POSTER
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EGRIFTA® VISUAL ANALOG SCALE (VAS) UTILITY ASSESSMENT AND VALUE DEMONSTRATION IN LIPODYSTROPHY

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PURPLE SQUIRREL ECONOMICS

BACKGROUND

- Utility is often collected for value demonstration or economic evaluation of medical technologies, and EQ-5D is often recognized as a standard measure for preference-based utility assessment.
- However, the variability of EQ-5D is often questioned, particularly if the 3L version is being used as it is not very sensitive for relatively stable patients and patients with mild or moderate diseases. Variability most often appears in severe patients.
- EQ-VAS, where utility is assessed using visual analog scale (VAS), is commonly included during data collection for EQ-5D but is rarely used directly in the economic evaluation.
- Data for this analysis is from a randomized placebo-controlled phase-3 trial. Investigator, sponsor, and patients were blinded to treatment assignment. Subjects were randomized 2:1 *EGRIFTA*® (N = 262) to placebo (N = 123) and instructed to self-administer treatment by subcutaneous injection once a day until the end of the study. EQ-VAS was available for 247 *EGRIFTA*® and 115 Placebo patients.

OBJECTIVES

In this study, we have assessed the use of EQ-VAS as a primary utility measure in lipodystrophy, a disease with mild short-term impacts, but potentially serious long-term complications.

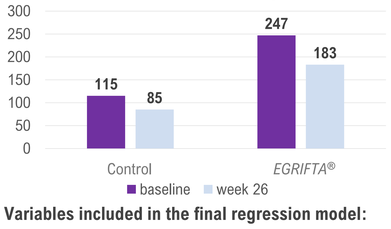
METHODS

- The variability of the EQ-5D-3L results in this trial was small and insignificant. The insensitivity of the 3L results in this context suggests low reliability. The VAS scale is less subject to a low variability issue since the patients rank their global status between 0 and 100. The VAS was used here, as the internal consistency seems superior.
- The primary outcome of this clinical trial was to evaluate the reduction of visceral abdominal fat (VAT), measured in cm^2. Participants were identified as responders to the treatment if they experienced ≥8% volume decrease of VAT.
- 2 data points were collected in the study and used in the analysis: baseline and week 26. Only week 26 stands as an assessment of the "on treatment" utility values.
- Descriptive data are first presented, followed by distribution analysis of the VAS data. Additionally, regression analysis (via a random effects model) is used to determine the impact of the responder status.

Data adjustment:

- Minor data imputations were used for 11 patients (seven missing and four 0/100 values considered incoherent) where the VAS was available at baseline, but not available at week 26. In these cases, if the utility (EQ-5D) was available at week 26 and baseline, an imputation of the VAS reduction/improvement based on the reduction of the EQ-5D was used as a proxy.
- 23 patients were removed from the sample since they had complete data for week 26, but no baseline VAS or utility values. Since the model is assessing the difference between the "on treatment" period (week 26) and baseline without treatment, including patients who only have the 26-week time point could generate bias, as the difference-of-difference calculation could not be adjusted for baseline values.
- VAS values at 0/100 significantly differing from the EQ-5D (4 patients) values were considered faulty and were excluded.

Figure 1: Final sample after data adjustment



Variables included in the final regression model:

- In order to adjust the VAS result and balance the 2 treatment groups, additional variables were added as baseline characteristics, including demographic variables (often included in QOL analysis).
- Since many variables are available, a backward stepwise regression was used, which started from a fully nested model (all variables) and subsequently removed the variables with a 0.2/0.1 p-value threshold, starting with the least significant.
- For the VAT response status calculation, a VAT responder flag was included in all final models.
- An additional series of backward stepwise regression were applied to Clinical/HRQOL variables alone, which included treatment arm, VAS at baseline, a VAT responder flag, CD4 count, and weight.

Regression analysis

- The model used in this analysis was a panel data linear random effects model (GLS regression). The use of a random effects model is confirmed with a Pagan Lagrangian multiplier test for random effects at a p-value of 1.000, rejecting the fixed effect model.
- The model fit was evaluated using between and overall r-square (R^2) values, and chi-square (chi^2) tests.

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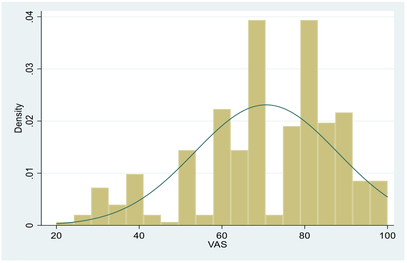
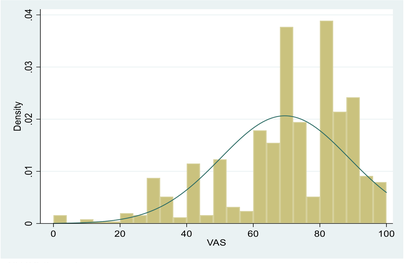
RESULTS

Figure 2: Distribution of reported VAS



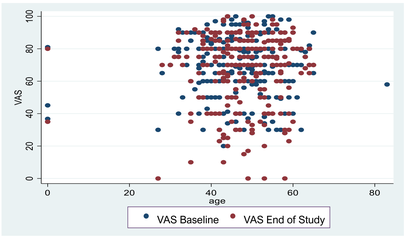
VAS at baseline



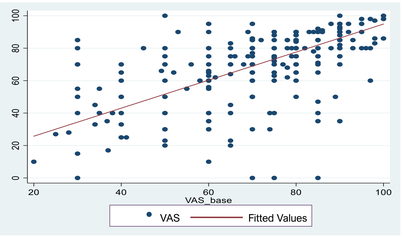
All VAS timepoints

- VAS does not seem to follow a strict normal distribution but has a slight left skew. This is not uncommon for QOL data.
- Non-normality can reduce the reliability of linear regression models.

Figure 3: Distribution of reported VAS by age & baseline



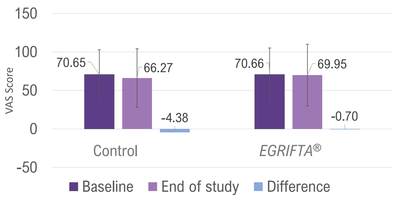
VAS at each timepoint (Y axis) and age (X axis)



VAS at week 26 (Y axis) and VAS at baseline (X axis)

- VAS is not significant impacted by age in this dataset (p = 0.72) but is significantly impacted by the baseline VAS (p = 0.00).

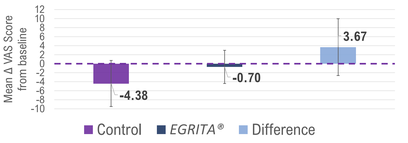
Figure 4: Difference between treatment arms



VAS difference between arms
Note: graph presents the standard deviation (SD) and not the standard error (SE)

- VAS is very similar at baseline (after the data adjustment), but the regression result will have superior validity versus descriptive results since baseline differences can have an impact on the outcome.

Figure 5: Difference between treatments from baseline



VAS difference between arms from baseline to week 26
Note: graph presents the standard deviation (SD) and not the standard error (SE)

- The descriptive change from baseline is not significant but is numerically in favor of *EGRIFTA*® by 3.67 SD(-2.63; 9.98).

Table 1: VAS by responder status

	Point estimate (95% CI)	
Variable	**Control**	***EGRIFTA*®**
Non-responder versus baseline	-2.96 (-9.18; 3.27)	-2.92 (-8.24; 2.4)
Responder versus baseline	-6.62 (-13.58; 0.35)	0.64 (-3.7; 4.97)
Responder versus non-responder	-3.66 (-11.98; 4.66)	3.55 (-2.56; 9.67)
Difference of difference		
EGRIFTA® responders versus control responders	7.25 (-0.95; 15.46)	

- The difference from baseline in responders' trends downwards in the control group with a much wider confidence interval, potentially identifying a subgroup of highly disappointed blinded placebo users.
- While not significant at a 5% margin of error, the difference of difference of responders in the treatment group versus placebo is 7.25, quite close to the clinically meaningful value of 8.

Table 2: Model Fit

Model type	Adjusted R^2	Chi^2 (p-value)	p
Clinical/HRQOL variables only	0.6615	1216 (0.000)	0.137
Nested model	0.684	1305 (0.000)	0.111
Stepwise model – 20%	0.6747	1317 (0.000)	0.064
Stepwise – 10%	0.673	1303 (0.000)	0.051
Clinical/HRQOL + stepwise 20%	0.6823	1320 (0.000)	0.101
Clinical/HRQOL + stepwise 10%	0.6791	1307 (0.000)	0.079

**The models that will be carried forward are stepwise 20%, stepwise 10%, and nested model*

Table 3: Regression Analysis

Nested		Stepwise - 20%		Stepwise - 10%	
Point Estimate (95%CI)	p	Point Estimate (95%CI)	p	Point Estimate (95%CI)	p
Treatment effect					
1.53 (-0.35; 3.41)	0.11	1.8 (0; 3.61)	0.05	1.91 (0.1; 3.72)	0.04
Response effect					
-1.59 (-3.76; 0.58)	0.15	-1.04 (-3.02; 0.94)	0.30	-1.14 (-3.13; 0.84)	0.26
Placebo - no response					
69.19 (67.58; 70.79)	0.00	68.87 (67.36; 70.38)	0.00	68.82 (67.31; 70.34)	0.00
Placebo - response					
67.6 65.32; 69.87)	0.00	67.83 (65.61; 70.05)	0.00	67.68 (65.46; 69.9)	0.00
***EGRIFTA*® - no response**					
70.72 (69.57; 71.86)	0.00	70.68 (69.54; 71.81)	0.00	70.73 69.6; 71.87)	0.00
***EGRIFTA*® - response**					
69.13 (67.18; 71.07)	0.00	69.63 (67.86; 71.4)	0.00	69.59 (67.82; 71.36)	0.00

DISCUSSION

- A within-trial VAS was used instead of EQ-5D-3L in lipodystrophy. The long-term complications of lipodystrophy can be severe, but the short-term impact tends to be related to decreased physical abilities. Treatment with *EGRIFTA*® is therefore aimed to prevent the more serious long-term complications linked to VAT, such as cardiovascular diseases or gastrointestinal complications.
- The results of descriptive VAS analysis show a difference-of-difference between the two treatments of 3.67 SD(-2.63; 9.98) in favor of *EGRIFTA*®. While the result is not statistically significant, the numerical trend can indicate an important difference. However, since the minimally meaningful change is often considered to be 8 (Zanini 2015; Hoehle 2019; Pickard 2007), the difference between treatments here is not considered clinically meaningful.
- When analyzing the responder effect in Table 1 for *EGRIFTA*® versus placebo, *EGRIFTA*® responders had a 7.25 95% CI:(-0.95; 15.46) difference versus the placebo responders. While not significant, this difference is close to the meaningful difference of 8.
- When evaluating the treatment marginal effect in the random effect models, the nested model and stepwise (20% threshold) model generate non-significant treatment effects ranging between 1.53 and 1.80 of VAS change (p = 0.11 and 0.05, respectively). When using the parsimonious stepwise model with 10% threshold and VAT responder flag, the model generates significant treatment effect at 1.91 (p = 0.039).
- The response marginal effect seems illogical in the analysis since it is negative, but it could be attributed to patients' expectations. Additionally, it seems that the VAT response flag is potentially multi-correlated with other variables, and most of the statistical power is taken by the continuous clinical variables, such as CD4+ and VAT at baseline.

LIMITATIONS

- While VAS is an interesting measurement for utility in the absence of better data, it is often considered as a validation tool for EQ-5D rather than the other way around. In this analysis, we are using VAS as the base case since the EQ-5D proves difficult to use in this case and is potentially invalid.
- VAS can only be quantified between 0 and 100, and therefore does not allow for negative values. This limitation is unlikely to severely impact the validity of this analysis since the patients are in a stable disease state, and the impact of the disease complications will only affect the long term.
- The data imputation adjustment allowed retention of 11 patients in the sample, but 23 had to be removed for missing data. Additionally, 94 patients had no VAS (or EQ-5D) values at week 26, reducing the sample further. While the sample remains large for a QOL analysis (362 patients at baseline), it is relevant to note that the trial was not powered or randomized for this VAS analysis. Therefore, to correct for potential bias in baseline characteristics or the absence of randomization, variables were added to the regression model.
- VAT responder status seems to be highly correlated to other clinical variables and is not a significant VAS driver. CD4 and VAT at baseline are highly significant variables and potentially take the power of VAT responder status, which is a binary variable and therefore has limited variability.

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