A Phase I, Dose Escalation Study to Evaluate the Tolerability of ABR-215757 in patients with Systemic Lupus Erythematosus (SLE)

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Conclusions

- ABR-215757 was well tolerated up to at least 3 mg/day
- Maximum tolerated dose (MTD) was concluded to be 4.5 mg/day
- The majority of the Adverse Events (AEs) were mild or moderate and transient
  - Most frequently reported AEs were arthralgia and myalgia
  - Some effects on markers of inflammation and liver enzymes were observed, most evidently at doses ≥ MTD
  - No clinical important changes in vital signs or ECG parameters
- ABR-215757 induced changes in the gene expression profile of PBMCs from SLE patients, including several IFN-responsive genes

Objective

To establish the maximum tolerable dose (MTD) of ABR-215757.

Background

ABR-215757 is a small molecule compound intended for chronic oral treatment of SLE. The compound belongs to the quinoline 3-carboxamides, a group of immunomodulators interacting with a defined target, S100A9 (Björk 2009) causing reduction of autoreactive T cell proliferation without general immune suppression. Multiple disease parameters including serological disease markers and histopathological manifestations are affected by ABR-215757. **ABR-215757 effectively inhibits disease in experimental SLE** (Fig.1).

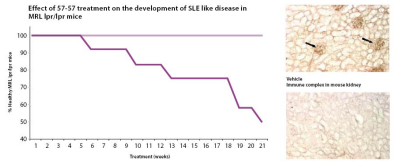

Figure 1 Left: MRLlpr/lpr mice given ABR-215757 (light purple), Control animals (dark purple).

Right: ABR-215757 inhibits deposition of complement factor 3 in the kidneys

Methods

Patients fulfilling at least 4 criteria for SLE as defined by ACR, and with clinically inactive disease at inclusion were included in this randomized, double-blind study. The patients received escalating doses (1.5, 3.0, 4.5 and 6.0 mg/day) of ABR-215757 (3/group) or placebo (1/group) in addition to standard maintenance treatment during 12 weeks. If 1 dose limiting toxicity (DLT) occurred, another group of 4 patients was enrolled at the same dose level. MTD was defined as the highest dose where not more than 1 out of 6 ABR-215757-treated patients experienced DLT. Safety assessments involved analysis of hematology and clinical chemistry, ECG measurements and recording of adverse events (AEs). In addition, the effect on global gene expression was studied by microarray analysis.

Results

Twenty SLE patients, 19 Caucasian and 1 Hispanic, were included; 90% were female.

Table 1. Demography and baseline characteristics

Parameter	Placebo (n=4)		1.5 mg (n=3)		3.0 mg (n=3)		4.5 mg (n=7)		6.0 mg (n=3)	
	Mean	Range	Mean	Range	Mean	Range	Mean	Range	Mean	Range
Age (years)	29.3	24 - 38	61.3	61 - 62	42.3	31 - 60	40.0	27 - 50	58.3	49 - 69
Weight (kg)	62.93	51.0 - 70.0	63.07	50.6 - 71.8	64.33	59.0 - 73.5	68.26	50.1 - 88.4	69.87	47.8 - 87.5
Height (cm)	167.5	158 - 174	164.0	157 - 176	163.3	158 - 170	166.6	155 - 178	167.0	165 - 171
BMI (kg/m^2)	22.37	20.1 - 24.8	23.43	20.0 - 27.1	24.04	23.1 - 25.4	24.49	20.3 - 33.3	25.26	16.3 - 32.1

ABR-215757 was well tolerated at the 1.5 and 3 mg/day dose levels, and the majority of the AEs were mild or moderate. The most common AEs were arthralgia and myalgia (Table 2).

Table 2. Number of patients by dose with treatment emergent, related AEs, by system organ class and most frequent preferred term

System Organ Class	Preferred term	Placebo (n=4)	1.5 mg (n=3)	3.0 mg (n=3)	4.5 mg (n=7)	6.0 mg (n=3)	Total (n=20)
Gastrointestinal disorders	Abdominal pain				1	1	2
General disorders and administration site conditions	Chest pain			1	1	1	3
	Pyrexia				1	1	2
Infections and infestations	Pneumonia		1	1	1		3
	Respiratory tract infection		1		2		3
	Upper respiratory tract infection				1	1	2
Investigations	Hepatic enzyme increased				1	2	3
Musculoskeletal and connective tissue disorders	Arthralgia	1			3		4
	Myalgia				3	1	4
Nervous system disorders	Dizziness	1		1			2
	Headache	2					2
Respiratory, thoracic and mediastinal disorders	Pharyngolaryngeal pain				2		2

There were no Serious Adverse Events (SAEs) at doses up to and including 3 mg/day. At 4.5 mg and higher some AEs of severe intensity were reported and a total of eight SAEs were recorded in 6 patients. The SAEs were chest pain (2), pulmonary embolism, myocarditis, pneumonia, pleuritis, arthralgia and abdominal pain.

No medically relevant changes were observed in vital signs, ECG or chest X-ray at any dose level.

Changes in relevant laboratory parameters in patients treated with ABR-215757 are presented in Figure. 2.

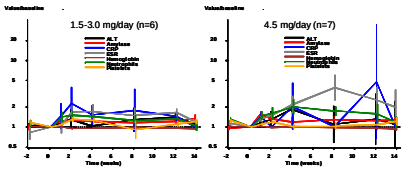

Figure 2. Changes over time in laboratory parameters, value/baseline (Median ± SE)

Maximum Tolerated Dose was concluded to be 4.5 mg/day. Three patients experienced AEs that were classified as DLTs: One at 4.5 mg/day, two at 6 mg/day (Table 3).

Table 3. Dose limiting toxicities

Dose (mg/day)	Adverse event
4.5	Myalgia
6.0	Abdominal/chest pain
6.0	Abdominal pain

As a consequence of the DLT at 4.5 mg, 4 additional patients were recruited into this dose group, none of which experienced any DLTs. Treatment was therefore escalated to 6.0 mg where 2 DLTs occurred.

ABR-215757 induced changes in gene expression patterns in PBMC of SLE patients, including a number of IFN-responsive genes. Microarray analysis was used to define ABR-215757-induced changes in the gene expression profile of PBMCs from the SLE patients (Figure 3). Decreased expression of a number of IFN-regulated genes indicate that ABR-215757 treatment could normalize pathways known to be important in SLE disease pathogenesis. The results also suggest a number of candidate genes that could be used to follow effects of ABR-215757 in the further clinical development.

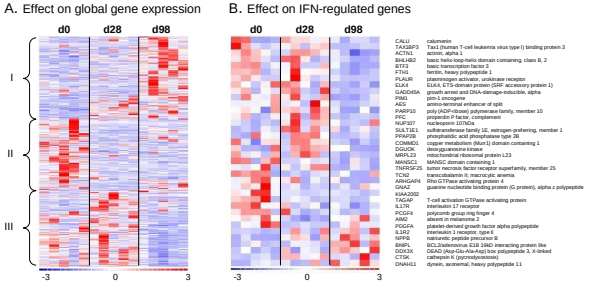

Figure 3. Microarray analysis of PBMCs sampled at d0, d28 and d98

A. Heatmap showing 472 probe sets up- or downregulated between d0/28, 28/98 or d0/d98 in 5 patients exposed to 4.5 mg/day ABR-215757 (filtering criteria were >1.5 fold difference of lower 90% confidence bound). Three major clusters of genes with similar expression patterns (I-III) could be identified, the same pattern could not be seen in two placebo controls (data not shown). **B.** Heatmap showing IFN-regulated genes that changed in expression during ABR-215757 treatment. IFN-regulated genes were identified using the Interferome database (www.interferome.org, Samarajiwa *et. al.* 2009).

References

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