



Personalised medicines for Duchenne muscular dystrophy

**9th International Annual
Duchenne Conference**

Pádraig Wright

GSK Rare Diseases

Medical need is overwhelming

Rare diseases are not rare ... collectively

Highly committed advocacy organisations

.....

New technologies

GSK Rare Muscle Diseases

Duchenne muscular dystrophy

Myasthenia gravis

Steinert myotonic dystrophy

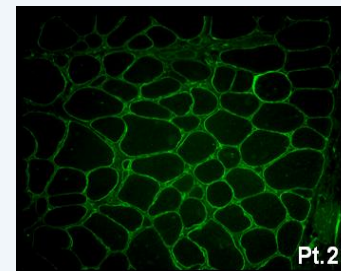
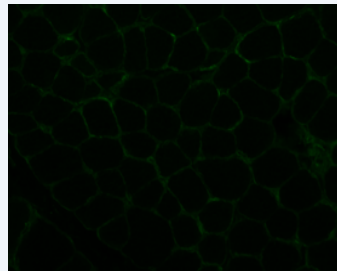
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Alliance to fight Duchenne Muscular Dystrophy

GSK and Prosensa, the Dutch based biopharmaceutical company focusing on RNA modulating therapeutics, announced that they have entered into an exclusive worldwide collaboration for the development and commercialisation of RNA based therapeutics for Duchenne Muscular Dystrophy.

PRO-051 (Exon 51 **)

- Proof of mechanism **
- Proof of concept



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- Proof of concept extension study
- Phase II and III clinical trials for regulatory approval have commenced

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Local Dystrophin Restoration with Antisense Oligonucleotide PRO051

Judith C. van Deutekom, Ph.D., Anneke A. Janson, B.S., Ieke B. Ginjaar, Ph.D.,
Wendy S. Frankhuizen, B.S., Annemieke Aartsma-Rus, Ph.D.,
Mattie Bremmer-Bout, B.S., Johan T. den Dunnen, Ph.D., Klaas Koop, M.D.,
Anneke J. van der Kooi, M.D., Ph.D., Nathalie M. Goemans, M.D., Ph.D.,
Sjef J. de Kimpe, Ph.D., Peter F. Ekhart, M.Sc., Edna H. Venneker, M.D.,
Gerard J. Platenburg, M.Sc., Jan J. Verschuuren, M.D., Ph.D.,
and Gert-Jan B. van Ommen, Ph.D.

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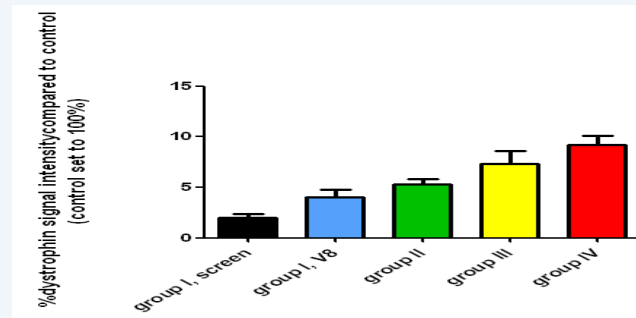
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ORIGINAL ARTICLE

Systemic Administration of PRO051 in Duchenne's Muscular Dystrophy

Nathalie M. Goemans, M.D., Mar Tulinius, M.D., Ph.D.,
Johanna T. van den Akker, Ph.D., Brigitte E. Burm, Ph.D., Peter F. Ekhart, M.Sc.,
Niki Heuvelmans, Tjadine Holling, Ph.D., Anneke A. Janson,
Gerard J. Platenburg, M.Sc., Jessica A. Sipkens, M.Sc., J.M. Ad Sitsen, M.D., Ph.D.,
Annemieke Aartsma-Rus, Ph.D., Gert-Jan B. van Ommen, Ph.D.,
Gunnar Buyse, M.D., Ph.D., Niklas Darin, M.D., Ph.D.,
Jan J. Verschuuren, M.D., Ph.D., Giles V. Champion, M.D.,
Sjef J. de Kimpe, Ph.D., and Judith C. van Deutekom, Ph.D.

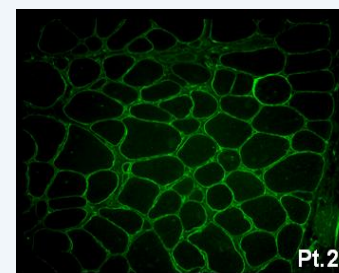
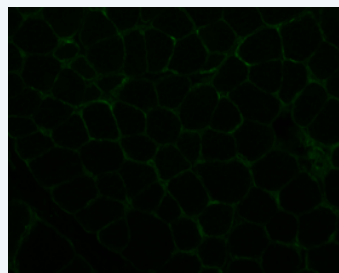
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PRO-051

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- Proof of concept



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- Proof of concept extension study – 1 year data
- Phase II and III clinical trials for regulatory approval had commenced – 1 year later

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Proof of concept extension study

A Phase II open label study of 6 mg/kg/wk subcutaneously in ambulant boys with Duchenne muscular dystrophy who participated in PRO-051 proof of concept study

Current countries: Belgium, Sweden
(N=12 : **RECRUITMENT COMPLETE**)

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Injection site reactions

Protein in urine

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Mean change in 6MWT from extension baseline: boys able to complete the 6MWT at start of extension study

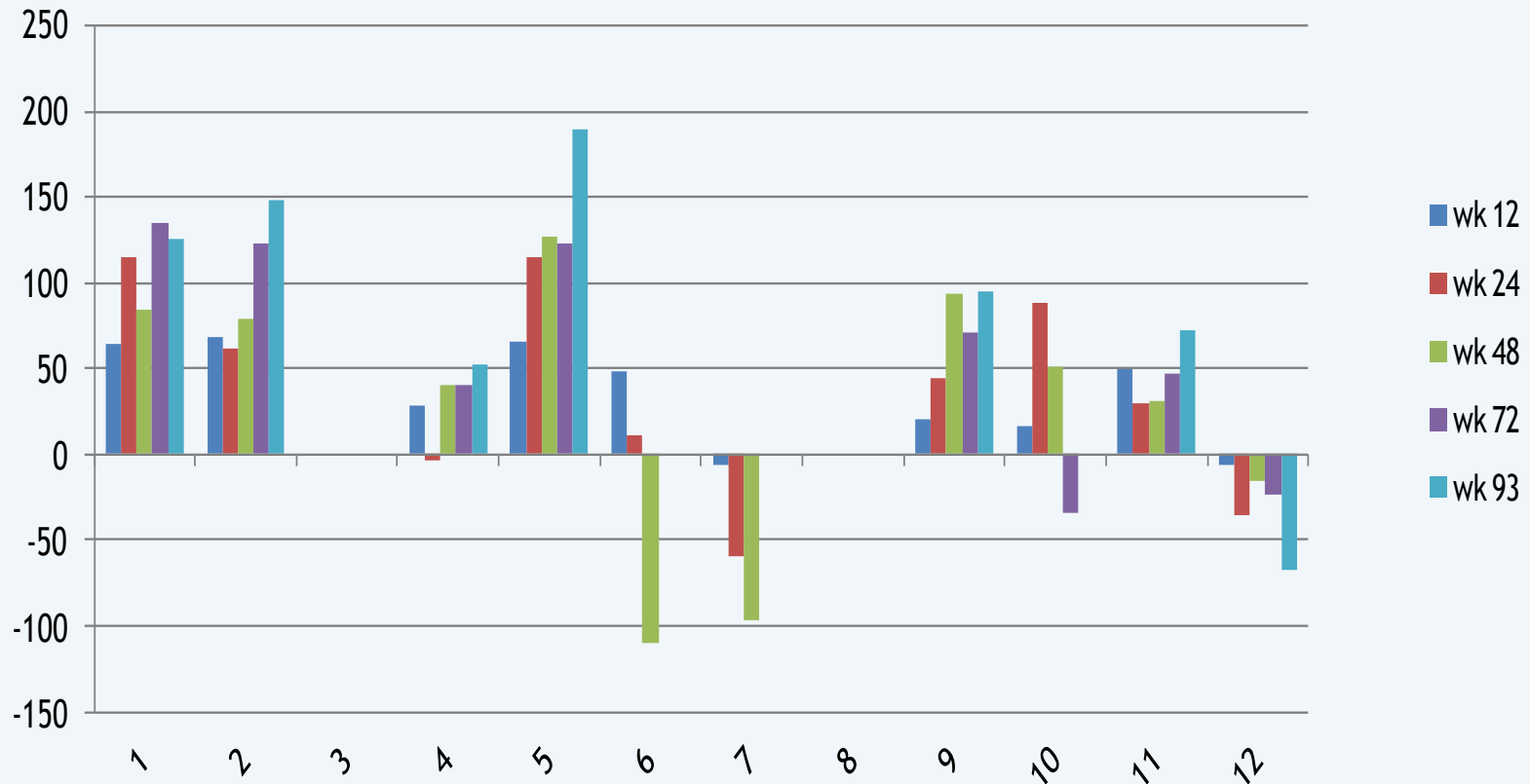
- missing values replaced by zero for boys who became unable to complete the test at later visits

	n	Mean (SD) m	Median (range) m
Week 12	10	+35 (29)	+39 (-6 to +69)
Week 24	10	+37 (60)	+37 (-59 to +115)
Week 48	10	+29 (80)	+46 (-110 to +127)
Week 72	10	-2 (144)	+44 (-263 to +135)
Week 93	10	+11 (157)	+63 (-263 to +190)

N=10 (subjects who completed all 6-minute walk test [6MWT] assessments). One subject stopped test early and one subject was non-ambulant at baseline. Two subjects were unable to attempt the 6MWT at 93 weeks; still included in mean change.

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Individual change in 6MWT from extension baseline: boys able to complete the 6MWT at start of extension study



N=10 (subjects who completed all 6-minute walk test [6MWT] assessments). One subject stopped test early and one subject was non-ambulant at baseline. Two subjects were unable to attempt the 6MWT at 93 weeks; still included in mean change.

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DMD114117

A Phase II double blind exploratory parallel group placebo controlled study to assess two dosing regimens of GSK2402968 for efficacy, safety, tolerability and pharmacokinetics in ambulant boys with Duchenne muscular dystrophy

Current countries: Australia, Belgium, France, Germany, Netherlands, Spain, Turkey, UK

(N=53 : **RECRUITMENT COMPLETE**)

ORPHA236148

(www.orpha.net)

NCT01153932

(www.clinicaltrials.gov)

114117

(www.gsk-clinicalstudyregister.com)

GSK2402968

DMD114044

A Phase III randomised double blind placebo controlled study to assess the efficacy and safety of GSK2402968 in ambulant boys with Duchenne muscular dystrophy

Current countries: Argentina, Belgium, Brazil, Canada, Chile, France, Germany, Italy, Japan, Korea, Netherlands, Poland, Russia, Taiwan

(N=180 : **RECRUITING**)

ORPHA265656

(www.orpha.net)

NCT01254019

(www.clinicaltrials.gov)

114044

(www.gsk-clinicalstudyregister.com)

GSK2402968

DMD114876

A Phase II randomised double blind placebo controlled study to assess two doses of GSK2402968 for efficacy, safety, tolerability and pharmacokinetics in ambulant boys with Duchenne muscular dystrophy

Current countries: USA
(N=54 : **RECRUITING**)

NCT01462292
114876

(www.clinicaltrials.gov)

(www.gsk-clinicalstudyregister.com)

GSK2402968

DMD114118

A double blind randomised placebo controlled study to assess escalating single doses of GSK2402968 for pharmacokinetics, safety and tolerability in non-ambulant boys with Duchenne muscular dystrophy

Current countries: USA, France
(N=32 : **RECRUITMENT COMPLETE**)

NCT01128855
11404118

(www.clinicaltrials.gov)

(www.gsk-clinicalstudyregister.com)

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Acknowledgements

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SUMMARY

- **12 boys treated open label with GSK2402968 for 2 years**
 - injection site reactions (N=12)
 - protein in urine (N=12)
 - dystrophin expressed at week 24 (N=12)
 - encouraging results from 6MWT
- **large scale double blind placebo controlled clinical trials are required**
- **these studies are underway**
 - ambulant boys (N~300)
 - non-ambulant boys (N~80)
- **personalised medicines for Duchenne muscular dystrophy**
 - exon 51, exon 44 ...
 - ambulant, non-ambulant ...
 - dystrophin replacement ... muscle replacement ... dystrophy prevention