SUMMARY OF NEBA CLINICAL INVESTIGATION – KEY RESULTS

BACKGROUND

Because ADHD symptoms overlap with other diagnoses, it may be difficult for clinicians to determine if ADHD is the primary cause, ADHD symptoms are secondary to other diagnoses, or ADHD is simply comorbid with other diagnoses. The NEBA System includes a method to integrate an EEG biomarker for ADHD (standardized theta/beta ratio) with a clinician's ADHD evaluation to help determine whether ADHD is the primary diagnosis. Investigators conducted a triple-blinded, multi-site, clinical cohort investigation to demonstrate whether NEBA would augment a clinician's ADHD evaluation.

OUTLINE OF NEBA INTEGRATION METHOD

1. The clinician first performs a diagnostic evaluation and determines positive/uncertain/negative for ADHD as primary diagnosis.
2. The biomarker separates *patients with ADHD as primary diagnosis* into test-result subgroups with predefined designations regarding primary diagnosis:
   a. Subgroup with confirmatory support for presence of ADHD as primary diagnosis.
   b. Subgroup with recommendation for further testing with focus on other conditions before proceeding with ADHD as primary diagnosis.
3. The biomarker separates *patients with uncertainty regarding ADHD as primary diagnosis* into test-result subgroups with predefined designations regarding primary diagnosis:
   a. Subgroup with recommendation for further testing with focus on ADHD.
   b. Subgroup with recommendation for further testing with focus on other conditions.
4. The clinician always solely determines negative for ADHD as the primary diagnosis.
   (*No ADHD primary diagnosis is possible without clinician's determination of ADHD criteria including "symptoms are not better accounted for by another condition".*)

OBJECTIVE

The overall objective was to evaluate NEBA's safety and performance (diagnostic accuracy) according to the intended use. Additionally, the clinical investigation was designed to evaluate reliability as well as risks and benefits in terms of clinical data.

SUBJECTS

Subjects were children (aged 6.00-11.99 years) and adolescents (aged 12.00-17.99 years) who consecutively presented with attentional and/or behavioral concerns to 13 geographically distinct clinics (5 Pediatric, 3 Psychological, and 5 Psychiatric) in the US. Of 364 subjects recruited, there were 275 subjects who met protocol criteria, completed the study, and had complete EEG recordings. All of the 275 subjects were included in the analysis of diagnostic accuracy per the intended use.

METHODS

Investigators conducted a triple-blinded, multi-site, clinical cohort investigation. At 13 clinical sites, investigators collected clinical evaluation data from 275 children and adolescents who had presented with attentional and behavioral concerns.

> Clinical evaluation data:
> - *clinician's interview based on DSM-IV-TR criteria,*
> - *semi-structured clinical interview, (KSADS-PL and supplements)*
> - *behavior rating scales, (ADHD-IV RS)*
> - *IQ and achievement testing, (WASI-long and WRAT-4)*
> - *scales of severity and dysfunction, (CGI-S and CGAS)*
> - *physical exam,*
> - *hearing and visions screens,*
> - *medical, neurological, and medication histories,*
> - *questionnaire on socioeconomic status, education, and family history,*
> - *any further testing if deemed necessary by the clinician.*

Using these data, site clinicians performed differential diagnosis and designated the primary diagnosis (blinded to EEG).

A separate team collected EEG (blinded to clinical evaluation data and clinician's diagnosis).

To minimize bias, blind-break and associated regulatory procedures were handled by an independent, third party vendor.

After blind-break, the integration method (NEBA) parsed subjects into test-result subgroups based on the clinician's ADHD diagnostic result and the EEG result (standardized theta/beta ratio). The integration method assigned to each subgroup predefined recommendations regarding ADHD as primary diagnosis.

To evaluate the accuracy of the recommendations, a reference standard was produced by a separate, off-site multidisciplinary team (child and adolescent psychiatrist, clinical psychologist, and neurodevelopmental pediatrician) which determined consensus best estimate diagnosis by review of the clinical evaluation data with blinding to EEG and prior diagnoses (as well as parent rating scales, to avoid the bias of repeating information already covered by K-SADS-PL).

RESULTS - *ACCURACY*

Diagnostic accuracies were compared between 'clinician plus NEBA' and 'clinician alone'. In the current summary, these results have been presented for the total population.

Table 1. Results support that a diagnosis rendered by a clinician using NEBA would be more likely to converge upon the diagnostic results of a multidisciplinary team (MDT).

	Clinician	95% CI - low	95% CI - high	n	Clinician + NEBA	95% CI - low	95% CI - high	n
specificity (%)	36	29	44	145	94	89	97	145
sensitivity (%)	89	83	93	130	82	74	87	130
positive predictive value (%)	56	49	62	209	92	86	96	115
negative predictive value (%)	79	67	87	66	85	79	90	160
overall accuracy (%)	61	55	67	275	88	84	91	275

Further analysis of the NEBA test-result subgroups showed 10 significant, between-group differences in presence of conditions that could impact ADHD as primary diagnosis.

Table 2. The NEBA test-result subgroup of "further testing – other conditions" was more likely to have complicating conditions that might have an impact on the clinician's decision regarding ADHD as primary diagnosis. (chi^2 *analysis*)

	Subject designation by NEBA		
Condition	Further testing – other conditions n=130 (n, % with condition)	Confirmatory support or further testing – ADHD n=115 (n, % with condition)	Difference P[*]
1) Psychiatric disorders that could lead to ADHD exclusion[i]	29 (22%)	18 (16%)	0.187
2) Medical or neurological conditions known to mimic ADHD[ii]	29 (22%)	5 (4%)	**<0.001**
3) Uncorrected vision or hearing problems	42 (32%)	23 (20%)	**0.029**
4) History of no improvement on ADHD medications	10 (8%)	1 (1%)	**0.010**
5) History of adverse events on ADHD medications	20 (15%)	6 (5%)	**0.010**
6) Presentation with primary concern of anger issues	22 (15%)	5 (4%)	**0.007**
7) Presentation with primary concern of aggression issues	49 (38%)	30 (26%)	0.052
8) Satisfactory academic and intellectual performance[iii]	17 (13%)	5 (4%)	**0.017**
9) Evidence of dissatisfaction with ADHD diagnosis[iv]	15 (12%)	3 (3%)	**0.008**
10) MDT: Further testing may be needed for conditions 1-9	66 (51%)	27 (24%)	**<0.001**
11) MDT: Information may be needed for differential diagnosis	29 (22%)	10 (9%)	**0.004**
12) Interviewing clinician: initial impression did not favor ADHD	50 (39%)	21 (19%)	**0.001**
13) Teacher rating scales: inconsistent with ADHD	34 (27%)	25 (22%)	0.424

*MDT= multidisciplinary team. *P value in bold when significant difference (P≤0.05) i) Disorders included pervasive developmental disorders, psychotic disorders, bipolar disorders, and disorders caused by a stressing event (post-traumatic stress disorder and adjustment disorder). ii) Conditions included head injury with ongoing impairment, sensory integration dysfunction, auditory processing disorder, substance abuse, tobacco exposure, anemia, headaches affecting attention, congenital encephalopathy, cerebral palsy, mild mental retardation, neuro-maturational delays/soft signs, and influence of asthma medications. iii) Reported in interview and/or questionnaire as doing well academically/intellectually; no special education; no repeated grade. iv) Patient may have presented because further evaluation was sought after a previous ADHD diagnosis, or because evaluation was sought for disorders other than ADHD. Patient may have had general dissatisfaction with ADHD treatment. All parent and teacher behavioral rating scale scores may have not been consistent with ADHD (all scale scores <80th percentile).*

Whereas the results in Table 2 are from analysis of characteristics of NEBA test-result subgroups, it should also be noted for reference that the overall *diagnostic* odds ratio for NEBA is 65.2. Further, the positive likelihood ratio is 13.7. These results further support that if an individual clinician uses NEBA as part of their ADHD evaluation, the clinician would strongly increase the likelihood that their ADHD primary diagnosis would agree with that of a multidisciplinary clinical team.

RESULTS - *GENERALIZABILITY AND RELIABILITY*

In support of the generalizable use of the device per the intended use, NEBA accuracy results were consistent across a significant range of demographics, patient characteristics, clinical sites, and communities. In support that the NEBA measure (EEG theta/beta ratio) can be reliably determined, the intraclass correlation coefficient (ICC) of repeated NEBA measures (test-retest reliability) was 0.83.

RESULTS - *SAFETY, RISK, AND BENEFITS*

Finally, physical use of the device has been shown to be safe; over the course of the clinical investigation, no adverse device events and no unanticipated adverse device events were reported by the clinical sites. In terms of patients presenting with attention and/or behavior concerns, a risk/benefit analysis supported that a clinician alone (without NEBA) could over-diagnose ADHD at a rate of 34% (as evaluated against results of a multidisciplinary team). The use of NEBA by a clinician could reduce potential for over-diagnosis of ADHD from 34% to 3%. The accompanying risk

is that 8% of patients may be delayed before receiving ADHD treatment while they are receiving unnecessary further testing due to incorrect recommendations by NEBA.

CONCLUSIONS

To evaluate the NEBA System, a clinical investigation was conducted that used as a reference standard the diagnostic evaluation results of a multidisciplinary team. Previous clinical findings have shown that when a multidisciplinary model is applied, a significant number of patients presenting with ADHD-like concerns may be determined as having other primary diagnoses. Similarly, the current investigation showed that a clinician could use NEBA to improve identification of ADHD-like patients who are more likely to have other conditions that could impact the primary diagnosis (10 significant results). By virtue of this improvement, a clinician using NEBA would be more likely to converge upon diagnostic evaluation results of a multidisciplinary team (overall accuracy: clinician plus NEBA, 88%; clinician alone, 61%). Therefore, the EEG integration method (NEBA) may augment a clinician's ADHD evaluation.

REFERENCES

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6. Snyder, S, Rugino, T, Hornig, M, et al. An electroencephalographic biomarker separated patients with attention-deficit/hyperactivity disorder into two subgroups with significantly different clinical profiles. International Congress on ADHD. May 2011.

7. Snyder, S M, Rugino, T A, Hornig, M, et al. EEG as a biomarker separated ADHD patients into clinically meaningful subgroups. European Society of Child and Adolescent Psychiatry. June 2011.

8. Snyder, S M, Rugino, T A, Hornig, M, Stein, M A. Validation of a method that integrates an electroencephalographic biomarker with a clinician's evaluation of attention-deficit/hyperactivity disorder. In preparation. 2013.

REGULATORY

1. CE Certification 552887, April 4, 2010

2. Health Canada Medical Device License 83888, September 9, 2010

3. FDA Approval for Marketing K112711, July 15, 2013

FUNDING

Contact: sales@nebahealth.net 753 Broad Street / Suite 701 / Augusta, GA 30901 USA / Phone: 00 +1 (888) 539-4267 / 00 +1 (706) 736-5864 / Fax: 00 +1 (706) 650-2160