticipated. Triplicates of each dosage were exposed to the sterile syringe and subretinal injection needle for 6hrs at ambient temperature or 30 minutes in cold storage, while control samples underwent identical preparation and storage conditions without exposure to the injection apparatus. Assays were conducted to evaluate vector concentration, vector infectivity, expression, and potency to determine any effects on therapeutic safety and efficacy. Results from these assays revealed no significant disparities in these crucial parameters between the exposed and non-exposed samples. Importantly, the observed differences fell within the margins of precision for each assay, indicating consistency and reliability. These findings remained consistent across both the low and high dosage sample sets.

Device Compatibility

Step 1: Dilution of study agent[1] to required dose per clinic manual.

T=0

Step 2: Incubation of study agent @ 2-8°C for 24 hrs.

T=24

Step 3: Incubation of study agent @ ambient temp. In injector & cannula for 6 hrs.

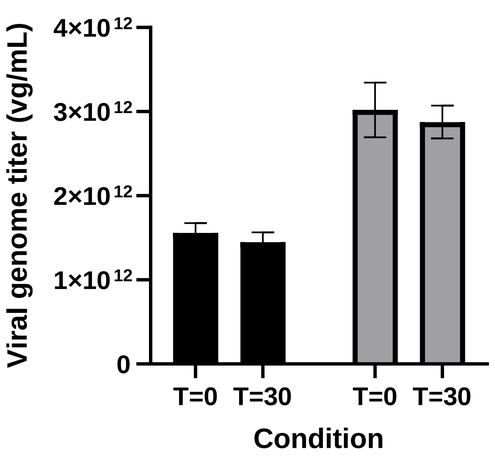
T=30

- Vector genome titer
- Infectious titer
- Expression
- Relative potency

[1]Study agent was diluted to cover doses tested in clinical studies.
Note: Study agent (high dose & low dose) sampled for analytical assays at each timepoint

ddPCR for measuring viral genome titer

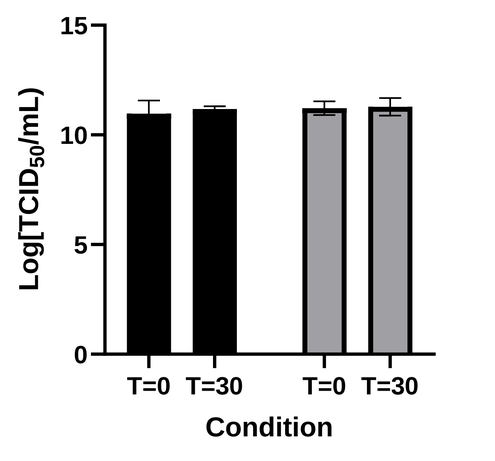
Viral genome titer comparison between T=0 and T=30 timepoints



- Samples exposed to the injection apparatus (T=30), showed marginal differences of 8% and 5% CV for LD and HD, respectively, in comparison with samples not exposed to the injection apparatus(T=0).
- Results fall within the variability acceptance criterion of the assay.

TCID50 for measuring infectious titer (qPCR endpoint)

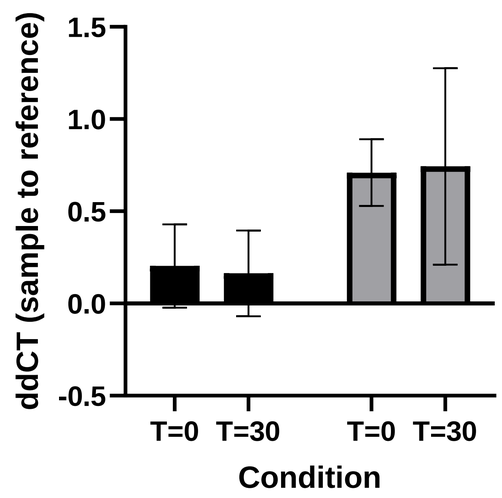
Infectious titer comparison between T=0 and T=30 timepoints



- Samples exposed to the injection apparatus (T=30), showed marginal differences as log variability of 0.21 and 0.06, for LD and HD, respectively, in comparison with samples not exposed to the injection apparatus(T=0),
- Results fall within the variability acceptance criterion of the assay.

mRNA Expression using a cell-based method (RT qPCR endpoint)

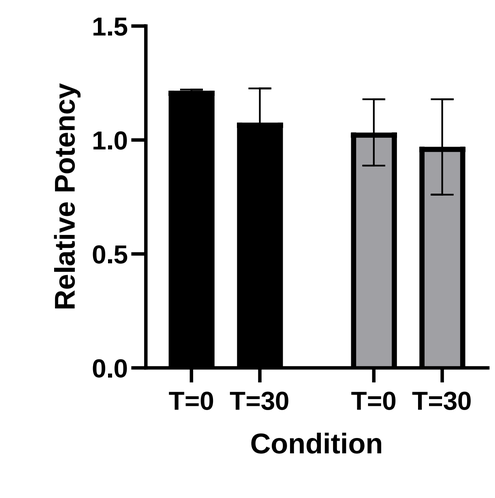
Expression comparison between T=0 and T=30 timepoints



- Samples exposed to the injection apparatus (T=30), showed marginal differences as ddCt of 0.16 and 0.00, for LD and HD, respectively, in comparison with samples not exposed to the injection apparatus(T=0),
- Results fall within the variability acceptance criterion of the assay.

Relative potency using a cell-based method (luminescence readout)

Relative potency comparison between T=0 and T=30 timepoints



- Samples exposed to the injection apparatus (T=30), and samples not exposed to the injection apparatus(T=0), tested within the 50-150% range.
- Results fall within the variability acceptance criterion of the assay.

Summary

The study's outcomes provide reassurance regarding the stability and integrity of drug product under conditions simulating clinically relevant exposure to the subretinal injection device. The absence of substantial effects on vector concentration, infectivity, expression and potency of the drug product suggests that exposure time to the injection apparatus within the specified duration does not compromise the therapeutic efficacy or safety profile of the drug in-vitro.

The study contributes valuable insights into the optimization of subretinal injection protocols for drug product administration (at a volume of 300 µL), emphasizing the importance of meticulous attention to procedural details in ensuring therapeutic consistency and patient welfare. Future research endeavors can build upon these findings to refine administration techniques and enhance the clinical utility of the drug product in addressing the unmet needs of patients afflicted with retinal diseases.

Aim higher

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