ATL1102 treatment reduces conversion of active multiple sclerosis lesions into persistent black holes

F Barkhof[a], V Limmroth[b], RA De Jong[a] , ML de Vos[a], P Lim[c], B Francis[c], G Tachas[d]
[a]VU Medical Centre (NL); [b]University of Cologne (DE); [c]CPR Pharma Services (AU); [d]Antisense Therapeutics Ltd (AU)

Introduction

ATL1102 is an antisense drug to the RNA for human CD49d, the alpha subunit of VLA-4.

A Phase II study of ATL1102 dosed for 8 weeks in relapsing remitting multiple sclerosis (MS) patients met its primary endpoint in reducing the cumulative number of new active MS lesions by 54% vs placebo at week 12 (P=0.01)[1].

Notably, ATL1102 treated patients had 90 % fewer new enhancing lesions than those receiving placebo at week 12 (P < 0.005) (Figure 1).

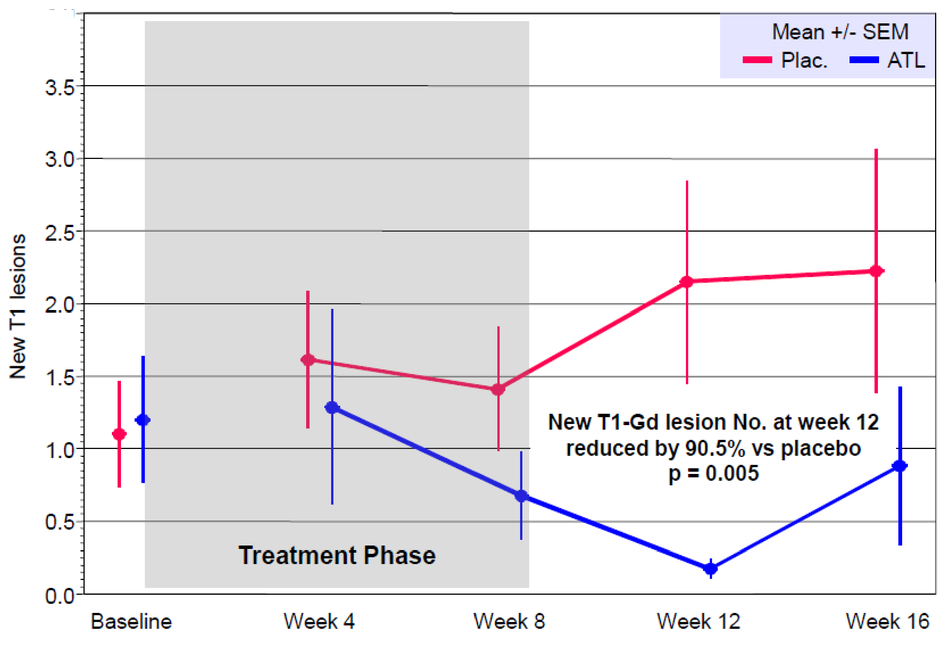

Fig 1. Reduction in the cumulative number of T1-GdE lesions at weeks 4, 8,12 and 16 following administration of ATL1102 (3 x 200mg in week 1 followed by 2 x 200mg per week for 7 weeks)

Objective

A post-hoc analysis of the magnetic resonance imaging data was conducted to measure the effect of ATL1102 on the conversion of remaining new active lesions to T1 black holes (BH), a marker of axonal loss and permanent tissue damage.

Methods

In the Phase II study, new active lesions were defined as either gadolinium-enhancing or new non-enhancing T2 or enlarged non-enhancing T2 lesions.

Evolution of active lesions into BH or T1 iso-intensity was determined by a blinded observer[2]. Data were analysed with a logistic regression of treatment groups with a binomial error distribution as required[3].

Results

There was a significant reduction in the proportion of active lesions at week 8 and 12 converting to BH at week 16 in ATL1102 treated patients (13.2%) compared to patients on placebo (27.6%).

The odds of converting to a BH in the placebo arm were 2.51 times the odds of converting in the treatment arm (95% Wald Confidence Interval: (1.054, 5.959), p= 0.0376).

Analysis Black Hole Evolution	Characteristics	Placebo (arm1)	ATL1102 (arm2)
Origin active lesions week 8–12 combined	N= number of patients	23	17
	Active lesions, mean (SD	7.1 (7.9)	3.1 (3.4)
	Active lesions, median (range)	4 (1-33)	2 (1-13)
	%BH Conversions[1],	45/163=27.6%	7/53=13.3%
	Overall Ratio[2], mean (SD)	23.6 (32.0)	19.2 (38.8)
Treatment Arm Comparison	P-value = 0.0376 Odds Ratio: Arm 1 v Arm 2 : 2.506, 95% CI, (1.054, 5.959) There is a significant difference between Placebo and ATL1102		
Notes:	(i) %BH Conversion is the sum of converted/sum of active in each arm, no standard deviations are derived for this measure. (ii) Overall Ratio = The average of individual Converted lesions/Active lesions in each arm.		

Table 1. Results of Logistic Regression Analysis of active lesions at Weeks 8-12 converting to BH at week 16

Conclusions

The positive effect of ATL1102 on reducing BH evolution suggests that along with its action in reducing the number of new inflammatory brain lesions, ATL1102 may also be neuroprotective by reducing damage to axons in residual new lesions.

Prof F Barkhof (left) & Prof V Limmroth (right)
Authors of the abstract

References

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Disclosures: VU Medical Centre, Amsterdam, the Netherlands, has received compensation for the MRI analysis.

CPR Pharma Services Pty Ltd Thebarton, Adelaide, SA, Australia has received compensation for the statistical analysis.

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