



Orphan Indication Therapies: Opportunities for a Patient Population without Options

Paper RGo1

Overview

- Focus on a recent study targeting Amyotrophic lateral sclerosis ('ALS', "Lou Gehrig' Disease")
- Definition
- Examples
- Analysis
- Analysis Datasets and AdAM
- Challenges
- Recommendations

What is ALS?

- A-myo-trophic comes from the Greek language.
 - "A" means no or negative.
 - "Myo" refers to muscle, and
 - "Trophic" means nourishment
 - ➔ "No muscle nourishment."
 - When a muscle has no nourishment, it "atrophies" or wastes away. "Lateral" identifies the areas in a person's spinal cord where portions of the nerve cells that signal and control the muscles are located. As this area degenerates it leads to scarring or hardening ("sclerosis") in the region.
- ALS can/does progress differently and there is a lot of variations among patients, two examples:

Lou Gehrig, the 'Iron Horse'



Noteworthy:

- At 17, he hit a baseball out of a major league ballpark
- Played 2,130 consecutive games

Born: June 19, 1903

Diagnosed: 1939

Died: June 2, 1941

Rapid Decline...

All-Time Rank (among batters): #1. [Babe Ruth](#)... #2. [Honus Wagner](#)... #3. LOU GEHRIG... #4. [Ted Williams](#)... #5. [Willie Mays](#)... #6. [Stan Musial](#)... [Vote](#)

Standard Batting [More Stats](#)

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Year	Age	Tm	Lg	G	PA	AB	R	H	2B	3B	HR	RBI	SB	CS	BB	SO	BA	OBP	SLG	OPS	OPS+	TB	GDP	HBP	SH	SF	IBB	Pos	Awards
1923	20	NYY	AL	13	29	26	6	11	4	1	1	9	0	0	2	5	.423	.464	.769	1.234	218	20		0	1			/3	
1924	21	NYY	AL	10	13	12	2	6	1	0	0	5	0	0	1	3	.500	.538	.583	1.122	189	7		0	0			/309	
1925	22	NYY	AL	126	497	437	73	129	23	10	20	68	6	3	46	49	.295	.365	.531	.896	127	232		2	12			*3/O97	MVP-24
1926	23	NYY	AL	155	696	572	135	179	47	20	16	109	6	5	105	73	.313	.420	.549	.969	152	314		1	18			*3	MVP-10
1927	24	NYY	AL	155	717	584	149	218	52	18	47	175	10	8	109	84	.373	.474	.765	1.240	220	447		3	21			*3	MVP-1
1928	25	NYY	AL	154	677	562	139	210	47	13	27	142	4	11	95	69	.374	.467	.648	1.115	193	364		4	16			*3	
1929	26	NYY	AL	154	694	553	127	166	32	10	35	126	4	3	122	68	.300	.431	.584	1.015	165	323		5	12			*3	
1930	27	NYY	AL	154	703	581	143	220	42	17	41	174	12	14	101	63	.379	.473	.721	1.194	203	419		3	18			*3/70	
1931	28	NYY	AL	155	738	619	163	211	31	15	46	184	17	12	117	56	.341	.446	.662	1.108	194	410		0	2			*3/O9	MVP-2
1932	29	NYY	AL	156	708	596	138	208	42	9	34	151	4	11	108	38	.349	.451	.621	1.072	181	370		3	1			*3	MVP-2
1933	30	NYY	AL	152	687	593	138	198	41	12	32	139	9	13	92	42	.334	.424	.605	1.030	177	359		1	1			*3	AS,MVP-4
1934	31	NYY	AL	154	690	579	128	210	40	6	49	165	9	5	109	31	.363	.465	.706	1.172	206	409		2	0			*3/6	AS,MVP-5
1935	32	NYY	AL	149	673	535	125	176	26	10	30	119	8	7	132	38	.329	.466	.583	1.049	176	312		5	0			*3	AS,MVP-5
1936	33	NYY	AL	155	719	579	167	205	37	7	49	152	3	4	130	46	.354	.478	.696	1.174	190	403		7	3			*3	AS,MVP-1
1937	34	NYY	AL	157	700	569	138	200	37	9	37	159	4	3	127	49	.351	.473	.643	1.116	176	366		4	0			*3	AS,MVP-4
1938	35	NYY	AL	157	689	576	115	170	32	6	29	114	6	1	107	75	.295	.410	.523	.932	132	301		5	1			*3	AS,MVP-19
1939	36	NYY	AL	8	33	28	2	4	0	0	0	1	0	0	5	1	.143	.273	.143	.416	10	4	2	0	0			/3	AS
17 Yrs				2164	9663	8001	1888	2721	534	163	493	1992	102	100	1508	790	.340	.447	.632	1.080	179	5060	2	45	106				
162 Game Avg.				162	723	599	141	204	40	12	37	149	8	7	113	59	.340	.447	.632	1.080	179	379		3	8				
				G	PA	AB	R	H	2B	3B	HR	RBI	SB	CS	BB	SO	BA	OBP	SLG	OPS	OPS+	TB	GDP	HBP	SH	SF	IBB	Pos	Awards

Farewell Speech

http://www.youtube.com/watch?v=_SKyfGK9brs

Farewell Speech...



Stephen Hawking



Noteworthy:

- At 17, began studies at Oxford
- *A Brief History of Time* stayed on the British *Sunday Times* best-sellers list for a record-breaking 237 weeks

Born: January 8, 1942

Diagnosed: 1963 (expected to live two years)

Died:

Stephen Hawking

- “... We have this one life to appreciate the grand design of the universe, and for that, I am extremely grateful.”

Analysis

- A type of Joint Rank Analysis
 - Death
 - Functional Decline based on validated survey
 - Tracheostomy
 - Rank
- Creating ADaM Datasets
 - TTE
- Evolving Analysis Based on Findings During the Conduct of the Study
 - Ongoing Safety Analysis
 - Adverse Events and 'Special Interest' AEs

Analysis Datasets and AdAM

- Version 1.0
- Time to Event (TTE) – Three scenarios covered:
 1. A Single Endpoint with a Binary Value for Censoring
 2. Single Endpoint with Multiple Values for Censoring
 3. Composite Endpoints

Example of TTE from AdAM

http://www.cdsc.org/stuff/contentmgr/files/0/Saee16f59e8d6bd2083db5c1639f224/misc/adam_tte-fi - Windows Internet Explorer

http://www.cdsc.org/stuff/contentmgr/files/0/Saee16f59e8d6bd2083db5c1639f224/misc/adam_tte_final_v1.1.pdf

File Edit Go To Favorites Help Convert Select

Standardized Medical Research... http://www.cdsc.org/st...

18 / 31 198% composite

Table 7.1.1 Time-to-Event Data Structure for a Composite Endpoint: PFS Example with Expansion of EVNTDESC to Explain Censoring Reason

Row	USUBJID	PARAM	PARAMCD	AVAL	STARTDT	ADT	CNSR	EVNTDESC
1	1001-0001	Progression Free Survival (days)	PFS	15	2007-01-01	2007-01-15	0	DOCUMENTED PROGRESSION
2	1001-0002	Progression Free Survival (days)	PFS	168	2007-01-01	2007-06-17	1	COMPLETED STUDY. CENSORED AT TIME OF LAST ASSESSMENT.
3	1001-0003	Progression Free Survival (days)	PFS	120	2007-01-01	2007-04-30	3	NEW ANTI-CANCER THERAPY. CENSORED AT TIME OF LAST ASSESSMENT.
4	1001-0004	Progression Free Survival (days)	PFS	28	2007-01-01	2007-01-28	2	EARLY DISCONTINUATION. CENSORED AT TIME OF LAST ASSESSMENT.
5	1001-1005	Progression Free Survival	PFS	30	2007-01-01	2007-01-30	0	DEATH

TTE Quiz

- Is TTE one record per subject?
 - A - It depends on which company you work for
 - B - It depends on which statistician you work with
 - C - It depends on which reviewer you have at the regulatory entity
 - D – It's entirely arbitrary
 - E – It depends on how many types of events are recorded in your study

Thoughts on TTE

- “It can handle a number of outcomes and support a broad array of potential analyses. It is generally recommended that time-to-event data be stored separately from non-time-to-event data even if they both fit within the ADaM BDS. It is Sponsor’s decision to determine how many ADTTE datasets would be adequate for a given study. There is no need to cram all time-to-event variables in one ADTTE dataset at the expense of clarity.”

Study-specific Challenges

- What is ‘different’?
 - Urgency
 - Unmet Medical Need
 - Imminent Death for Patients
 - Evolving Analysis
 - Adverse Events/‘Special Interest’ AE’s
 - How to track, report and analyze
 - How to track, report and analyze in a ***sustainable*** way
 - Sensitivity Analysis
 - Concomitant usage of another therapy approved for ALS

Evolving Analysis

- How these potential therapies originate:
 - In-house versus in-licensed?
 - Determine how many studies (e.g., Legacy, Partner, SAD/MAD and other Phase Is) have/are being conducted and who the key contacts are in case of questions about the data
- Ongoing Phase II study
- Single Pivotal Phase III Study
- Use of Investigator Sponsored trials (NEALS data)
 - Biomarkers that may be correlated with progression

Evolving Analysis...

- Many moving parts...

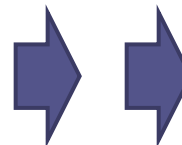
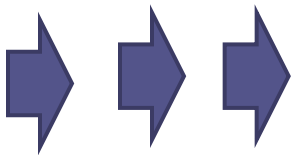
- Phase III



- Phase II



- Phase I's (SAD/MAD/Food Effect, Drug-Drug Interaction, etc.)



NEALS Data

- NEALS maintains and makes available the de-identified data from our trials, when possible. Currently NEALS has 6 ALS trial databases available for researchers to mine:
 - A Randomized, Placebo-Controlled Trial of Topiramate in Amyotrophic Lateral Sclerosis
 - Trial of Celecoxib in Amyotrophic Lateral Sclerosis
 - A Clinical Trial of Creatine in ALS
 - Tolerance of high-dose coenzyme Q10 in ALS
 - Study to Investigate the Safety and Efficacy of Lithium in Volunteers With Amyotrophic Lateral Sclerosis
 - A Multicenter, Dose Ranging Safety and Pharmacokinetics Study of Arimoclomol in ALS
- What do all of these trials have in common?
 - None were successful, all are publicly available.

Other Challenges

- Working within and updating the context of the current production environment
- Updating tools/processes as a result of the programming that was Creating ADaM Datasets
- Resourcing
 - Within group
 - Contractors
 - Vendor(s)
 - Partner(s)

Other Dimensions

- Ethical Implications?
 - Randomization
 - Impacting patient recruitment/retention
- Enrollment
 - Fast!
- Early Access Plans
- Patient Communities!
 - Engaging with patients

Recommendations

- Have programmers understand the disease, Protocol, Statistical Analysis Plan so that they can best determine how to apply AdAM
- Understand/document all the studies that have been run and which will be included in the potential submission(s)
- Work with team to determine what studies have not been mapped and whether to map them
- Have programs that are flexible and robust so that subset/sensitivity analysis can be generated in the most efficient way
- Have team members engaged and try to 'stay ahead of the curve'

Final Thoughts



"HOPE
THAT ONE DAY
WE WILL BE FREE FROM THESE
SPECTACULAR GRIEFS,
HOPE THAT ONE DAY THE SHACKLES WILL
DISINTEGRATE INTO TRAMPLED DUST
BENEATH DANCING FEET."

- RACHEL JONES

References / Recommended Reading

- ALS Association - <http://www.alsa.org>
- ALS Consortium
http://www.alsconsortium.org/clinical_trials_101.php
- Lou Gehrig Wiki site/Bio:
http://en.wikipedia.org/wiki/Lou_Gehrig
- CDISC AdAM: <http://www.cdisc.org/adam>
- NEALS Consortium:
http://www.alsconsortium.org/neals_historical_data.php

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