| | Visit 1 Month 0 | Visit 2 Month 3 | Visit 3 Month 12 | Visit 4 Month 24 | Visit 5 Month 36 | Visit 6 Month 48 | Visit 7 Month 49 ¹ |
|---|--------------------|--------------------|------------------------|------------------------|------------------------|------------------------|-------------------------------------|
| Informed consent | Х | | | | | | |
| Demographics | Х | | | | | | |
| Medical history | Х | | | | | | |
| Physical examination ² | Х | Х | Х | Х | Х | Х | |
| , Inclusion/exclusion criteria | Х | | | | | | |
| Randomisation | Х | | | | | | |
| Vital signs | Х | Х | Х | Х | Х | Х | |
| 12-lead ECG | Х | Х | Х | Х | Х | Х | |
| Hematology | Х | Х | Х | Х | Х | Х | |
| Clinical chemistry | Х | Х | Х | Х | Х | Х | |
| Pregnancy test ³ | Х | | Х | Х | Х | Х | |
| Corneal eye assessment | X | Х | X | X | X | X | |
| Treatment with nitisinone | | 1 | 1 | 1 | 1 | | |
| (treated group only) | ◀─── | | | | | | |
| 24 h urine for HGA | Х | Х | Х | Х | Х | Х | |
| sHGA, s-Tyr | Х | Х | Х | Х | Х | Х | |
| AKUSSI assessments | Х | | Х | Х | Х | Х | |
| Photographs for eye and ear pigmentation | х | | х | х | х | х | |
| Ultrasound abdomen and pelvis for prostate and renal stones | x | | x | x | x | x | |
| Bone mineral density of the hip | х | | х | х | х | х | |
| Adult fractures | Х | | Х | Х | Х | Х | |
| Tendon, ligament and muscle ruptures | х | | х | х | х | х | |
| Echocardiogram for aortic stenosis and sclerosis | x | | x | x | x | x | |
| Audiometry for hearing impairment | х | | х | х | х | х | |
| Otoscopy with photography of eardrum | х | | х | х | x | x | |
| Joint and spine pain | Х | | Х | Х | Х | Х | |
| Scintigraphic scan of joints and spine | х | | х | х | х | х | |
| X-Ray full spine for kyphosis and scoliosis | х | | х | x | х | х | |
| Arthroscopies and joint replacements | х | | х | х | х | x | |

| | Visit 1 Month 0 | Visit 2 Month 3 | Visit 3 Month 12 | Visit 4 Month 24 | Visit 5 Month 36 | Visit 6 Month 48 | Visit 7 Month 49 ¹ |
|---|--------------------|--------------------|------------------------|------------------------|------------------------|------------------------|-------------------------------------|
| Dispense nitisinone (treatment group only) | х | х | х | х | х | | |
| Drug accountability (treatment group only) | | х | х | х | х | х | |
| Prior and concomitant medication | х | х | х | x | х | x | х |
| Adverse Events ⁴ | Х | Х | Х | Х | Х | Х | Х |

Supplementary Table S3. Procedures performed during the SONIA2 study. ¹Telephone contact only, ²Including weight and height, ³Women of childbearing potential, ⁴All serious adverse events reported to the follow-up visit (Visit 7), or at least 28 days after Visit 6, and thereafter only serious adverse

events judged to be related to the investigational medicinal product.