Nusinersen in spinal muscular atrophy type 1 from neonates to young adult: 1-year data from three Asia-Pacific regions

INTRODUCTION
Spinal muscular atrophy type 1 (SMA1) is the most common and severest form of SMA. According to natural history studies, affected babies never achieve independent sitting, and the combined median age of death or permanent ventilation is 13.5 months. Nusinersen, an antisense oligonucleotide that modifies survival motor neuron (SMN2) splicing to enhance full-length SMN protein expression, is the first of many promising approved SMA treatments. The ENDEAR nusinersen clinical trial on SMA1 in patients aged <7 months showed promising motor milestone achievements and improved survival. Through this multinational study, we provide the first Asian real-world data on patients with SMA1 after 1 year of nusinersen treatment.

METHODS
This retrospective observational cohort study, involving eight institutes in three Asian regions (Hong Kong SAR, Taiwan and South Korea) evaluated the baseline clinical characteristics, motor outcomes and changes in ventilation needs of participating patients with SMA1, from pre-treatment (M0) to 6 months (M6) and 10 months (M10) post-treatment. All participants started nusinersen under the Expanded Access Programme (EAP) between 2017 and 2019. Baseline information—newborn screening where applicable, SMN1 mutation, SMN2 copies, gestational age at birth, sex, age of symptom onset, body weight, respiratory support, feeding status, musculoskeletal status and age of first nusinersen—was collected. The motor outcomes before and after nusinersen initiation, measured by Hammersmith InfantNeurologic Exam-ination Part 2 motor milestones score (HINE-2), CHOP INTEND and motor milestone achievements, were recorded. We used CHOP INTEND increased ≥4 points in HINE-2 scores from baseline at M6 and M10 compared with those with two copies (p=0.003). A more significant difference was observed in CHOP INTEND (p<0.001) (online supplemental table 3, figure 2). At M10, more patients (87.5%; 7/8) with three SMN2 copies had CHOP INTEND gained ≥4 points, compared with only 54.3% (6/11 patients) in those with two SMN2 copies. The only patient with nusinersen started >2 years of age and achieved independent sitting was an adult patient with spinal fusion, with three SMN2 copies who first received nusinersen at 24 1/2 years old.

RESULTS
Online supplemental table 1 presents the demographic data and clinical characteristics of the 40 patients with SMA1. Two-thirds of patients had two SMN2 copies. Over half of the cohort (57%) began nusinersen ≤2 years old. For the nine patients (22.5%) identified by newborn screening, eight started nusinersen ≤7 months. All patients started nusinersen at the symptomatic stage. The median nusinersen initiation age was 20 months (range 0.35–294 months).

Survival and motor outcome
1. 95% of patients continued the EAP programme. One patient died before M6 due to respiratory failure. Another patient dropped out before M10 due to lack of improvement. Both had two SMN2 copies (online supplemental table 2).
2. Patients who started nusinersen at aged ≤2 years had better motor milestone gains. Of the patients who started nusinersen at ≤2 years old, 36.4% (8/22 patients) achieved assisted standing; three (13.6%) also attained assisted standing. At M10, 61.1% (11/18 patients) gained ≥5 points in HINE-2, with the median gain of 7.5. In contrast, for those who started nusinersen >2 years old, only 6.7% (1/15 patients) achieved unassisted sitting. At M10, only 7.1% (1/14 patients) gained ≥5 points in HINE-2 with the median gain of 0.5 only (table 1) (online supplemental files 1, 2). Despite having one SMN2 copy, the patient who started nusinersen aged 2 months gained 5 HINE-2 points at M10.
3. Patients with three copies of SMN2 had better motor responses than those with two copies. In table 1, patient with three SMN2 copies had greater increases in median HINE-2 scores from baseline at M6 and M10 compared with those with two copies (p=0.003). A more

Statistical analysis
Baseline demographics and clinical characteristics were presented using descriptive statistics. Changes in the median scores of HINE-2 and CHOP INTEND were calculated using one-way repeated measures ANOVA and paired t-test for quantitative and qualitative variables, respectively. Missing data were excluded. A p value of <0.05 was regarded as statistically significant. A multiple regression model was performed to find the predictor variables of motor outcomes. We used IBM SPSS Statistics V.25 for analyses.

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DISCUSSION
We found patients with SMA1 from the neonatal to adult age benefit from nusinersen treatment. Newborn screening, shorter disease duration and higher baseline HINE-2 score may predict better milestone gains. In the ENDEAR study,2 28% of patients gained ≥5 HINE-2 points (M10) and a mean nusinersen starting age of 5.4 months. For our eight patients who started nusinersen at <7 months old and with two SMN2 copies, they had an earlier mean nusinersen starting age at 2.7 months, and a higher percentage (61.1%; 5/8 patients) gained ≥5 HINE-2 points (M10). While newborn screenings
enable the identification of affected pre-symptomatic babies, our patients began treatment only after symptom onset. As illustrated by the NURTURE study and the AVXS-101 phase 1/2A clinical trials, the best motor outcomes for SMA1 treatment are to asymptomatic affected babies and those with earlier dosing aged <3 months. Support for earliest treatment is therefore necessary.

CONCLUSION

This multinational collaborative retrospective observational cohort study in Asia provides real-world data on first-year treatment that nusinersen is safe and beneficial to patients with SMA1 from the neonatal to adult age. Newborn screening that promotes early treatment initiation can maximise treatment efficacy.

Sophelia Hoi-Shan Chan, Jong-Hee Chae, Yin-Hsiu Chien, Tae-Sung Ko, Jee Hun Lee, Yun Jeong Lee, Sang Ook Nam, Yuh-Jyh Jong

1Department of Paediatrics and Adolescent Medicine, Queen Mary Hospital, The University of Hong Kong, Hong Kong SAR, China
2Department of Pediatric, Seoul National University Children's Hospital, Seoul National University College of Medicine, Seoul, The Republic of Korea
3Rare Disease Center, Seoul National University Hospital, Seoul, The Republic of Korea
4Department of Medical Genetics and Pediatrics, National Taiwan University Hospital, Taipei, Taiwan
5Department of Pediatrics, Asan Medical Center Children's Hospital, University of Ulsan College of Medicine, Seoul, The Republic of Korea
6Department of Pediatrics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, The Republic of Korea
7Department of Pediatrics, Kyungpook National University Hospital, Kyungpook National University College of Medicine, Daegu, The Republic of Korea
8Department of Pediatrics, Pusan National University Children's Hospital, Pusan National University College of Medicine, Vangsan, The Republic of Korea
9Departments of Pediatrics and Laboratory Medicine, Queen Mary Hospital, The University of Hong Kong, Hong Kong SAR, China
10Graduate Institute of Clinical Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan
11Departments of Pediatrics and Laboratory Medicine, and Translational Research Center of Neuromuscular Diseases, Kaohsiung University Medicine Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan
12Department of Biological Science and Technology, National Chiao Tung University, Hsinchu, Taiwan

Correspondence to Dr Sophelia Hoi-Shan Chan, Department of Paediatrics and Adolescent Medicine, Queen Mary Hospital, The University of Hong Kong, Hong Kong SAR, China; sophelia@hku.hk and Professor Yuh-Jyh Jong, Departments of Pediatrics and...
Laboratory Medicine, and Translational Research Center of Neuromuscular Diseases, Kaohsiung University Medicine Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan; yjyong@gking.kmu.edu.tw

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Collaborators Queen Mary Hospital, LKS Faculty of Medicine, The University of Hong Kong, HKSM: Department of Paediatrics and Adolescent Medicine - Godfrey Chi-Fung CHAN, So-Lun LEE, Yiu-Ki NG, Christy CHAU, Ka Ka SIU, Wilfred WONG, Ronnie CHENG, Yuk-Shuen CHAU, Chun-Wai LO. Department of Orthopaedics and Traumatology - Evelyn KUONG, Kenny KWAN. Physiotherapy Department - Pricilla LAM, Pearl CHENG, Maggie NG, Yvonne YUE, Nathan KWONG. Seoul National University Children’s Hospital, Seoul National University College of Medicine, Seoul, South Korea: Department of Pediatrics -Young kyu SHIM, Soo Yeon KIM, Huung Ik SHIN, Jee Hun LEE, Anna CHO. National Taiwan University Hospital, National Taiwan University, Taipei, Taiwan: Department of Medical Genetics and Pediatrics -Wen-Chin WENG, Wu-Liang HWU, Jeng-Yi SHEH, Hsi-Wen HUANG. Kaohsiung University Medicine Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan: Departments of Pediatrics and Laboratory Medicine, and Translational Research Center of Neuromuscular Diseases - Wen-Chen LIANG, Hao-Wei CHUNG, Jong-Hau HSU, Wan-Yi HSU, Wan-Yi HSU, Chen-Hua WANG, Hsiang-Hung SHIH, Yun-Hui CHOU, Yun-Hui CHOU, Tzu-Hsiu HUANG, Su LEE, Yi-Ching WU.

Contributors SH-SC, J-HC, Y-HC, JHL, T-SK, YL, SON, Y-JJ are the principal investigators of the SMA EAP study in their medical centres. SH-SC designed the study, undertook data collection, analysis and evaluation, initial drafting, revision and finalisation of the manuscript. J-HC collected and evaluated data and assisted data collection from the other five centres in the South Korea, assisted the analysis of data interpretation and revised the manuscript. Y-HC collected the data and assisted the analysis of the data interpretation and revised the manuscript. F-SK, SON, JHL, YL collected and evaluated data. Y-JJ designed the study, collected the data and assisted the analysis of data interpretation and the revision of the manuscript.

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ORCID iD
Sophelia Hoi-Shan Chan http://orcid.org/0000-0002-2990-0163

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