יולי 2024

רופא/ה נכבד/ה
רוקח/ת נכבד/ה,

הריני להודיעכם כי העלון לרופא של התכשיר עודכן:

SPINRAZA **ספינרזה**

SOLUTION FOR INJECTION

מרכיב פעיל : NUSINERSEN

התוויות מאושרות :

Spinraza is indicated for the treatment of 5q Spinal Muscular Atrophy except type 0 and type IV.

להלן העדכונים בעלון לרופא המהווים החמרות -

5.1 Pharmacodynamic properties

To allow for long term follow up of these patients, at the end of Study CS3B, 89 patients (Spinraza: n=65; sham-control: n=24) enrolled in Study CS11 (SHINE). Study CS11 is an open label extension study for SMA patients who previously participated in the other Spinraza clinical studies. In patients randomised to Spinraza in Study CS3B and including the extension of treatment with Spinraza in Study CS11 ~~all,~~ patients received the medication ~~Spinraza, with the length of treatment ranging from~~ for 6~~5~~ to ~~592~~ 3043 days (median ~~289~~ 2443 days) ~~at the time of interim analysis~~. . In patients randomised to sham in Study CS3B and initiating Spinraza in Study CS11, patients received the medication for 65 to 2520 days (median 2090 days).

Improvements in motor function were observed among patients continuing Spinraza from Study CS3B, as well as those who initiated Spinraza in Study CS11 (Figure 3), with the greatest benefit observed in those with earlier treatment initiation. ~~Among patients without permanent ventilation at the baseline of Study CS11, a majority were alive and without permanent ventilation at the time of interim analysis.~~ The majority of patients were alive at their last visit after initiating treatment with Spinraza in either Study CS3B or Study CS11. ~~In p~~Patients ~~randomized to~~ initisting Spinraza in Study CS3B were of median age 5.5 months (range 1.7 to 14.9 months). From Spinraza initiation and including ~~the experience~~

Medison Pharma
10 Hashiloach St., P.O.B 7090, Petach-Tikva 4917002 Israel
Tel. +972.3.925.0250, Fax. +972.3.922.5740
medisonpharma.com

extension of treatment in Study CS11, the median time to death or permanent ventilation was ~~73 weeks~~ 1.4 years. At the ~~time~~ end of ~~a~~ Study CS11 ~~interim analysis~~, 6~~1~~0 out of ~~65~~ 81 patients (~~9~~74%) were alive and 41 out of 81. ~~Of the 45~~ patients ~~who~~(51%) were alive and had not met study CS11 the definition of permanent ventilation ~~in Study CS3B, 38 patients (84%) were alive without permanent ventilation in Study CS11 at the time of interim analysis. Further improvement in m~~Mean |HIDE-2 total motor milestone ~~(HINE-Section 2) (2.1;~~ score increased by5.3 (SD ~~4.36~~ 4.6; n=~~22~~ 52) and CHOP INTEND score increased by 18.4 (SD 14.7 ~~(4.68~~; ~~SD 3.993,~~ n=~~22~~38) ~~scores were observed from baseline to Study Day 304 in Study CS11.~~ points from initiation of Spinraza to follow up visit day 394 and 2198 respectively.

Patients ~~who first initiated Spinraza treatment in Study CS11 (n=24;~~randomised to sham ~~control~~ in Study CS3B~~)~~ and initiating Spinraza in Study CS11 were of a median age of 17.8 months (range 10~~ - 23 months) and had a mean CHOP INTEND score of 17.25 (range 2.0 - 46.0) at baseline in Study CS11. At the time of interim analysis, 22 out of 24 patients (92%) were alive. Of the twelve~~.1 to 23.0 months). Prior to Spinraza initiation 12 out of 24 patients (50%) ~~who~~ had ~~not~~ met the Study CS11 definition of permanent ventilation~~ in Study CS3B, 7 patients (58%) were alive without permanent ventilation in Study CS11.~~. The median time to death or permanent ventilation was ~~50.9 weeks~~2.76 years after initiation of Spinraza ~~treatment in Study CS11.~~in Study CS11. At the end of Study CS11, 19 out of 24 patients (79%) were alive and 6 out of 12 patients (50%) were alive without permanent ventilation. Improvement in mean total motor milestone ~~(HINE-Section 2) (1.2;~~ score of 1.4 (SD 1.8; n=12) and CHOP INTEND ~~(3.58;~~ score of 11.5 (SD ~~7.051~~12.2, n=~~12~~10) scores were observed from Study CS11 baseline to ~~Study Day 304 in Study CS11~~follow up visit day 394 or 2198 respectively.

[…]

Upon completion of Study CS4 (CHERISH~~)~~), 125 (83 Spinraza and 42 sham) patients enrolled in Study CS11 (SHINE~~),~~) where all patients received Spinraza. The~~ length of treatment ranged from 74 to 474 days (median 250 days) at the time of the interim analysis. A~~ majority of Spinraza treated patients experienced stabilization or improvement in motor function, with the greatest benefit observed in those with earlier treatment initiation.~~

~~Of patients who initiated Spinraza treatment in Study CS4 (n=39), stabilization or additional improvements in mean HFMSE (0.2; SD 3.06) and RULM (0.7; SD 2.69) scores were observed from baseline to Study Day 265 in Study CS11.~~

~~Patients who initiated Spinraza treatment in Study CS11 (n=20) had a median age of 4.0 years (range 3 - 8 years). Of these patients, stabilization or improvement in mean HFMSE (1.4; SD 4.02) and RULM (2.1; SD 2.56) scores were observed from baseline to Study Day 265 in Study CS11.~~

Patients initiating Spinraza in Study CS4 were of a median age 4.1 years (range 2.1 to 9.2 years). From Spinraza initiation and including extension of treatment in Study CS11, patients received the medication for a median time of 7.2 years (range 1.3 to 8.4 years). HFMSE mean score increased 1.3 (SD 9.4 n=54) and RULM mean score increased by 6.4 (SD 6.5 n=54) at follow up visit day 2070.

Patients randomised to sham in Study CS4, initiated treatment with Spinraza in Study

CS11 at a median age of 4.9 years (range 3.3 to 9.0 years). From Spinraza initation in Study CS11, patients received the medication for a median time of 5.8 years (range 2.7 to 6.7 years). HFMSE mean score decreased by 1.3 (SD 9.3 n=22) and RULM, score increased by 4.2 (SD 4.4 n=23) points at follow up visit day 2070.

In contrast, the natural disease course of untreated patients of similar age and clinical characteristics shows a progressive loss of motor function over time, with an estimated mean decline in HFMSE of
6.6 points over a similar period of 5 years

[…]

Pre-symptomatic *Presymptomatic* infants

Study CS5 (NURTURE) is an open-label study in ~~pre-symptomatic~~presymptomatic infants genetically diagnosed with SMA, who were enrolled at 6 weeks of age or younger. Patients in this study were deemed most likely to develop Type I or II SMA. Median age at first dose was 22 days.

An interim analysis was conducted when patients had been on study for a median of ~~27~~48.3 months (36.6 to 57.1 months ~~(15.1 - 35.5 months~~) and were of a median age at last visit of ~~26~~46.0 months (~~14.0 -~~34.~~3~~0 to 57.1 months). At the interim analysis, all 25 patients (2 SMN2 gene copies, n=15; 3 SMN2 gene copies, n=10) were alive without permanent ventilation. The primary endpoint, time to death or respiratory intervention (defined as invasive or non-invasive ventilation for ≥6 hours/day continuously for ≥7 consecutive days ~~OR~~or tracheostomy), could not be estimated as there were too few events. Four patients (2 SMN2 copies) required respiratory intervention >6 hours/day continuously for ≥7 days, all of whom initiated ventilatory support during an acute reversible illness.

Patients achieved milestones unexpected in Type I or II SMA and more consistent with normal development. At the interim analysis, all 25 (100%) patients had achieved the WHO motor milestone of sitting without support, ~~22 (88~~23 (92%) patients were walking with assistance~~. Among patients older than the WHO defined window for expected age of achievement (95th percentile), 17 of 22 (77%)~~ and 22 (88%) had achieved walking alone. ~~The mean~~Twentyone (84%) patients achieved the maximum attainable CHOP INTEND score ~~at last assessment was 61.0 (46 - 64) amongst patients with 2 SMN2 copies and 62.6 (58 - 64) amongst those with 3 SMN2 copies. All patients had the ability to suck and swallow at last assessment, with 22 (88%) infants achieving a maximal score on the HINE Section 1.~~ of

~~The proportion of~~64. All patients had the ability to suck and swallow at last visit (Day 788), with 22 (88%) infants achieving a maximal score on the HINE Section 1.

Patients developing clinically manifested SMA was assessed ~~amongst patients who reached the Day~~ at Day 700 visit ~~at the interim analysis (n=16).~~. The protocol-defined criteria for clinically manifested SMA included age-adjusted weight below the fifth WHO percentile, a decrease of 2 or more major weight growth curve percentiles, the placement of a percutaneous gastric tube, and/or the inability to achieve expected

age--appropriate WHO milestones (sitting without support, standing with assistance, hands-and-knees crawling, walking with assistance, standing alone and walking alone). At day 700, 7 out of 1115 patients (64 (47%) with 2- SMN2 gene copies and 0 out of 5 patients (0%) with 3 SMN2 copies, met the protocol-defined criteria, of clinically manifested SMA, however, these patients were gaining weight and achieving WHO milestones, inconsistent with Type I SMA. A comparison of motor milestone achievement among the patients with symptomatic infantile-onset SMA and pre-symptomatic SMA is shown in Figure 3.

Type I SMA. A comparison of motor milestone achievement among the patients with symptomatic infantile-onset SMA and presymptomatic SMA is shown in Figure 3.

Study CS5 (NURTURE) is an open-label study in pre-symptomatic infants genetically diagnosed with SMA, who were enrolled at 6 weeks of age or younger. Patients in this study were deemed most likely to develop Type I or II SMA. Median age at first dose was 22 days.

An interim analysis was conducted when patients had been on study for median of 27.1 months (15.1 -35.5 months) and were of a median age at last visit of 26.0 months (14.0 - 34.3 months). At the interim analysis, all 25 patients (2 SMN2 gene copies, n=15; 3 SMN2 gene copies, n=10) were alive without permanent ventilation. The primary endpoint, time to death or respiratory intervention (defined as invasive or non-invasive ventilation for ≥6 hours/day continuously for ≥7 consecutive days OR tracheostomy), could not be estimated as there were too few events. Four patients (2 SMN2 copies) required respiratory intervention >6 hours/day continuously for ≥7 days, all of whom initiated ventilatory support during an acute reversible illness.

Patients achieved milestones unexpected in Type I or II SMA and more consistent with normal development. At the interim analysis, all 25 (100%) patients had achieved the WHO motor milestone of sitting without support, 22 (88%) patients were walking with assistance. Among patients older than the WHO defined window for expected age of achievement (95th percentile), 17 of 22 (77%) had achieved walking alone. The mean CHOP INTEND score at last assessment was 61.0 (46 - 64) amongst patients with 2 SMN2 copies and 62.6 (58 - 64) amongst those with 3 SMN2 copies. All patients had the ability to suck and swallow at last assessment, with 22 (88%) infants achieving a maximal score on the HINE Section 1.

The proportion of patients developing clinically manifested SMA was assessed amongst patients who reached the Day 700 visit at the interim analysis (n=16). The protocol-defined criteria for clinically manifested SMA included age-adjusted weight below the fifth WHO percentile, a decrease of 2 or more major weight growth curve percentiles, the placement of a percutaneous gastric tube, and/or the inability to achieve expected age-appropriate WHO milestones (sitting without support, standing with assistance, hands-and-knees crawling, walking with assistance, standing alone and walking alone). At day 700, 7 out of 11 patients (64%) with 2 SMN2 gene copies and 0 out of 5 patients (0%) with 3 SMN2 copies, met the protocol-defined criteria, of clinically manifested SMA, however, these patients were gaining weight and achieving WHO milestones, inconsistent with Type I SMA. A comparison of motor milestone achievement among the patients with symptomatic infantile-onset SMA and pre-symptomatic SMA is shown in Figure 3.

Medison Pharma
10 Hashiloach St., P.O.B 7090, Petach-Tikva 4917002 Israel
Tel. +972.3.925.0250, Fax. +972.3.922.5740
medisonpharma.com

MEDISON

Pharmacokinetic properties

Single- and multiple-dose pharmacokinetics (PK) of nusinersen, administered via intrathecal injection, were determined in paediatric patients diagnosed with SMA.

Absorption

Intrathecal injection of nusinersen into the CSF allows nusinersen to be fully available for distribution from the CSF to the target central nervous system (CNS) tissues. ~~Mean CSF trough concentrations of nusinersen accumulated approximately 1.4- to 3-fold after multiple loading and maintenance doses, and reached a steady state within approximately 24 months.~~The average increase in trough CSF levels from the start of the maintenance phase through to the last observation timepoint across all patients was approximately 3.2-fold and 2.3-fold in the later-onset and infantile-onset populations respectively. Overall, cumulative CSF PK data collected through to the end of CS11 indicated that in infantile and later onset SMA patients, the standard dosing regimen (12 mg every 4 months) leads to a steady state CSF concentration by 7 to 8 years of treatment. Following intrathecal administration trough plasma concentrations of nusinersen were relatively low compared to the trough CSF concentration. Median plasma T_{max} values ranged from 1.7- to- 6.0 hours. Mean plasma C_{max} and AUC values increased approximately dose proportionally over the evaluated dose range. There is no accumulation in plasma exposure measures (C_{max} and AUC) after multiple doses.

העלון לרופא נמצא בקישור וכן הועבר לפרסום במאגר התרופות שבאתר משרד הבריאות, וניתן לקבלו מודפס על ידי פניה לבעל הרישום.

בברכה,
מדיסון פארמה בע"מ

Medison Pharma
10 Hashiloach St., P.O.B 7090, Petach-Tikva 4917002 Israel
Tel. +972.3.925.0250, Fax. +972.3.922.5740
medisonpharma.com