**Supplementary Text 1. Sensory examination protocol.**

The objective of the Sensory Examination is to identify clinically relevant deficits in sensory function at baseline and to re-assess the same following investigational treatment with QUTENZA™. Examinations will be performed by neurologists as well as by non-neurologist physician-investigators given study training and findings will be captured using pre-defined scales. Ideally, assessments should be performed by the same person. The demonstration or control sites are different for HIV-AN and for PHN subjects and, indeed, for patients with other aetiologies for their neuropathic pain.

**Allodynia**

●Ask subject to identify their usual most painful or sensitive areas of neuropathic pain (e.g., subject should point to areas if possible, and/or describe the location of such area[s]).

●Using a skin marker, mark the boundaries of the usual most painful or sensitive area(s) on the subject’s skin, using a solid line.

●Using a cotton swab, gently stroke subject’s skin from outside the usual most painful or sensitive area(s) towards the center, from 6 to 8 directions (from above, below, left, right, etc.).

●At exact location where a light swab stroke becomes painful (if applicable), mark the boundary of allodynia, using a dashed line.

●Trace the boundaries of the area(s) of allodynia onto a fresh piece of tracing paper or plastic transparency, and count the total surface area of allodynia (in cm2). Note and label any anatomical or skin landmarks on the tracing.

●Clearly label tracing with “Allodynia”, Visit number/identifier, subject initials/number, tracer’s initials & date, and retain as source documentation.

**Brief Sensory Pain Examination**

The following tests will be performed within the boundaries of the usual most painful or sensitive area(s) and not in additional areas of allodynia. The assessments should be performed at several locations, and only the most intense sensation evoked should be rated. Details of the brief sensory pain examination are provided below.

***Light Brush***

Demonstration Area:

Unaffected mirror-image area on the other side (PHN) or anterior thigh or upper forearm (HIV-AN) or other area as appropriate to the location of the area of neuropathic pain.

Procedure:

●Light brush will be assessed by gently stroking the subject’s skin with a cotton swab.

Ask the subject to keep his/her eyes closed during the assessment.

●As a demonstration, gently stroke the subject’s skin of the unaffected control area using a cotton swab and ask the subject to rate what he/she feels.

●Subsequently, gently stroke the affected skin and ask the subject what he/she feels.

●Capture the subject’s ratings according to the Light Brush Rating Scale, below.

**Light Brush Rating Scale**

0 = Cotton swab is not felt (absent)

1 = Cotton swab is barely felt (diminished)

2 = Cotton swab is felt normally (normal)

3 = Cotton swab is felt more than usual, but not paresthetic/dysesthetic nor painful (increased)

4 = Cotton swab is felt more than usual, and is paresthetic/dysesthetic but not painful (increased and abnormal)

5 = Cotton swab is felt more than usual, and is painful (increased and painful)

***Vibration Sensation***

Demonstration Area:

●Unaffected mirror-image area on the other side (PHN) or anterior thigh or upper forearm (HIV-AN) or other area as appropriate to the location of the area of neuropathic pain.

Procedure:

●Assess vibration sensation by striking a 128-Hz tuning fork on the base of the palm hard enough so that a sound is audible.

●Immediately place the tip of the tuning fork in the treatment area.

●The procedure may be demonstrated on the unaffected area.

●Ask the subject what he/she feels.

●Record the findings according to the Vibration Rating Scale, below.

**Vibration Rating Scale**

0 = Vibration is not felt (absent)

1 = Vibration is barely felt (diminished)

2 = Vibration is felt normally (normal)

3 = Vibration is felt more than usual, but not paresthetic/dysesthetic nor painful (increased)

4 = Vibration is felt more than usual, and is paresthetic/dysesthetic but not painful (increased and abnormal)

5 = Vibration is felt more than usual, and is painful (increased and painful)

***Warm Sensation***

Demonstration Area:

●Unaffected mirror-image area on the other side (PHN) or anterior thigh or upper forearm (HIV-AN) or other area as appropriate to the location of the area of neuropathic pain.

Procedure:

●Assess warm sensation using a warmed electronic thermometer (e.g. Traceable® Surface Dial Thermometer, Cat. No. 4355, CONTROL COMPANY, Friendswood, TX or equivalent; to be provided to all study centers by the Sponsor).

●Heat the thermometer probe in hot water, removed and dry it and allow it to cool, if needed, until the displayed temperature is 43ºC –44ºC. *To avoid injury, the thermometer should never exceed 44º C when placed in contact with the subject.*

●Ask the subject to keep his/her eyes closed during the assessment.

●As a demonstration, apply the distal flat end of the warmed thermometer to the unaffected area for **2-3 seconds** and ask the subject to rate what he/she feels. ●Subsequently, re-warm the thermometer in hot water, remove and dry it and allow it to cool, if needed, until the displayed temperature is 43-44º C.

●Apply the distal flat end in sequence to the test area for **2-3 seconds**. Re-warm the thermometer following each application or as often as needed to maintain a displayed temperature of 43ºC –44ºC prior to a subsequent application.

●Ask the subject to rate what he/she feels during each application of the thermometer.

●Capture the subject’s ratings according to the Warm Rating Scale below.

**Warm Rating Scale**

0 = Warm probe is not felt (absent)

1 = Warm probe is barely felt (diminished)

2 = Warm probe is felt normally (normal)

3 = Warm probe is felt more than usual, but not paresthetic/dysesthetic nor painful (increased)

4 = Warm probe is felt more than usual, and is paresthetic/dysesthetic but not painful (increased and abnormal)

5 = Warm probe is felt more than usual, and is painful (increased and painful)

***Pinprick***

Demonstration Area:

●Unaffected mirror-image area on the other side (PHN) or anterior thigh or upper forearm (HIV-AN) or other area as appropriate to the location of the area of neuropathic pain.

Procedure:

●Pinprick will be assessed using a device (e.g. Neuropen® Owen Mumford, Marietta, GAor equivalent; to be provided to all study centers by the Sponsor).

●Ask the subject to keep their eyes closed during the assessment.

●As a demonstration, apply the device to the subject’s unaffected area every **2-3 seconds.**

●Subsequently, apply the device to several locations of the treatment area in the same manner.

●Perform the assessments at several locations within the treatment area, and only rate the most intense sensation evoked.

●Ask the subject to rate what he/she feels during each application.

●Capture the subject’s rating application using the Pinprick Rating Scale below.

●Since pinprick may be considered painful even by normal subjects, the sensation should be compared with the unaffected reference area and should be documented as normal if the evoked sensation is the same.

**Pinprick Rating Scale**

0 = Pinprick is not felt (absent)

1 = Pinprick is barely felt (diminished)

2 = Pinprick is felt normally (normal)

3 = Pinprick is felt more than usual, but not paresthetic/dysesthetic nor painful (increased)

4 = Pinprick is felt more than usual, and is paresthetic/dysesthetic but not painful (increased and abnormal)

5 = Pinprick is felt more than usual, and is painful (increased and painful)

***Deep Tendon Reflex***

Test Areas, performed on left and right sides:

●Ankle tendon reflex (Achilles or “ankle jerk”)

Procedure:

●Test ankle reflexes with the subject seated on an examination table, or kneeling backwards on a chair or examination table.

●Percuss the Achilles’ tendon by striking it with the rubber bumper of a long-handled Queen’s Square reflex hammer after bending the foot to be slightly dorsiflexed.

●A normal reflex response results in plantar flexion of the foot.

●Rate the left and right ankle reflexes in terms of muscle tone and velocity of response according to the Reflex Rating Scale, below.

**Reflex Rating Scale**

0 = no response (absent)

1 = hypoactive (diminished)

2 = normal

3 = hyperactive (more brisk than normal)

4 = clonus (very intense)

***Cold Sensation***

Demonstration Area:

●Unaffected mirror-image area on the other side (PHN) or anterior thigh or upper forearm (HIV-AN) or other area as appropriate to the location of the area of neuropathic pain.

For HIV-AN or other neuropathic pain involving the feet test areas, performed on left and right sides (see diagram):

1. Ball of foot

2. Midpoint of plantar surface of foot

3. Dorsal surface of great toe (proximal to the nail bed)

4. Midpoint of distal dorsal surface of foot

5. Medial malleolus

Procedure:

●Assess cold sensation using the tuning fork dipped in ice water and dried.

●Ask the subject to keep his/her eyes closed during the assessment.

●As a demonstration, apply the distal flat end of the tuning fork to the anterior thigh or upper forearm for **2-3 seconds** and ask the subject to rate what he/she feels (“not cold, slightly cold, cold, or painfully cold”).

●Apply the distal flat end in sequence to each of the 5 test areas on each foot for **2-3 seconds**. *Make sure to dip the tuning fork in ice water to cool back down following each application.*

●Ask the subject to rate what he/she feels during each application of the tuning fork (“not cold, slightly cold, cold, or painfully cold”).

●Capture the subject’s ratings for each test area according to the Cold Rating Scale, below.

**Cold Rating Scale**

0 = tuning fork is felt as not cold (absent)

1 = tuning fork is felt as slightly cold (diminished)

2 = tuning fork is felt as cold (normal)

3 = tuning fork is felt as painfully cold (increased)

4 = tuning fork is felt more than usual, and is paresthetic/dysesthetic but not painful (increased and abnormal)

5 = tuning fork is felt more than usual, and is painful (increased and painful)

