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| **Supplemental Table S1: Primary reasons for seeking LDN prescription** | | | |
|  | **All  participants** | **Male  participants** | **Female participants** |
| **Primary Reasons** | n (%) | n (%) | n (%) |
| Reduce inflammation | 3,809 (31.4) | 943 (30.9) | 2,866 (31.5) |
| Reduce aches & pains | 3,019 (24.9) | 723 (23.7) | 2,296 (25.3) |
| Reduce fatigue | 1,772 (14.6) | 488 (16) | 1,284 (14.1) |
| Encourage weight loss | 1,328 (10.9) | 262 (8.6) | 1,163 (12.8) |
| Improve mood | 841 (6.9) | 247 (8.1) | 579 (6.4) |
| Addiction control | 658 (5.4) | 165 (5.4) | 411 (4.5) |
| Other | 707 (5.8) | 221 (7.2) | 486 (5.3) |

*LDN: low-dose naltrexone*

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| **Supplemental Table S2: SF-36 and ISQ outcomes for LDN QoL cohort** | | | | |
| **Healthspan category** | **Baseline**  mean (SD) | **On-treatment**  Mean (SD) | **% improvement  (absolute % mean change)** | **p-value** |
| Social functioning | 62.5 (28.7) | 70.9 (26.6) | 13.4 | <0.001 |
| Physical functioning | 69.1 (27.6) | 72.6 (26.8) | 5.0 | <0.001 |
| Energy and fatigue | 32.2 (22.6) | 42.5 (22.8) | 31.9 | <0.001 |
| Emotional wellbeing | 63.3 (20.1) | 69.8 (18.0) | 10.2 | <0.001 |
| General health | 49.7 (22.8) | 54.0 (21.9) | 8.7 | <0.001 |
| Physical role limitations | 49.5 (42.6) | 62.7 (40.2) | 26.9 | <0.001 |
| Emotional role limitations | 65.1 (42.4) | 76.6 (38.0) | 17.7 | <0.001 |
| Pain | 55.3 (26.3) | 62.7 (23.1) | 13.2 | <0.001 |
| Overall SF-36 | 55.8 (21.3) | 64.0 (19.8) | 14.7 | <0.001 |
| Immune function (ISQ) | 59.3 (27.3) | 69.2 (25.2) | 16.7 | <0.001 |

*ISQ: immune status questionnaire; LDN: low-dose naltrexone; SD: standard deviation; SF-36: short form 36; QoL: quality of life.*

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| **Supplemental Table S3: SF-36 and ISQ outcomes for responders\* in LDN QoL cohort** | | | | |
| **Healthspan category** | **Baseline**  mean (SD) | **On-treatment**  mean (SD) | **% improvement** (absolute % mean change) | **p-value** |
| Social functioning | 57.3 (28.0) | 74.8 (24.0) | 30.5 | <0.001 |
| Physical functioning | 67.1 (27.9) | 74.3 (25.5) | 10.7 | <0.001 |
| Energy and fatigue | 29.2 (21.2) | 45.9 (22.3) | 57.2 | <0.001 |
| Emotional wellbeing | 60.7 (19.6) | 71.8 (16.1) | 18.3 | <0.001 |
| General health | 48.0 (22.7) | 56.0 (21.8) | 16.7 | <0.001 |
| Physical role limitations | 42.0 (41.9) | 68.6 (38.1) | 63.3 | <0.001 |
| Emotional role limitations | 58.1 (43.7) | 80.6 (34.6) | 38.8 | <0.001 |
| Pain | 51.6 (26.3) | 65.6 (22.0 | 27.5 | <0.001 |
| Overall SF-36 | 51.7(20.5) | 67.2(18.3) | 29.9 | <0.001 |
| Immune function (ISQ) | 56.4(27.4) | 70.3(24.8) | 24.6 | <.0001 |

*ISQ: immune status questionnaire; LDN: low-dose naltrexone; SD: standard deviation; SF-36: short form 36; QoL: quality of life. \*Responders were defined as those participants with any change in total SF-36 scores between baseline and on-treatment assessment.*

**Supplemental Figure Legends**

**Supplemental Figure S1: Study flow chart**