

NCT#: 04228445

To: PVP-19IC01 Principal Investigators

From: Provepharm PVP-19IC01 Study Team

**RE: Videography procedures to be conducted for protocol PVP-19IC01 amendment #1:
An Open-Label, Randomized, Multicenter Study to Evaluate the Safety, Efficacy,
Pharmacokinetics and Physician Satisfaction of Two Different Doses of 3,3'-Dioxo-2,2'-
bisindolyldiene-5,5'-disulfonate disodium 0.8% Solution When Used as an Visualization Aid
in the Determination of Ureteral Patency.**

This Clarification Letter is to clarify and update the videography process noted in the PVP-19IC01 protocol, Amendment # 1 dated 10 December 2019.

This protocol is studying the use of indigo carmine as a visualization aid during ureter patency checks. As the protocol is written, during the ureter patency check each subject receives normal saline and the surgeon observes the ureter orifices for up to 10 minutes or until the surgeon determines the ureters are patent. The subject then receives indigo carmine and the ureters are observed again, for 10 minutes or until the ureters are confirmed by the surgeon to be patent. The ureter patency checks are videotaped during this period so an independent reviewer can confirm the ureter visualization scores seen by the surgeon. The protocol allows for one continuous video that includes both the saline and indigo carmine treatment periods.

This process is being slightly modified for two reasons: first it would be preferable for the saline and indigo carmine treatment periods to be captured on separate video clips so that the videos can be pooled and blinded, as described in the protocol, prior to undergoing independent review. Secondly, the ability for the surgeons to stop the video once they determine the ureter is patent pre-disposes the independent reviewer to believe they must also see the ureter jet since the video ended, which implies the surgeon deemed the ureter to be patent.

In order to minimize bias, we are making a small change with regards to recording only. Two separate 10-minute digital files should be collected: one 10-minute video for the saline treatment period and one 10 minute video for the indigo carmine treatment period. Each video clip should continue for a full 10 minutes to remove any bias for the independent reviewer regardless of when the surgeon determines that both ureters are patent. The current ICF does specify that the videos may continue for 20 minutes so a change to the ICF is not required at this time. There is no additional risk to the patient, so a protocol amendment is not required for this change.

Please sign and date in the acknowledgment section below, return a copy of the signed document to Provepharm, Inc. and file the original in the current protocol section of your investigational site file.

Approvals:

Sponsor

[Redacted]

Director, Clinical Operations

[Redacted]

[Redacted]

[Redacted]

Signature and Date

Medical Monitor

[Redacted]

[Redacted]

Signature and Date

Acknowledged:

Principal Investigator:

Printed Name

Signature and Date