

11 EFFICACY RESULTS

11.1 Efficacy Results and Tabulations of Individual Patient Data

11.1.1 Primary Efficacy Evaluation

The primary efficacy variable was defined as the baseline change of haemoglobin (Hb) measurements. Hb values above a threshold of 11.2 g/dl were considered treatment effects. Hb measurements were done prior to randomisation (visit 1, 2 (=baseline, i.e. week 0)) and after 4, 6, 8, 10, 12, 14 weeks and at a last measurement 6-8 weeks after birth.

Table 9 and the corresponding plots in Figure 1 & 2 display the time course of Hb values. Comparable Hb means were documented at baseline followed by an increase in mean values under treatment leading to higher values under Floradix® mit Eisen.

The predefined treatment success threshold of 11.2 g/dl was reached in the Floradix group within the first 4 weeks and remained above this level as compared to the ferro sanol group in which mean values above 11.2 g/dl were only reached from week 10.

Table 9 Hb measurements (g/dl) in the course of the trial – FAS

	Floradix (n=12)	ferro sanol (n=12)
Time (week)	Mean ± Std. dev. (n)	
-1	10.8 ± 0.4 (12)	10.6 ± 0.5 (12)
0	10.8 ± 1.1 (12)	10.6 ± 0.7 (12)
4	11.6 ± 0.7 (12)	10.9 ± 0.8 (12)
6	11.8 ± 0.6 (12)	11.0 ± 0.8 (12)
8	12.3 ± 0.9 (12)	11.1 ± 1.0 (12)
10	12.3 ± 0.7 (11)	11.5 ± 0.9 (11)
12	12.6 ± 0.6 (11)	11.8 ± 1.1 (9)
14	13.4 ± 0.7 (5)	11.8 ± 1.3 (3)
After birth	13.5 ± 0.9 (10)	13.1 ± 0.8 (10)
<i>Post-text table(s): 14.2.1.1, 14.2.1.2</i> <i>Data appendix: 5.1</i> <i>Figure(s): 1& 2</i>		

The statistical analysis revealed a positive group difference after 4, 6, 8, 10 and 12 weeks in favour of Floradix® mit Eisen (Table 10) with a significant mean difference of nearly 1 g/dl at week 8 and a borderline significant difference of 0.5 g/dl already at week 6.

The baseline changes during the relevant treatment interval (w4 to w12) were always significant within the Floradix group and at week 6, 10 and 12 also for the ferro sanol group as shown in table 10 and figure 1 below:

Table 10 Hb measurements (g/dl), baseline differences – FAS

	Statistic	Floradix (n=12)	ferro sanol (n=12)
Time (w=week)			
w4-w0	Mean ± Std. dev. Baseline change ¹ Mean group difference ²	0.73 ± 0.71 p=0.0045	0.30 ± 0.59 p=0.1055 0.43 (p=0.1197)
w6-w0	Mean ± Std. dev. Baseline change Mean group difference	0.92 ± 0.77 p=0.0017	0.40 ± 0.54 p=0.0272 0.52 (p=0.0731)
w8-w0	Mean ± Std. dev. Baseline change Mean group difference	1.44 ± 0.99 p=0.0004	0.49 ± 0.80 p=0.0577 0.95 (p=0.0174)
w10-w0	Mean ± Std. dev. Baseline change Mean group difference	1.45 ± 0.92 p=0.0004	0.85 ± 0.71 p=0.0027 0.60 (p=0.1029)
w12-w0	Mean ± Std. dev. Baseline change Mean group difference	1.72 ± 1.35 p=0.0018	1.27 ± 0.84 p=0.0019 0.45 (p=0.3740)
¹ t-test of differences; ² 2-sample t-test (satterthwaite extension)			
Post-text table(s): 14.2.1.1, 14.2.1.2 Data appendix: 5.1			

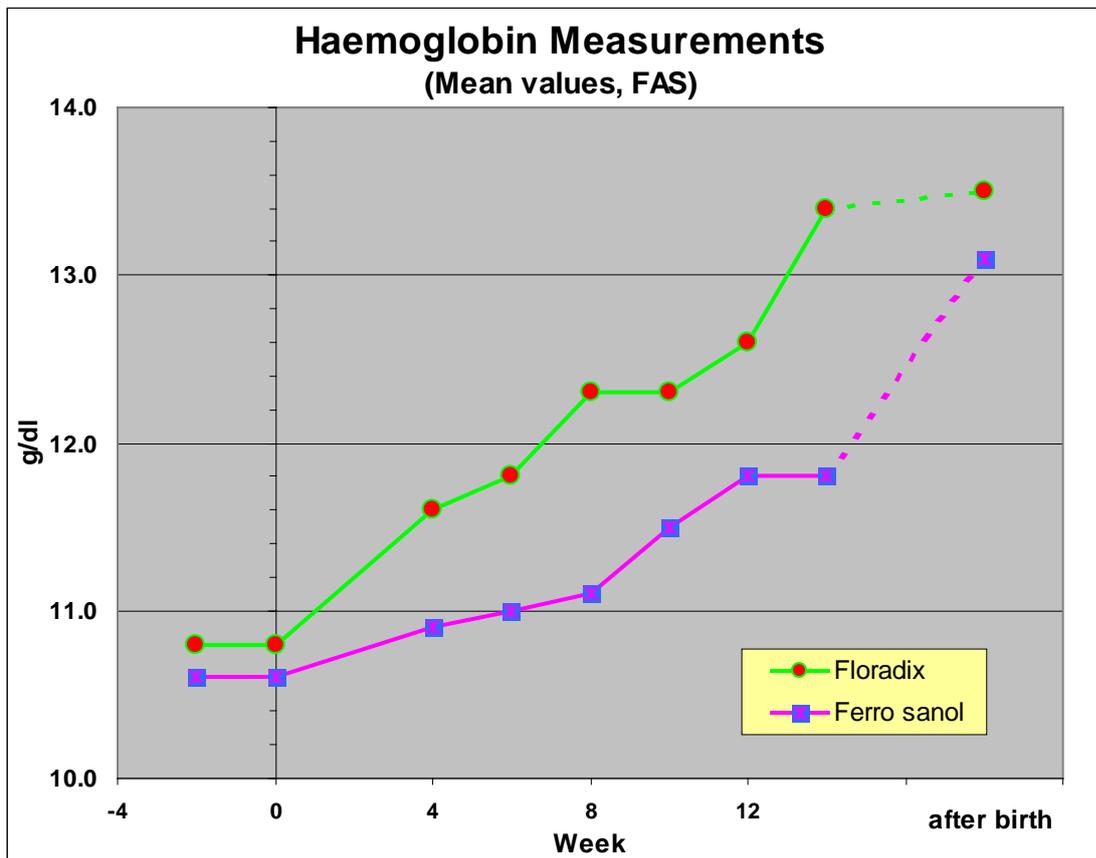


Figure 1: Time pattern of variable haemoglobin (mean values)

Due to the numerous missing values of Hb measurements, the validity of mean estimators may be questionable and median values provide estimators that are more robust to describe the underlying distributions. Indeed the calculation of median values demonstrates that Hb levels in the Floradix group are constantly about 0.7 g/dl higher than those for the reference ferro sanol group.

The time pattern of the Hb median values is displayed in Figure 2 below which shows a similar time curve than Figure 1 above for means:

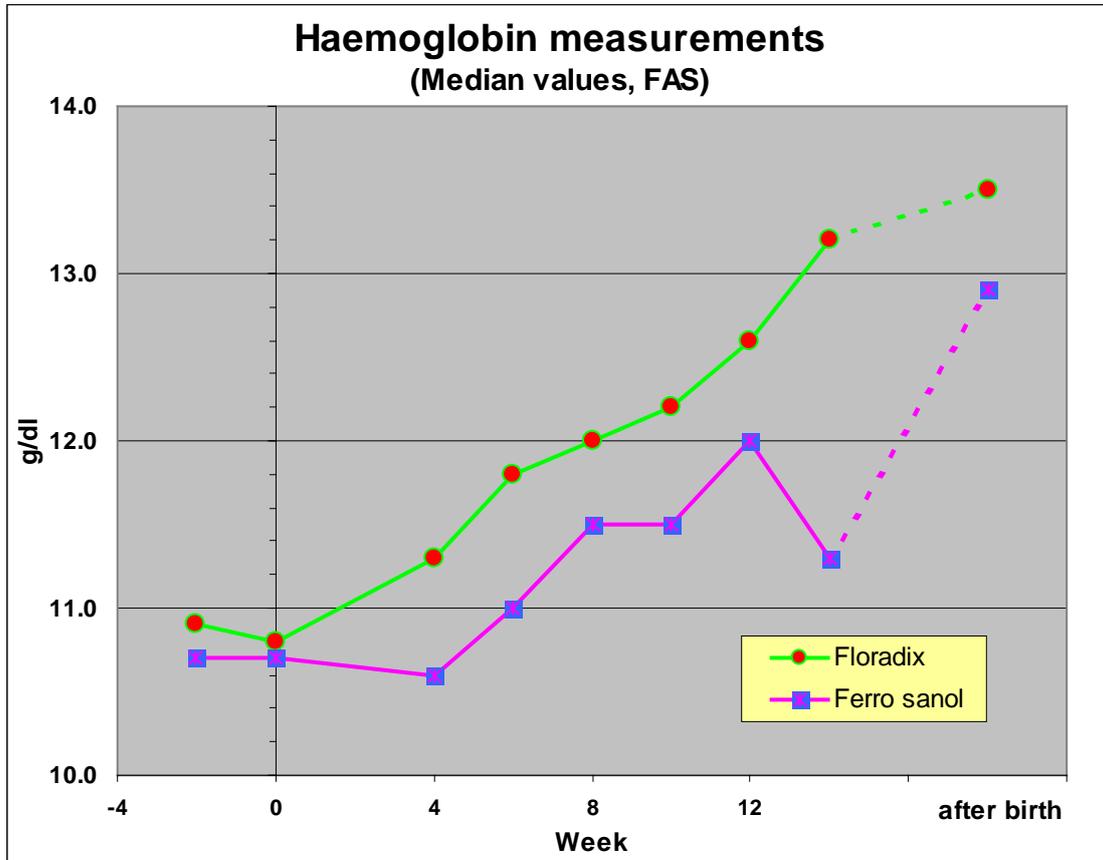


Figure 2: Time pattern of variable haemoglobin (median values)

11.1.2 Secondary Efficacy Evaluation

11.1.2.1 Time pattern of specific FE-Laboratory variables

Transferrin, transferrin saturation, ferritin and soluble transferrin receptor as additional markers for iron deficiency were all descriptively evaluated within the measured time frame.

The basic assumption of approximately normal distributed lab variables could not be validly proven due to observable mean-median differences of these lab variables.

The statistical analysis was therefore focused on time pattern of median values which are considered more robust for evaluation in such situations.

Transferrin

Both, baseline values and last documented values of the treatment groups were comparable and no relevant differences in the time patterns of median values could be observed (Table 11 and Figure 3 in section 14.2).

Transferrin saturation

Again, baseline values and last documented values of the treatment groups were comparable. The ferro sanol group, however, showed at least 5%-lower median values within the time interval of week 6 to week 12 (Table 11 and Figure 4 in section 14.2).

Table 11 Transferrin measurements (median values) – FAS

	Floradix (n=12)	ferro sanol (n=12)	Floradix (n=12)	ferro sanol (n=12)
Time (week)	Transferrin (g/l)		Transferrin saturation (%)	
-1	3.86	3.73	9.5	9.9
0	3.71	4.00	10.9	8.5
4	3.72	3.51	16.9	22.1
6	3.60	3.84	22.8	17.1
8	3.75	3.68	24.8	15.8
10	3.62	3.47	22.7	14.2
12	3.89	3.97	20.9	14.4
14	3.53	3.82	19.4	21.5
After birth	2.88	2.79	22.9	20.8

*Post-text table(s): 14.2.2.0, 14.2.3.0,
Data appendix: 5.2 Figure(s): 3, 4*

Ferritin

Baseline values and last measured values in both groups were comparable. The ferro sanol group, however, revealed lower median values from week 6 to week 14 (Table 12 and Figure 5 in 14.2).

Soluble Transferrin Receptor

Baseline values and last measured values in both groups were comparable and did not differ remarkably during the course of the trial.

Table 12 Ferritin & soluble transferrin receptor (median values) – FAS

	Floradix (n=12)	ferro sanol (n=12)	Floradix (n=12)	ferro sanol (n=12)
Time (week)	Ferritin (ng/ml)		Sol. transferrin receptor (mg/l)	
-1	7.5	7.6	1.33	1.30
0	7.5	8.7	1.39	1.34
4	12.8	10.9	1.26	1.34
6	14.4	9.2	1.18	1.16
8	15.9	10.2	1.16	1.25
10	16.8	14.2	1.11	1.20
12	16.9	14.5	1.29	1.21
14	22.3	7.7	1.27	1.27
After birth	30.5	29.2	1.42	1.47

*Post-text table(s): 14.2.4.0, 14.2.5.0,
Data appendix: 5.2 Figure(s): 5, 6*

11.1.2.2 Iron deficiency symptoms

A list of 11 predefined clinical iron deficiency symptoms had to be recorded by the patients on a 6-point scale. The whole group of symptoms could be subdivided into two sets of items: one set with scaling points: 1="never" up to 6="always" and another with scaling points: 1="not existing" up to 6="severe intensity".

All items are listed in the Post-text Tables (section 14). As usual, total scores ((total 1 = sum (sym1 to sym6) and total 2 = sum (sym7 to sym11)) were calculated under the assumption, that these quasi metric scores a) are statistically more robust and b) are approximately normal distributed.

Table 13 contains basic statistics (means & standard deviations) of the totals 1 and 2, respectively.

Item total 1 (comprising symptoms 1-6)

The baseline values slightly differed between both treatment groups. During the treatment period a small decrease could be observed in the ferro sanol group and a nearly unchanged time pattern for the Floradix group.

Item total 2 (comprising symptom 7-11)

Again, baseline values slightly differed between both treatment groups and during the treatment period only a small decrease could be observed in both treatment groups.

Table 13 Item totals 1&2 of iron deficiency symptoms (mean values) – FAS

	Floradix (n=12)	ferro sanol (n=12)	Floradix (n=12)	ferro sanol (n=12)
Time (week)	Item total 1¹		Item total 2	
0	13.1 ± 4.2	17.8 ± 3.4	9.8 ± 3.2	12.5 ± 5.5
4	11.7 ± 2.7	15.9 ± 3.0	7.8 ± 1.9	11.8 ± 5.6
6	10.6 ± 2.9	13.9 ± 3.5	6.9 ± 1.6	11.3 ± 6.3
8	11.0 ± 2.9	12.9 ± 2.5	7.3 ± 2.0	11.3 ± 6.2
10	11.2 ± 2.9	12.5 ± 2.7	7.3 ± 2.4	9.6 ± 4.2
12	11.3 ± 2.8	12.5 ± 3.5	7.1 ± 2.0	9.0 ± 4.9
After birth	12.4 ± 4.8	12.4 ± 4.9	9.0 ± 3.7	9.3 ± 4.4
¹ mean values ± std. dev. Post-text table(s): 14.2.6.1 - 14.2.6.7 Data appendix: 6.1 Figure(s): 7, 8 and single item plots				

11.2 Efficacy Conclusion

The FAS comprised 24 patients (12 Floradix® mit Eisen and 12 ferro sanol® duodenal mite 50mg). This limited group of patients clearly determined results for the primary endpoint in favour of Floradix® mit Eisen:

Baseline values were comparable in both groups and in the group of patients treated with **Floradix® mit Eisen**-a significant increase in Hb values was measured after **4, 6, 8, 10 and 12** weeks of treatment, while in the group treated with ferro sanol® duodenal mite 50mg a significant increase was only measured after 6 weeks of treatment. The Hb increase was on average less pronounced than in the Floradix group and at week 8 the significance level was missed. Mean and median results showed similar patterns and results.

The predefined treatment success threshold of 11.2 g/dl was reached in the Floradix group within the first 4 weeks and remained stable above this level as while in the ferro sanol group mean values above 11.2 g/dl were reached only from week 10 onwards.

Variable	Floradix®	ferro sanol®
Baseline (mean) for Hb	10.8 g/dl	10.6 g/dl
Increase w4 - w0	6.8% (p=0.0045)	2.8% (p=0.1055)
Increase w6 - w0	8.5% (p=0.0017)	3.8% (p=0.0272)
Increase w8 - w0	13.3% (p=0.0004)	4.6% (p=0.0577)
Increase w10 - w0	13.4% (p=0.0004)	8.0% (p=0.0027)
Increase w12 - w0	15.9% (p=0.0018)	12.0% (p=0.0019)

(intra-individual comparison with paired t-Test)

The secondary efficacy parameters did not show a clear tendency in favour of any of the investigated products. Case numbers may have been too small for rather discrete effects in combination with the fact that baseline values differed between treatment groups.